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Hepatology Highlights

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Non-alcoholic fatty liver disease and the metabolic syndrome in an urbran hospital serving an African community

Onyekwere C.A, *et al*. The term *nonalcoholic fatty liver disease* (NAFLD) is used to describe a spectrum of histologic findings ranging from simple steatosis to nonalcoholic steatohepatitis with progressive fibrosis.[1] Diabetes, obesity and metabolic syndrome are risk factors for NAFLD, and it is present in 50% of diabetics and 76% of obese individuals.[2] In a large population based cohort study, NAFLD was detected in one third of the American adults.[3] In this issue, Onyekwere, *et al.*, present data on the prevalence of NAFLD in Nigeria, and compare the prevalence of the disease in the diabetic and non-diabetic subjects. This prospective cross sectional study was carried out in an endocrinology clinic of an urban university teaching hospital in Lagos, Nigeria. One hundred and fifty subjects were recruited from October 2009 to August 2010, 106 were diabetics and 44 non-diabetics, with the latter group serving as the comparator group. A questionnaire on liver disease symptoms and physical examination were undertaken. Blood work including fasting blood sugar and lipid profile, liver biochemistry, hepatitis B and C virus serology were collected and all subjects had an upper abdominal ultrasound scan to determine the radiological prevalence of fatty liver.

The overall prevalence of NAFLD among all study subjects was 8.7%, and was higher in the diabetic group but this was not statistically significantly (9.5% *vs.* 4.5%, p = 0.2). The mean body mass index (BMI) was similar in both groups (31 *vs.* 30 kg/m^2), suggesting that both groups were, by definition, "obese", however, waist circumference (WC) was significantly higher in people with fatty liver (112 cm *vs.* 94 cm, p = 0.003). The prevalence of metabolic syndrome was higher in subjects with NAFLD than in those without fatty liver, but this wasn't statistically significant.

The interesting aspect of this study is that the prevalence of NAFLD in this study is less than the reported ones in American and European studies in non-African populations. Based on non-African studies, one would have expected a higher prevalence of NAFLD in this Nigeria cohort, given the higher incidence of metabolic syndrome (ie. the study group had diabetes mellitus and both study and control groups were obese). The finding of a surprisingly low prevalence of NAFLD in an African population at high risk, is similar to the findings of studies performed to evaluate the prevalence of NAFLD in African Americans.[4,5] The mechanism behind less fatty liver disease among African American is unclear; and difference in body fat distribution between different ethnic groups is thought to play role in the pathophysiology of NAFLD. The interesting aspect of Onyekwere, *et al.*'s study is that it is one of the few to study fatty liver disease in a purely African patient population, a fact that assumes greater epidemiologic significance when one considers that African Americans may constitute a distinct population from an African population. Certainly, further larger studies with an African population are required to study NAFLD.

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The efficacy of anti-viral therapy on hepatitis B virus-associated glomerulonephritis: A systematic review and meta-analysis

Yi Z, *et al.* Hepatitis B virus (HBV)-related renal disease is common in endemic areas, especially in children, and carries with it significant morbidity and mortality.[6] These renal diseases include membranous nephropathy (MN), IgA nephropathy, minimal change disease, focal segmental glomerulosclerosis, and membranoproliferative glomerulonephritis. However, the commonest histology type is membranous nephropathy.[7] Uncontrolled observations have suggested that corticosteroid and immunosuppression therapy have little benefit and may lead to increase viral replication and exacerbation of chronic hepatitis.[8]

In this issue, Yi, *et al.*, performed a systematic review and meta-analysis of the existing evidence for anti-viral therapy for treatment of HBV-related glomerulonephritis (GN). The aim of the analysis was to evaluate the evidences of tolerability and efficacy of anti-viral therapy in adult and pediatric patients. Primary outcome was remission of proteinuria. Secondary outcome was clearance of hepatitis B e-antigen (HBeAg). In the included adult studies, remission of proteinuria was associated with treatment with a significant relative risk (of remission) of 18.06 (2.97 to 109.93, p = 0.002). Analysis of complete remission also had a significant relative risk of 4.37 (1.18 to 16.11, p = 0.03).

In the included pediatric studies remission of proteinuria favoured antiviral treatment with a significant relative risk (of remission) of 5.6 (1.77 to 17.75, p = 0.003). However, analysis of complete remission was not performed due to clinical and statistic heterogeneity. Subset analysis for membranous nephropathy revealed a remisison of proteinuria and complete remission in the treatment arm with a relative risk of 14.52 (1.72 to 122.42) and 10.41 (0.82 to 59.39) respectively. Secondary outcome for HBeAg seroconversion while on anti-viral therapy had a relative risk of 15.14 (5.68 to 40.04, p < 0.00001).

This meta-analysis confirms that treatment of HBV-GN and MN with anti-viral therapy significantly increases the rate of proteinuria remission in both adult and pediatric populations. Treatment with anti-viral therapy also increased the incidence of HBeAg seroconversion. Factors to include in clinical practice include the type and dosage of anti-viral drugs.

Hepatobiliary laboratory abnormalities among patients with chronic or persistent immune thrombocytopenia (ITP)

Enger C, *et al.* Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by thrombocytopenia and increased risk of bleeding.[9] Although ITP is usually a transient disease in children, most adults develop chronic or persistent ITP. The incidence and prevalence of abnormal hepatobiliary laboratory values are not well characterized in this group, and poses a problem for future drug development and clinical trial planning.

The aim of this study is to determine the incidence and prevalence of abnormal hepatobiliary laboratory values in the persistent or chronic ITP adult population. Primary outcome of elevated ALT and AST was defined by > 3x upper limit of normal (ULN), total bilirubin > 1.5x ULN, and ALP > 2x ULN. Patient population was identified by having two diagnosis codes for ITP six-months apart through a U.S. health insurance plan affiliated with i3 Drug Safety, a global health services company.

3,244 patients were identified. A sub-group of 805 (25%) had baseline hepatobiliary laboratory test within 12-months from diagnosis. 37 patients had elevated ALT, which is a prevalence of 1.14% (95% confidence interval (CI) of 0.83-1.57%) in the entire ITP cohort (assuming those without baseline values did not have liver disease) and 4.60% (CI 3.35-6.27%) in those with baseline values. 30 patients had elevated AST, a prevalence of 0.92% (CI 0.65-1.32%) in entire cohort and 3.37% (CI 2.62-5.27%) in the sub-group. 1.05% (CI 0.75-1.46%) of the entire cohort and 4.22% (CI 3.04-5.84%) of sub-group had elevated bilirubin. 15 patients had elevated ALP, which is a prevalence of 0.46% (CI 0.28-0.76%) in entire cohort and 1.86% (CI 1.13-3.05%) in the sub-group.

Those patients with co-morbidities related to secondary thrombocytopenia (such as lupus, blood cancers, HIV) were excluded in the incidence sub-cohort of 2,557 patients. 6 patients had newly identified ALT elevation during follow up, an incidence rate of 1.24 per 1,000 person-years (CI 0.52-2.56 per 1,000 person-years). 2 patients with elevated AST,

which is an incidence rate of 0.41 per 1,000 person-years (CI 0.08-1.32 per 1,000 person-years). The incidence rate for elevated bilirubin is 2.69 per 1,000 person-years (CI 1.51-4.47 per 1,000 person-years) and 1.03 per 1,000 person-years (CI 0.39-2.26 per 1,000 person-years) for elevated ALP.

Factors that were significantly associated with new or recurrent elevated ALT included male gender, history of diabetes, history of liver disease, history of co-morbidities related to secondary thrombocytopenia, history of alcohol use, on high dose of corticosteroids, treatment with interferon and treatment with cyclosporine. Factors significantly associated with new or recurrent elevated bilirubin include age, male gender, history of congestive heart failure, history of liver disease, history of alcohol use, and treatment with interferon.

Compared to prevalence rates reported in the atrial fibrillation population, the estimates obtained from this study in adults with persistent or chronic ITP is higher.[10] This study highlights the prevalence of abnormal hepatobiliary laboratory values in the adult ITP population and postulates that distinguishing drug-induced liver toxicity in this population will be a challenging task.

Dose pre-liver transplant HBV DNA level affect HBV recurrence or survival in liver transplant recipients receiving HBIg and nucleos(t)ide analogues?

Compos-Varela I *et. al.* Despite advances in treatment of chronic hepatitis B virus (HBV) infection, liver transplantation remains the only hope for many patients with end-stage liver disease related to HBV. The role of liver transplantation in management of individuals infected with HBV has undergone a fundamental shift over the past 2 decades. In 1980s, the rate of graft reinfection was as high as 80-100%, and this often led to significant liver damage and shorten graft survival.[11-13] Since the introduction of hepatitis B immunoglobulin (HBIG), the rate of graft reinfection had decreased to 20-40%[14] and the rate was further reduced to 0-10% with subsequent use of antiviral drugs.[15,16] High levels of HBV DNA at the time of liver transplantation had been associated with higher risk of graft reinfection, and other risk factor for HBV recurrence including viral resistance.[17]

In this current issue, Campos-Verela *et al.,* re-evaluate the risk factors for HBV recurrence and the prognosis of liver transplantation. Eight hundred fifty nine patients underwent orthotopic liver transplantation between 1988 and 2008 in Hospital Universitario Vall d'Hebron in Barcelona, Spain. Out of those, 60 cases (7%) were secondary to HBV and of these, 49 patients were included in the analysis. Seven (14%) patients received HBIG alone for HBV recurrence prophylaxis and 42 (82%) received combination of HBIG and antiviral drugs.

Eight of 49 patients (16%) had recurrent HBV infection: 5 HBIG monoprophylaxis and 3 combination HBIG and antiviral drugs. The univariate analysis of this group revealed a correlation between high HBV DNA levels ($>10^4$ IU/ml) and risk of reinfection ($p = 0.004$). As well as HBIG monoprophylaxis ($p \leq 0.0001$). Interestingly, there were no differences in HBV re-infection according to preoperative HBV DNA levels in patients receiving both HBIG and antiviral drugs ($p = 0.32$). Furthermore, in the multivariate analysis the only variable significantly associated with higher risk of HBV recurrence was using HBIG as a monoprophylaxis with RR of HBV recurrence of 27 (95% Cl 5.2-147.2, $p < 0.0001$).

Thirteen out of 49 patients (26%) died after liver transplantation; 4 deaths were related to HBV recurrence and all 4 patients were receiving HBIG monoprophylaxis. Again in the multivariate analysis, HBIG monoprophylaxis was the only variable associated with poor outcome post liver transplantation with RR of death of 6.5 (95% Cl 2.1-19.8, $p = 0.001$).

In this study the risk of HBV recurrence was strongly influenced by the type of prophylaxis administered post-transplantation. This supports the previously reported data on significant reduction of reinfection rate with using combination prophylaxis (HBIG and antiviral drugs). Although, the study found a significant association between high levels of HBV DNA in HBIG monoprophylaxis and reinfection, notably, this did not occur in patients receiving combination prophylaxis. Although the sample size of the combination group was small suggesting a possible beta error, similar observations have been reported in published systematic review and meta-analysis on the subject.[18] This study encourages discussion around HBV DNA level measurement and it's clinical significance pre-transplant. It also suggests that HBIG will remain relevant in transplantation in the near future.

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