Gastroenterology and Hepatology From Bed to Bench.

Short Cut

David Al Dulaimi

Department of Gastroenterology, Alexandra Hospital, Redditch, UK

Razavizade M, et al. ***The effect of pioglitazone and metformin on liver function tests, insulin resistance, and liver fat content in nonalcoholic fatty liver disease: a randomized double blinded clinical trial.*** *Hepat Mon 2013;13(5):e9270.*

The role of insulin sensitisers in nonalcoholic fatty liver disease (NAFLD) remains controversial particularly as the burden of disease expands alongside a global obesity epidemic.In this double blind randomized controlled trial, 80 adult patients (85% male, mean age 35.27±7.98) with presumed NAFLD (persistently elevated serum alanine transaminase (ALT)and 'NAFLD liver fat score' greater than -0.64) were prescribedeither metformin or pioglitazone for four months. The effect on liver function tests and metabolic indices of NAFLD was investigated.

At four months following treatment with pioglitazone or metformin there was a significant reduction in body weight($p \leq 0.04$), serum aspartate aminotransferase ($p<0.01$), ALT ($p<0.01$), alkaline phosphatase ($p<0.01$), cholesterol ($p<0.01$), low density lipoprotein ($p<0.01$), fasting plasma glucose ($p<0.01$), homeostasis model assessment-insulin resistance ($p<0.01$) and liver fat content ($p<0.01$) and a significant increase in serum high density lipoprotein ($p<0.01$). Serum triglyceride levels were unchanged with either treatment.Only weight loss, greater with metformin, was significantly different between treatment groups ($p=0.05$) at four months compared with baseline.

In addition to incorporating agreater sample size and treatment period, this study could be improved by investigating placebo and combined pioglitazone/metformin treatment. To enhance the validity of conclusions, patients with biopsy-proven NAFLD should be included and potential confounding by patient exercise should be controlled.This study is particularly topical in light of recently published guidelines on the diagnosis and management of NAFLD by the American Association for the Study of Liver Diseases, American College of Gastroenterology and the American Gastroenterological Association which did not recommend metformin as a specific treatment for patients with NAFLD.

Wang X, et al. ***Regional differences in islet distribution in the human pancreas - preferential beta-cell loss in the head region in patients with type 2 diabetes.*** *PLoS ONE 2013 June;8(6):e67454.*

Regional differences in islet cell distribution in the human pancreas remain relatively unexplored particularly in disease states such as diabetes mellitus. In this cell-based study, cadaveric pancreatic tissue was examined for regional differences in islet cell distribution, cellular composition and architecture in diabetic and non-diabetic patients. In both patient groups a more than two fold increase in the total area of each endocrine cell mass was identified in the tail region compared with the pancreatic head or body which contained similar islet densities (diabetic: 2.24±0.32%, 0.73±0.08% and 0.97±0.10%; non-diabetic: 2.37±0.25%, 1.22±0.12% and 1.07±0.12% respectively).

In non-diabetic patients there was no regional difference in islet size distribution or size-dependent cellular composition and the insulin secretory response of isolated islets to *in vitro* glucose treatment was similar. Compared with non-diabetics, pancreatic tissue from type 2 diabetic patients revealed significant beta-cell loss in the pancreatic head region leading to an overall reduction in the total islet area. Future studies should investigate this susceptibility of the pancreatic head to beta-cell loss which may be implicated in pancreatic cancer development.

Sasaki Y, et al. ***Determining timing of hepatectomy for colorectal cancer with distal metastasis according to imaging-based tumor shrinkage ratio.*** *Int J Med Sci 2013;10(9):1231-41.*

Although surgery and neoadjuvant chemotherapy are key in the treatment of liver metastases from colorectal cancer (CRC), further evidence is required to better inform the timing of surgery and the regimen which constitutes first-line chemotherapy. This retrospective single-centre study investigated the clinical timing of hepatectomy based on results of neoadjuvant chemotherapy in 50 patients (76% male, mean age 62.3±11.5) with metastatic liver tumors from CRC who presented between 2006 and 2010. A role for RNF8, a molecule involved in the repair of DNA double-strand breaks, was evaluated as a biomarker to gauge chemotherapy responsein resected CRC and metastases from CRC in 113 patients.

Neoadjuvant treatment with 5-fluorouracil/folinic acid with oxaliplatin (FOLFOX)as first line chemotherapy lead to an average tumor shrinkage rate of 0.4%/day during the first 100 days of treatmentwhich was maintained until 210 days, with no difference if bevacizumab was combined.Disease free survival markedly improved when the radiologically-determinedtumor shrinkage rate at 12 weeks was greater than 0.35% compared witha rate at/less than 0.35% (338±25 days vs 137±27.5 days respectively, p=0.003).

IncreasedRNF8 mRNA expression was associated with early CRC Tis (p=0.001) and the absence of synchronous distal metastases (p=0.04) or hepatic metastases (p=0.0069). RNF8 expression was significantly lower in patients with partial response to FOLFOX than with standard disease (p=0.017) and a positive correlation was observed between RNF8expressionand resistance to oxaliplatin (p=0.028).

The authors concludethat 12 weeks of neoadjuvant FOLFOX should be offered to patients with liver metastases from CRC followed by hepatectomy, particularly where the tumor shrinkage rate exceeds 0.35%.

Dagnell Met, al. ***Selective activation of oxidized PTP1B by the thioredoxin system modulates PDGF-β receptor tyrosine kinase signaling.****PNAS 2013 August 13;110(33):13398-13403.*

By modifying growth-factor signalling, protein tyrosine phosphatases (PTPs) play an important role in several disease processes including inflammation and cancer. An improved understanding of PTPs may therefore unlock novel therapeutic targets. This study analysed therole of the thioredoxin (Trx) system in reactivation of PTPs (PTP1B and SHP2) using *in vitro* and cell-based assays. Cells lacking the major Trx reductase (TrxR1) displayed increased oxidation of PTP1B however SHP2 oxidation remained unchanged. *In vivo*-oxidized PTP1B was reduced by exogenous Trx system components with no effect on SHP2 oxidation. Similarly Trx1, the major TrxR1 substrate, reducedonly oxidized PTP1B *in vitro*. The alternative TrxR1 substrate, TRP14 also reactivated oxidized PTP1B but not SHP2. Cells genetically lacking Trx reductase or in the presence of an exogenous inhibitor displayed increased phosphorylation of the PDGF-β receptor. Overallthe Trx system, including Trx1 and TRP14, had variable effects on the oxidation of individual PTPs with a preference for PTP1B over SHP2. Further studies are required to better define the clinical usefulness of these findings.

Tooth D, et al. ***Characterisation of faecal protease activity in irritable bowel syndrome with diarrhoea: origin and effect of gut transit.*** *Gut 2013;0:1-8*

Although the underlying aetiology of irritable bowel syndrome (IBS) remains unknown, recent studies have suggested a link between faecal serine protease (FSP) activity and colonic hypersensitivity in diarrhoea predominant IBS. This study, comprising multiple parts,structurally and functionally characterised FSPs in patients with diarrhoea predominant IBS and healthy controls.

In contrast with other studies suggesting a bacterial origin for FSPs this study found that several major FSP components were human derived. Furthermore, faecal protease (FP) concentrations increased with colonic bacterial depletion by MoviPrep bowel cleanse in healthy controls (n=23) (p=0.0007).Compared with healthy controls (n=9), FP activity was greater in patients with diarrhoea predominant IBS (n=36)(p=0.038) particularly when faecal amylase concentrations exceeded27.3 μL-1 (p=0.03) which

was also associated with greater patient anxiety scores (p=0.006).FPactivity negatively correlated with whole gut transit time in patients with IBS (n=79) (r=-0.32 (95% CI -0.51 to 0.09), p=0.005) and healthy controls(n=20) (r=-0.55 (95% CI -0.81 to 0.11),p=0.014).Consistent with this, FS activity positively correlated with the number of days/week with urgency described by IBS patients (n=73) (r=0.26 (95% CI 0.03-0.47), p=0.02).
Although additional studies are required to further characterise FSPs, modulation of FSP activity may represent a novel therapeutic target in diarrhoea predominant IBS by reducing colonic hypersensitivity.

Hajmanoochehri F, et al. ***Patho-epidemiological features of esophageal and gastric cancers in an endemic region: a 20-year retrospective study.*** *Asian Pac J Cancer Prev 2013;14(6):3491-97.*

The importance of keeping abreast with changes in the patho-epidemiological features of esophageal and gastric cancers is clear particularly in view of their devastating mortality rates. This retrospective study of pathological reports from 405 esophageal and 729 gastric cancer biopsies collected at endoscopy between 1989 and 2009 at Boo-Ali Sina (Avicenna) hospital evaluated patho-epidemiological trends in esophageal and gastric cancers.
The incidence of esophageal and gastric cancer did not change significantly during the study period. The mean age of cancer diagnosis of either type increased from 61.1±12.6 years to 67.8±11.8 years (p<0.001). A male predominance for esophageal and gastric cancer (sex ratios 1.53/1 and 3.04/1 respectively) was observed. The lower and middle esophageal portions were the most common sites for esophageal cancer in males (54.5%) and females (40.8%) respectively (p=0.037). Regarding esophageal cancer morphology, adenocarcinoma became more common (57.2% to 66.9%) and squamous cell carcinoma less common (25.2% to 20.2%) (p=0.007) during the study period. The most common gastric cancer site in both sexes was the gastric pylorus/antrum. In gastric cancer morphology, the ratio of diffuse to intestinal adenocarcinoma increased during the study period. This descriptive study provided a useful insight into recent patho-epidemiological trends in two major cancers in an endemic region.

Papers were prepared by:
Drs Luke Materacki and **Ishfaq Ahmad,** Department of Gastroenterology, Alexandra Hospital, B98 7UB, UK