Letters

IGF-I as a marker of disease activity and nutritional status in patients with inflammatory bowel disease

Inflammatory bowel disease (IBD) is characterized by chronic inflammation and catabolism.[1] The inflammation is mediated by cytokines.[2] The mechanism of catabolism is multifactorial. Reduced absorption of nutrients along with increased loss of protein from the inflamed intestinal mucosa may be responsible;[3,4] the catabolism may be mediated by insulin-like growth factors (IGF).[5] We evaluated serum levels of IGF-I, and markers of inflammation and nutritional status in different stages of IBD.

The diagnosis of IBD was based on clinical, laboratory, endoscopic, and histological criteria. Besides IGF-1, C-reactive protein (CRP), as a marker of inflammation, and serum album level were measured. Measurements were performed at baseline on the day of admission to our hospital, and after six months of treatment.

Serum was separated by centrifugation, followed by storage at -20°C until analysis. Total concentrations of IGF-I were determined in the neutralized acid–ethanol extracts of serum using classical competitive binding systems employing highly specific antibodies as the reagents, and the respective radioactively labelled ligands as the tracers.[6] Briefly, the IGF-I radioimmunoassay was performed using human IGF-I (ICN Biomedicals Inc., Aurora, USA) labelled with ^{125}I as tracer and polyclonal rabbit antibodies to human IGF-I (Biogenesis, Poole, UK) as the reagent. It was standardized against the reference preparation (WHO 87/518). Recovery of this reference IGF-I added to serum before extraction was 99.6±17.1%. Reproducibility was checked by including fresh extracts of two human serum pools with each assay. The mean coefficient of variation was 8.6%. The Ethic Committee of our institution approved the study and all patients gave an informed consent prior to inclusion in this investigation.

Statistical analysis was performed using SPSS® (version 14.0). Student's *t*-test was used to compare paired data.

We included 30 patients (mean age 38.0 [13.8] years; 8 men) with IBD in active phase of the disease. Seventeen patients had ulcerative colitis, and 13 had Crohn's disease. The concentrations of IGF-1 and albumin were higher, and CRP were lower after 6 months of treatment as compared to baseline (Table).

Table: Values of various parameters at baseline and after six months

Parameter	*Baseline*	*After treatment*
C-reactive protein (mg/L)	42.98 (39.96)	5.31 (3.18)
Serum albumin (g/L)	21.63 (5.08)	39.83 (7.27)
IGF-I (mmol/L)	14.7 (8.77)	26.14 (12.97)

Values are as mean (SD). p values <0.05 for all

Advances in the understanding of the pathophysiology of IBD have resulted in the evaluation of therapeutic agents with novel actions. A single trial, which evaluated growth hormone (GH) treatment in patients with Crohn's disease, concluded that GH stimulates production of IGF-I, which has a trophic effect on the intestinal mucosa.[7]

Changes in GH and IGF-I have previously been assessed in patients with IBD, and conflicting results concerning GH secretion have been published.[8] The anabolic effects of GH are primarily mediated by IGF-I. Reduced IGF-I levels have been found in patients with disease activity, with improvement during treatment with either corticosteroids or an elemental diet.[9,10]

Our study indicates that IGF-I may be used as indicator for determination of IBD activity and estimation of nutritional status. Further studies related to IBD type of disease and therapy regimen are needed to draw attention to the clinical importance of these results.

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Helicobacter pylori positivity in esophageal and esophagogastric junction adenocarcinoma

Recent studies have shown a decreasing incidence of antro-pyloric gastric malignancy[1] and a simultaneous increase in proximal gastric and esophageal adenocarcinoma.[2] Richter *et al* suggested that infection by CagA strains of *Helicobacter pylori* may be protective against adenocarcinoma of esophagus and esophagogastric junction.[3] There are no studies on this aspect from India.

Eighteen consecutive patients with histologicaly - proven esophageal and esophagogastric junction adenocarcinoma over a two - year period from August 2005 to August 2007 were studied. Patients with associated gastrointestinal disorders, history of treatment with *H pylori* eradication therapy and patients with history of consumption of proton pump inhibitors in the month preceding the presentation were excluded from the study. Thirty-one patients who were admitted to the hospital, and did not have any gastrointestinal symptoms formed the control group. After informed consent, the prevalence of *H. pylori* infection in both the groups was determined by serological test using commercial *H. pylori* CagA ELISA kit (Smartest Diagnostics, Israel) which detects IgG Cag A antibodies. Sensitivity and specificity of this ELISA kit as provided by the manufacturer was 98%. Blood samples were stored at - 20^0C and all estimations were done at the end of the study. There is no evidence that storage results in deterioration of sample quality.

The mean (SD) age of patients with esophageal and esophagogastric junction adenocarcinoma was 51.0 (6.9) years with 15 men, the mean age in men (50.1 years [6.3]) and women (55.6 [9.5] years) was similar (p= 0.374). Controls were matched for gender and age (mean age 47.1 [9.3] years (p= 0.134). In control group there were 22 men (p=0.49). Thirteen of 18 patients with carcinoma (72.2%) and 20 of 31 controls (64.5%) were CagA *Helicobacter pylori* positive (p=0.75) (OR 1.43, 95% CI 0.40-5.07).

Martel *et al* showed that the prevalence of *H. pylori* seropositivity and specifically the CagA strains was lower in patients who later developed esophageal adenocarcinoma compared to age and gender matched controls for *H. pylori* (OR 0.37, 95% CI 0.16 -0.88) and for CagA strains (OR 0.44, 95% CI 0.15-1.27).[4] Vicari *et al* showed that prevalence of CagA *H. pylori* is lower in patients with Barrett's esophagus with adenocarcinoma compared to controls.[5] The protective effect of CagA *H. pylori* infection is considered to be due to the more virulent organism producing pangastritis and hypochlorhydria and therefore reducing the risk of development of Barrett's esophagus.

There are no studies available from developing countries regarding CagA *H. pylori* in esophageal and esophagogastric junction adenocarcinoma. We found that CagA prevalence was not different between the controls and esophageal adenocarcinoma in a small sample. These results need to be replicated in larger study.

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Cholestatic hepatitis due to azathioprine and tacrolimus in a adult renal allograft recipient

Hepatic complications of azathioprine, namely bland cholestasis, cholestatic hepatitis with bile duct injury, zonal necrosis and vascular toxicity are rare. Tacrolimus is a comparatively new immunosuppressant, the complete toxicity profile of which is unknown. There are only two reports, one adult and pediatric case of tacrolimus-induced cholestatic hepatitis in literature.[1,2] We report a case of cholestatic hepatitis due to both azathioprine and tacrolimus in a renal allograft recipient.

A 43-year-old diabetic woman who underwent renal transplantation two years back, and was recently detected to have hepatitis C infection, presented with jaundice and loss of appetite since twenty days. She had no past or family history of liver disease. There was no history of recent travel, blood transfusions and tattoos. Her current medications included corticosteroids, azathioprine, tacrolimus and metformin. Physical examination showed icterus, pedal edema, and hepatomegaly; the liver span was 18 cm. The liver was soft, smooth and nontender. There was no other organomegaly or ascites.

Investigations revealed an abnormal liver biochemistry (Table). The complete blood count, lipid profile, blood glucose and renal function tests (serum creatinine - 0.7 mg/dL, blood urea – 40.2 mg/dL) were normal. HCV RNA by PCR was positive. Other viral markers (HBsAg, IgM-anti HbC, anti-HAV, anti-HEV and cytomegalovirus) were nonreactive. Her serum autoimmune markers, alpha-1 antitrypsin levels, ceruloplasmin levels, 24-hour urinary copper excretion, serum iron studies and ferritin levels were all within normal range. Her ultrasonography of abdomen was normal. The initial possibility of cholestatic hepatitis due to azathioprine was kept. Azathioprine was stopped and patient was continued on conservative treatment. However, her jaundice and abnormal liver function tests persisted for next three months (Table).

A percutaneous liver biopsy demonstrated marked ballooning and feathery degeneration of the hepatocytes along with foci of spotty necrosis. Portal tracts were expanded and infiltrated by inflammatory cells such as lymphocytes and neutrophils with spill into adjacent parenchyma. An occasional lymphoid aggregate was also seen. There was a focus of intrahepatic cholestasis along with bile ductular proliferation. Reticulin stain showed increased portal fibrosis without diffuse peri-cellular fibrosis (Figure). Thus a possibility of drug-induced cholestatic hepatitis was kept. Granulomatous hepatitis and fibrosing cholestatic hepatitis in the differential diagnosis were thus ruled out. The patient's drug history was reviewed. She was receiving tacrolimus, whose side effects were still incompletely understood. Therefore, tacrolimus was stopped, and cyclosporine initiated. After two months, the patient's liver profile became normal.

Table: Serial liver function tests of the patient

Parameter	*Time**		
	1	*2*	*3*
Total bilirubin (mg/dL)	8.20	3.40	0.08
Direct bilirubin (mg/dL)	5.15	2.70	0.06
Aspartate aminotransferase (U/L)	276	287	53
Alanine aminotransferase (U/L)	370	285	48
Alkaline phosphatase (U/L)#	766	1175	143
Total proteins (g/dL)	6.70	6.80	6.90
Albumin (g/dL)	3.50	3.80	3.70
Globulins (g/dl)	3.20	3.00	3.20
Prothrombin time (INR)	1.4	1.5	1.4

*Time: 1 – After 2 years of combined use of azathioprine and tacrolimus; 2 – Three months after stopping azathioprine; 3 – Two months after stopping tacrolimus

#Laboratory normal values 39-117 IU/L

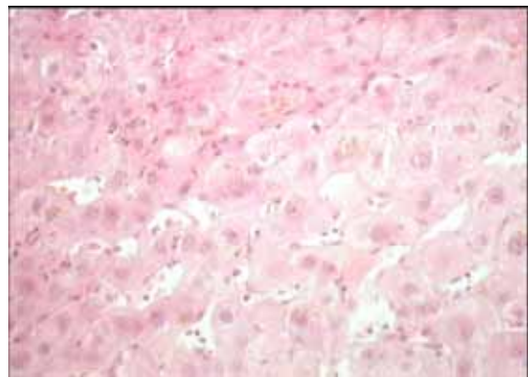

Figure: Photomicrograph showing ballooning and feathery degeneration of hepatocytes along with foci of intrahepatic cholestasis (H&E 40X)

In our patient, the onset of cholestatic hepatitis occurred 2 years after starting both azathioprine and tacrolimus. Three months after stopping azathioprine, the bilirubin decreased partially, aminotransferases remained elevated, and the alkaline phosphatase further increased. The liver biopsy then revealed cholestatic hepatitis. Two months after stopping tacrolimus, the liver functions nearly normalized. This temporal profile suggests that both azathioprine and tacrolimus were responsible for the cholestatic hepatitis in this patient.

Hepatic complications of azathioprine are rare (frequency <0.1%). Of these, cholestatic hepatitis is the commonest, occurring 2 weeks to 22 months after starting azathioprine. After discontinuation, bilirubin and transaminases improve early (2 weeks), but the alkaline phosphatase and gamma-glutamyl transferase may normalize or remain elevated for up to 4 months.[3,4,5]

Tacrolimus, a calcineurin inhibitor, rarely causes liver injury. Tacrolimus-induced cholestatic hepatitis has been recently reported in an adult liver transplant recipient[1]. On decreasing tacrolimus dose, the patient improved. Ganschow *et al*[2] reported cholestatic liver disease in 6 pediatric liver transplant patients after use of tacrolimus for steroid-resistant graft rejection. On stopping tacrolimus, the liver injury resolved in all.

The exact mechanism of tacrolimus-induced cholestasis is unknown. The drug affects the bile salt dependent or

independent bile flow.[6] In rat models, tacrolimus in high doses induces cholestasis by inhibiting biliary excretion of glutathione and bicarbonate without altering bile acid secretion significantly[7]. In clinical setting, hepatotoxicity caused by tacrolimus has been described with toxic levels of the drug by Fisher *et al.*[8]

Thus, we report cholestatic hepatitis induced by both azathioprine and tacrolimus in an adult renal transplant recipient. Azathioprine-induced cholestatic hepatitis is rare but known. Cholestatic hepatitis due to tacrolimus, a newer immunosuppressant, is even rarer. Early recognition of this side effect of azathioprine and tacrolimus would minimize the liver-related morbidity.

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Pajamas with a hole: a holistic solution to an embarrassing problem

Sigmoidoscopy and colonoscopy are commonly performed endoscopic procedures. Patients prefer special attention to their privacy during the procedure. We are often unable to provide this as most of the endoscopy suites are busy, have frequent movement of patients and staff, and occasionally two concurrent endoscopies are being done side-by-side in the same room. The standard practice has been to use drapes over the patients after asking them to undress. However, drapes often slip down during change of patient position, which is often required during colonoscopy.

Three years ago, we designed a pajama with a 12 cm^2 – 15 cm^2 hole on the postero-inferior aspect to allow the passage of scope and examination of the perianal area. This covers the private parts of the patients effectively, and puts the patient at ease. This has been welcomed by the patients and staff alike. Pajamas of 2-3 standard sizes have been designed. The pajamas are stocked in our endoscopy suite and reused after washing. We propose that other endoscopy suites also may adopt this system which has benefited us. Disposable panties can also be used as an alternative in low volume centers as well as for patients who can afford them.

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Liver transplant for hepatocellular cancer beyond Milan criteria

We read with interest the manuscript by Pandey *et al* regarding living donor liver transplantation (LDLT) in patients with hepatocellular cancer (HCC) beyond Milan criteria and the accompanying editorial.[1,2] The authors are to be commended for their results.

The authors[1] have rightly expressed the need for offering LDLT to patients with tumors beyond Milan criteria, as this allows more patients a chance for disease-free and overall survival.

A recent report from Hangzhou has reported similar results with tumors beyond Milan criteria.[3] In this report, the authors have also put forward new extended criteria (with tumors up to 8 cm, or larger than 8 cm but well-differentiated and with AFP <400 ng/mL) which will allow an additional 37% patients with HCC beyond Milan

criteria to be eligible for transplant with survival similar to that of patients meeting the Milan criteria. The use of these criteria, if validated would be better than other extended criteria such as UCSF, Tokyo, Kyoto and Asan criteria thus allowing more patients to benefit from liver transplant.[4,5]

Donor autonomy is supreme in LDLT as the organ is a gift from the donor to a specific recipient. Decision to donate an organ to a loved one is a highly emotional and personal decision, and it is the duty of the transplant team to provide accurate information to the prospective donor, as also to not proceed with LDLT if the outcome is predicted to be dismal.

Since the results of non-transplant therapies in patients with large tumors, who are not eligible for resectional surgery (nor eligible for cadaver organs in countries with good cadaveric donation programs), have been consistently poor, there is tremendous pressure on both the treating team and the prospective donors to consider LDLT. For this reason better predictive models which incorporate variables that determine the biological behaviour of the tumor (such as serum AFP and tumor grade, which have been used in the Hangzhou criteria, microvascular invasion, etc) will need to be developed.[6]

Additionally, there is a need to effectively tackle the problems of tumor recurrence, which is likely due to circulating cancer cells and may not be impacted by graft size (small for size syndrome), immunosuppression (with or without rapamycin), background of hepatitis C cirrhosis and reperfusion injury.[4,6]

The aim should be to be able to offer transplant even to patients with advanced tumors by developing strategies to decrease post-transplant recurrence using not only refinements in surgical technique, but also targeted therapies based on tumor biology.

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Reply from the author

We thank Kapoor and Behde for their interest in our work[1] and appreciate their support of our position on living donor liver transplantation (LDLT) for hepatocellular carcinoma (HCC) beyond Milan criteria. Indeed, there is a pressing need for better predictive models incorporating the staging as well as biologic factors in order to select patients with HCC who would benefit from liver transplantation. The criteria put forward by the report from Hangzhou[2] is an effort in that direction and may possibly be an improvement on the criteria of Milan, UCSF, Asan and so on.

One must also realize, however, that there is no effective alternative option to transplantation for patients with nonmetastatic HCC which is unresectable because of size, multicentricity, cirrhosis. Liver transplantation in such a situation still offers a potential for cure. While we agree that the oncologic outcome of tumors beyond a certain criteria (say Milan) would certainly be poorer than those within, this is an unfortunate reality in oncologic practice.

The central issue in LDLT, therefore, is not the advanced nature of the nonmetastatic HCC, but the genuinely justified concern for the healthy donor. So long as the donor autonomy is respected, complete information about the donor and recipient outcome shared in a transparent manner, and meticulous surgical and postoperative efforts made towards ensuring donor safety, LDLT will continue to find its place in the management of HCC.

The major challenge now is to find an effective adjuvant treatment that would further improve upon the surgical results of either resection or transplantation for HCC. We have reported the value of multimodality treatment in large HCC undergoing resection.[3] A similar approach is

urgently required following transplantation so that future recurrences could be minimized.

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Acute pancreatitis in viral infections with possible progression to chronic pancreatitis

The case series of acute pancreatitis in viral infections[1] lends further credence to the enlarging body of literature on this association whether causative or not. In addition to the viruses discussed, hepatitis E virus has also been associated with acute pancreatitis with the difference that the pancreatitis was severe with multiorgan failure possibly due to longer period of viremia, though the patient finally managed to recover.[2]

Regarding progression to chronic pancreatitis, it is observed that both the cases where this occurred (cases 1 and 5) had other risk factors for chronic pancreatitis e.g. cassava intake, alcohol ingestion and both occurred after recurrent attacks where viral association was obscure. Pancreatitis usually occur during viremic phase so it would have been interesting to know whether there was subclinical viral infection or protracted viremia during subsequent attacks as detected by antiviral antibody titer. As it is known for alcohol that an attack of acute pancreatitis might initiate the process for the subsequent development of chronic pancreatitis with or without further overt attacks, whether this is also true for viral infection alone can be material for future study.

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Reply from the author

The true prevalence of pancreatitis in viral infections is probably underestimated. As mentioned in our article,[1] there is a paucity of literature on the natural history of pancreatitis following viral pancreatitis.

Subclinical viral infection or protracted viremia is difficult to demonstrate objectively in a clinical setting. Our observations are consistent with the hypothesis by Whitcomb's group wherein chronic pancreatitis is a complication of recurrent acute pancreatitis. In the presence of metabolic and environmental stresses, patients with inadequate injury protection, chiefly genetic mutations, acute pancreatitis can progress to recurrent acute pancreatitis. The subset of patients with an altered immune response favoring fibrosis develop chronic pancreatitis.[2,3] Though acute pancreatitis has been reported following a single alcohol binge, it is widely believed that underlying chronic pancreatitis usually exists in chronic alcohol drinkers at the time of first attack of "acute" pancreatitis. Recently chronic hepatitis has been demonstrated following hepatitis E infection in patients with organ transplants.[4,5] In a previous report, the patient with hepatitis E had severe pancreatitis with multi organ failure.[6]

A corollary to our observations is that there exists a possibility of viral infections contributing to the spectrum of acute idiopathic recurrent pancreatitis. However currently there are no guidelines for testing for viral serology in this group of patients.[7]

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