



Editorial commentary on *Indian Journal of Gastroenterology*— November–December 2021

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Fetuin-A in newly detected type 2 diabetes mellitus as a marker of non-alcoholic fatty liver disease

A growing body of evidence implicates hepatokines such as fetuin-A and fetuin-B in the prognoses of non-alcoholic fatty liver disease (NAFLD), its associated complications and in the development of obesity, hyperglycemia, hypertriglyceridemia, and chronic diseases, such as metabolic syndrome, type 2 diabetes mellitus (T2DM), and cardiovascular disease [1]. The association between Fetuin-A in newly diagnosed T2DM (NDD) and its correlation with NAFLD is less well understood.

Yamasandhi and colleagues from Ramaiah Memorial Hospital, Bangalore, India, report a case–control study measuring fetuin-A levels in 60 NDD's with and without NAFLD [2]. Fetuin-A was significantly higher in NDD with NAFLD compared to those without NAFLD and showed an increasing trend with the advancement of fibrosis. A cut-off value of 1239 mcg/mL was able to differentiate NAFLD patients with area under curve (AUC) of 0.667 (sensitivity 75%; specificity 61%) and remained significant after adjustment for potential confounders such as age, weight, blood pressure, lipids, and liver enzymes. These findings need validation, but open up new perspectives in early diagnosis, identification of novel biomarkers, and providing novel targets for pharmacological interventions.

Baseline serum cystatin C as a marker of acute kidney injury in patients with acute-on-chronic liver failure

Serum cystatin C is a low-molecular-weight protein, is glomerularly filtered, reabsorbed by the proximal tubule (and subsequently catabolised), and is a biomarker of kidney function. It follows a similar kinetic profile to creatinine, increasing 12 to 24 h after the onset of acute kidney injury (AKI). Cystatin C levels have demonstrated strong statistical performance in detecting AKI, being less prone to confounding by age, muscle mass, and diet compared with creatinine [3]. There are limited data examining relative changes in cystatin C level to define AKI in cirrhosis, although the published literature suggests that increased cystatin C level is associated with the development of AKI. Jha and colleagues from the Indira Gandhi Institute of Medical Sciences, Patna, India, report a prospective observational study on 47 hospitalized patients with acute-on-chronic liver failure (ACLF), 34% of whom developed AKI [4]. Cystatin C at a baseline level of 1.47 mg/L was an independent predictor of AKI with a sensitivity and specificity of 0.94 and 0.68, respectively. On receiver operating curve (ROC) curve analysis, cystatin C (area under curve [AUC] 0.85) outperformed creatinine (AUC 0.69); Child-Turcotte-Pugh (CTP) (AUC 0.66); and MELDNa (model for end-stage liver disease) (AUC 0.64). Novel kidney markers, cystatin C, and now neutrophil gelatinase-associated lipocalin (NGAL) hold promise for the diagnosis and prognostication of AKI in this vulnerable population.

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Endoscopic sleeve gastroplasty—minimally invasive treatment for non-alcoholic fatty liver disease and obesity

Visceral obesity and insulin resistance are amongst the most important risk factors for non-alcoholic fatty liver disease (NAFLD). The efficacy of drug therapy is limited.

Lifestyle interventions are necessary, but rarely result in adequate and sustained weight loss [5]. Bariatric surgery can achieve significant and durable weight loss with improvement in insulin resistance, but high morbidity costs, and necessarily stringent selection criteria underpin the need for minimally invasive options. Endoscopic sleeve gastroplasty (ESG) is a minimally invasive bariatric procedure that has demonstrated efficacy and safety of ESG to achieve substantial weight loss in patients with obesity [6]. Jagtap and colleagues, from the Asian Institute of Gastroenterology, Hyderabad, India, report their experience of ESG in 26 consecutive patients with NAFLD (mean weight 99.43 kg) over a 6-month period [7]. Significant improvements in ALT (baseline 59.54 IU/L \pm 17.02 to 49.50 IU/L \pm 11.72 and 48.42 IU/L \pm 13.22) and NAFLD fibrosis score (0.228 at baseline to -0.202 and -0.552) were noted at 6 and 12 months. Significant improvements were also noted in mean hepatic steatosis index, fibrosis-4 index, and aspartate aminotransferase (AST)-to-platelet ratio at 6 and 12 months (p 0.001). Total body weight loss of 18.07% was achieved at 12 months, with significant improvements in HbA1c. No major adverse event was noted. Further prospective studies including more nuanced and detailed assessment of liver injury provided by the standard criterion with liver biopsy and long-term follow-up to characterize the potential role for ESG in managing advanced metabolic disease are needed.

Combination of portal vein embolization and neoadjuvant chemotherapy for locally advanced gallbladder cancer requiring extended hepatectomy—A novel approach

Gallbladder carcinoma (GBC) is a rare, aggressive biliary tract malignancy, with a 5-year survival of less than 5% [8]. Extensive liver infiltration or unilateral hilar involvement necessitates extended hepatectomy to achieve microscopically negative resection margins, but this may place patients at risk of postoperative liver failure. The size of the liver remnant is a major determinant of post-surgical hepatic dysfunction and associated complications. Neoadjuvant chemotherapy (NACT) may downstage tumors to resectability and prevent progression, enabling the liver remnant to grow [8]. In this issue of the *Indian Journal of Gastroenterology*, Singh and colleagues from the Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, India, report a retrospective experience of combining NACT with portal vein embolization (PVE) in 14 patients with locally advanced GBC requiring major hepatectomy [9]. The median future liver remnant was 25% achieving hypertrophy of 8.8% after PVE. Seven patients underwent

curative resection with median survival of 27 months. Median survival in unresectable cancer was 15 months. Neoadjuvant chemotherapy has the potential to improve the prognosis of patients with advanced gallbladder cancer.

Baveno criteria perform better than expanded Baveno and Rete Sicilia Selezione Terapia–hepatitis C virus criteria for predicting varices needing treatment

Variceal bleeding is one of most catastrophic complications of cirrhosis, with a mortality rate of up to 20% in 6 weeks. Patients with cirrhosis must have clinically significant portal hypertension before they develop esophageal varices. Although varices are present in around 70% of Child–Pugh B or C patients, these are present only in approximately 40% of Child–Pugh A patients, implying that endoscopy may not identify all patients with varices [10]. Baveno, expanded Baveno, and Rete Sicilia Selezione Terapia–hepatitis C virus (RESIST-HCV) criteria predict varices non-invasively in patients with cirrhosis. Aggarwal and colleagues from All India Institute of Medical Sciences, New Delhi, India assessed the performance of these criteria for predicting varices needing treatment (VNT) amongst 295 treatment-naïve cirrhotic patients, of viral etiology (hepatitis B = 154; or hepatitis C = 141) [11]. The spared endoscopy rate (SER) and missed VNT rates were as follows: Baveno criteria: 18.3% and 6.2%; expanded Baveno: 35.3% and 29.2%; and for RESIST-HCV criteria: 37.3% and 22.9%. The sensitivity, specificity, positive predictive value, and negative predictive value were 93.7%, 21.9%, 18.9%, and 94.7% for Baveno criteria; 70.8%, 42.3%, 19.3%, and 88.1% for expanded Baveno; and 77.1%, 44.5%, 21.3%, and 90.9% for RESIST-HCV criteria, respectively. The authors conclude that Baveno criteria are useful in avoiding unnecessary screening endoscopy in patients with cirrhosis of viral etiologies. Although expanded Baveno criteria and RESIST-HCV criteria spare more endoscopies, a high missed VNT rate limits their applicability.

Tacrolimus as rescue therapy for steroid dependent/steroid refractory ulcerative colitis: Experience from tertiary referral centre in India

The use of oral Tacrolimus for the induction of remission in moderate to severe steroid refractory ulcerative colitis (SRUC) or steroid dependent (SDUC) is uncommon. Two randomized controlled trials from Japan evaluating 122 hospitalized patients with moderate to severe UC demonstrated benefit of oral Tacrolimus with trough levels of 10–15 ng/mL for clinical response by week 2 but rates of clinical remission were not significantly different from placebo [12, 13]. Sud and colleagues from the G B Pant Institute of Postgraduate Medical Education and

Research, India, report a prospective study of 31 patients with SDUC and 21 patients with SRUC treated with Tacrolimus (0.05–0.1 mg/kg) [14]. Clinical response (decrease in Mayo Clinic score, MCS by ≥ 3 points) was seen in 29 patients (56%) at week 8, whereas clinical remission (MCS ≤ 2) was seen in 25 patients (48%). Combined clinical and endoscopic remission was seen in 18 (35%) patients. Treatment failure occurred in 7 patients, 4 underwent colectomy, and 3 patients were switched to infliximab by week 8. The authors suggest that this may be a viable and cheaper option than escalation to biologics. Larger prospective and randomized controlled studies are needed to evaluate the long-term outcomes of this strategy.

Spectrum of height in patients with celiac disease

Celiac disease (CeD) may present with a myriad of manifestations including but not restricted to anemia, diarrhea, failure to thrive, weight loss, and nutrient deficiencies [15]. Early diagnosis is key to the prevention of irreversible consequences such as short stature and neurological complications [15]. Aggarwal and colleagues from the All India Institute of Medical Sciences, New Delhi, India, present a retrospective study of 583 treatment-naïve patients (419 adults and 164 adolescents) with CeD [16]. Of 583 individuals, 19.6% adults and 57.9% adolescents had short stature as per Indian Academy of Paediatrics growth charts. Short stature was prevalent in a higher proportion of men compared to controls (32.2% vs. 20%, $p < 0.05$), a lower proportion of women (9.7% vs. 18.9%, $p < 0.001$). Adulthood was associated with a lower prevalence of short stature. The authors discuss the importance of an early diagnosis to address such potentially reversible consequences of this condition.

Impact of Corona Virus Disease 2019 pandemic on adherence to gluten-free diet in Indian patients with celiac disease

The corona virus disease 2019 (COVID-19) pandemic has had a cataclysmic global impact, with sudden and radical changes in people habits and lifestyles, drastically reducing social interaction, affecting everyday behaviors including eating habits [17]. Mehtab and colleagues from the All India Institute of Medical Sciences, New Delhi, India, report on the impact of COVID-19 on the adherence to gluten-free diet (GFD), symptom control, and quality of life (QOL) in people living with CeD [18]. A web-based questionnaire was sent to 3130 patients via social media and 505 responses were received. Poor compliance to

GFD was reported by 6.7% ($n = 34$) in the pre-pandemic period (CeD Adherence Test > 17) but increased to 12.6% ($n = 64$) during the pandemic. Twenty-five people (4.9%) contracted COVID-19. The majority of patients (73.2%) preferred virtual over face-to-face consultations. The most common difficulties faced during lockdown were cost and high delivery charges for gluten-free (GF) food (43% and 54.4% respectively) and travelling long distances to arrange GF food (44.9%). This study and its sobering observations may enable a much-needed understanding of the health-related effects of the pandemic on people following restrictive diets, unmasking, and highlighting socioeconomic and healthcare vulnerabilities.

Role of lactulose for prophylaxis against hepatic encephalopathy in cirrhotic patients with upper gastrointestinal bleeding: A randomized trial

Hepatic encephalopathy (HE) is a complex neurological syndrome seen in patients with cirrhosis, as a consequence of severe hepatocellular failure or the presence of large portasystemic shunts, and causing a wide spectrum of nonspecific neurological and psychiatric manifestations [19]. Primary prophylaxis of HE is recommended, in the case of upper gastrointestinal bleeding (UGIB) adopting therapies able to remove blood from the gastrointestinal tract. Rifaximin and lactulose have been used in preventing HE after UGIB [19].

Rattanasupar and colleagues, from Hatyai Hospital, Songkhla, Thailand, report a randomized, double-blinded, placebo-controlled, multicenter study in 46 cirrhotic patients presenting with acute UGIB randomized to receive lactulose or placebo for 5 days along with standard treatment [20]. Nine (19.6%) patients developed HE: 5 (22.7%) in the placebo group and 4 (16.7%) in the lactulose group ($p = 0.718$). On multivariate analysis, higher baseline Child-Turcotte-Pugh (CTP) score and presence of diarrhea were independent risk factors for the development of HE. The authors conclude that lactulose is ineffective as prophylaxis against HE in cirrhotic patients with acute UGIB.

Diagnostic yield of endoscopic ultrasound-guided fine-needle aspiration of tubercular lymphadenitis using combination of cytology and Gene Xpert Mycobacterium tuberculosis/rifampicin (MTB/RIF) genes

Drug-resistant tuberculosis (DRTB) is an emerging problem world-wide requiring a prompt diagnosis followed by an appropriate treatment. The dissemination of the Xpert MTB/

RIF; a fully automated real-time PCR-based assay for the detection of *M. tuberculosis* DNA and mutations associated with rifampicin resistance, directly in clinical specimens (recommended by the World Health Organization [WHO]) has radically increased the capacity to perform the detection of rifampicin-resistant TB cases [21].

Mohindra and colleagues from the Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India, evaluated the diagnostic yield of Gene Xpert on cytology samples acquired via endoscopic ultrasound (EUS)-guided fine-needle aspiration cytology (FNAC) in suspected tubercular lymphadenitis [22]. Microscopy, cytology, Gene Xpert MTB/RIF assay data on acid-fast bacillus (AFB), and traditional culture of lymph nodes were retrospectively analyzed in 31 patients with a myriad of presentations including fever, dysphagia, and recurrent subacute intestinal obstruction. Gene Xpert demonstrated higher sensitivity (30, 97%) compared to cytology, AFB smears, and conventional culture. The authors discuss the use of Gene Xpert testing and nuances in the diagnosis of tubercular lymphadenitis.

Endoscopic ultrasonographic diagnosis of pancreatic tuberculosis in immunocompetent patients—A case series from eastern India

Tuberculosis of the pancreas or of the peripancreatic lymph nodes is infrequent compared to hepatic involvement. Pancreatic involvement may be localized, as part of miliary tuberculosis, or at a site of reactivated disease [23]. The most likely mechanism of spread is lymphohematogenous dissemination from an occult focus in the lungs. Focal pancreatic lesions in pancreatic tuberculosis are usually demonstrated by ultrasound or computerized tomography (CT), closely mimicking pancreatic carcinoma or mucinous tumors of the pancreas. A definitive diagnosis of pancreatic tuberculosis is achieved with histologic confirmation demonstrating granulomatous inflammation with caseous necrosis and multinucleated giant cells. The success rate of image-guided fine-needle aspiration cytology in diagnosing pancreatic tuberculosis has been reported as approximately 50%.

In this issue of the *Indian Journal of Gastroenterology*, Chakraborty and colleagues, School of Digestive and Liver Diseases, IPGME & R, Kolkata, India, present a case series of 117 patients with a pancreatic mass lesion [24]. All patients underwent endoscopic ultrasound with fine needle aspiration for diagnosis. On retrospective review, 5 of these 117 (4.3%) patients were diagnosed having pancreatic TB and were treated successfully with anti-tubercular treatment. The clinical presentation and nuances of diagnosis are discussed in this case series.

Compliance with ethical standards

Conflict of interest JKL declares that he has no conflict of interest.

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