PATEY PRIZE 1

01 ACTIVATION OF THE PREGNANE X RECEPTOR AFTER LIVER TRANSPLANTATION REDUCES THE INCIDENCE OF ANASTOMOTIC BILIARY STRICTURES
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Introduction: Many complications following liver transplantation are linked to hepatic ischaemia reperfusion injury. Activation of the pregnane X receptor (PXR) has been shown to alleviate this process in animal models. The aim of this study was to investigate the effect of early PXR activation on postoperative complications and survival following clinical liver transplantation.

Method: This retrospective study included deceased donor liver transplants that took place at a single transplant centre from 2010-2016. Predicted PXR activation value (PPAV) was calculated for each patient on day 7 based on potency/total dose of PXR activators administered in the first week post-transplantation. Patients were divided into low and high PXR activation groups using median PPAV as cut-off value. Postoperative vascular, biliary and infective complication rates were compared between the two groups in addition to graft and patient survival.

Result: Overall, 240 liver transplants were included in this study. The high PXR activation group included 121 patients. Average PPAV was significantly lower in patients who developed anastomotic biliary strictures (17.7±5.5 versus 35.1±5.7 in stricture-free patients; P=0.03) and sepsis (16.4±7.1 versus 34.9±5.5 in sepsis-free patients; P=0.04). Patient survival was significantly improved in the high PXR group (5-year survival: 88.7±3.8% versus 70.7±5.8% in the low PXR group; Log-Rank P=0.023). Univariate and multivariate Cox regression analysis identified PPAV as a significant independent predictor of patient survival.

Conclusion: PXR activation within the first week of liver transplantation is an independent predictor of patient survival. This is likely due to lower biliary stricture and infection rates associated with PXR activation.

Take-home message: PXR activation within the first week of liver transplantation is an independent predictor of patient survival. This is likely due to lower biliary stricture and infection rates associated with PXR activation.

02 SUCCINATE ACCUMULATION IS THE KEY METABOLIC SIGNATURE AND THERAPEUTIC TARGET FOR TRANSPLANT ISCHAEMIA-REPERFUSION INJURY IN MOUSE, PIG AND MAN
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Introduction: Recent murine evidence suggests mitochondrial succinate accumulation during ischaemia is the key driver for generation of reactive oxygen species (ROS) during reperfusion injury. We examined if this specific metabolic pathway was conserved across species and whether it accounted for the detrimental impact of warm ischaemia during organ procurement from donation after circulatory death (DCD) compared to donation after brainstem death (DBD).

Method: Metabolomic analysis of myocardium tissue stored during warm and cold ischaemia was performed in mouse (whole hearts), pig [n=5] and human hearts [n=4], with apical heart tissue procured immediately after exsanguination in pigs and human DBD donors with ethical approval and informed consent. The impact of succinate dehydrogenase (SDH) inhibition by dimethyl malonate (DMM) upon reperfusion injury was examined in a heterotopic mouse heart transplant model.

Result: Succinate accumulation relative to normoxic controls was much greater after 12 mins of warm ischaemia than 240 mins of cold ischaemia in mouse (11.7±1.1 vs 6.3±0.6 p=0.003; n=5), pig (5.9±0.8 vs 1.7±0.8 p=0.01; n=5) and human (8.0±1.4 vs 3.2±0.9 p=0.03; n=4) myocardium. DMM inhibited the accumulation of succinate during warm ischaemia (431.6±17.3 vs 242.9±27.0 p=0.001; n=4) and administration to donor mouse hearts ameliorated myocardial injury after transplantation (24-hour serum troponin; 8.6±1.9 vs 3.0±0.4 p=0.03 [n=5-6]). Data are mean±SEM.

Conclusion: Greater succinate accumulation during warm ischaemia may underlie increased ischaemia-reperfusion injury and organ dysfunction following DCD compared to DBD transplantation. Prevention of succinate accumulation is a promising therapeutic strategy to ameliorate IR injury in organ transplantation.

Take-home message: Increased succinate accumulation during warm ischaemia may underlie the increased ischaemia-reperfusion injury and organ dysfunction that follows DCD compared to DBD transplantation. Preventing succinate accumulation using inhibitors of the enzyme succinate dehydrogenase is therefore a promising therapeutic strategy to ameliorate ischaemia-reperfusion injury in organ transplantation.

03 HUMAN OMENTAL ADIPOSE DERIVED REGENERATIVE CELLS (HOADRCs) FOR THE PREVENTION OF ANASTOMOTIC LEAK

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Introduction: Anastomotic Leak (AL) is one of the major causes of morbidity and mortality following gastrointestinal surgery. Adipose Derived Regenerative Cells (ADRCs) are autologous adult stem cells, and can promote wound healing. This project aimed to harvest ADRCs from human omentum for use in a bespoke gel implant to prevent AL.

Method: Human omental biopsies underwent proteolytic digestion. Harvested HoADRCs were characterised using immunocytochemistry and flow cytometry for Vimentin, CK 8+18, D7-Fib, CD31 and CD90. Growth factor production was detected by ELISA for VEGF, FGF-basic and TGFβ-1. In parallel, a novel, rapid-setting alginate hydrogel was formulated. MTT assays determined HoADRCs viability in the hydrogel. The ability of HoADRCs/gel implants to stimulate wound healing was investigated using wound scratch assays.

Result: HoADRCs consist of a mixed population of mesothelial cells (~45%), fibroblasts (~40%) and cells of mesenchymal origin (~12%) that secrete increasing concentrations of VEGF, FGF-basic and TGFβ-1 in culture. The 2% w/v alginate hydrogel set in <5 min at RT maintaining its structure for 72 h in simulated physiological conditions. HoADRCs remained viable in the hydrogel and proliferated over 7 days (increase of 64% SE+/-23.) Wound scratch assays demonstrated significantly quicker healing in the presence of HoADRCs/gel composites when compared to no-treatment controls at 24 h and 48 h (p<0.05).

Conclusion: Human omentum is a rich source of ADRCs, which remain biologically active in our bespoke hydrogel. HoADRCs/gel implants expedite wound healing in vitro. Future work will test the ability of HoADRCs/gel implants to prevent AL in an in vivo model.

Take-home message: Our novel human omental ADRCs/gel implant technology has the potential to expedite anastomotic wound healing. This would lead to safer gastrointestinal surgery and superior patient outcomes by reducing the incidence of anastomotic leak.

O4 HIGH INTENSITY INTERVAL TRAINING DOES NOT IMPROVE CARDIORESPIRATORY FITNESS WITHIN NHS CANCER WAITING TIME TARGETS IN COLORECTAL CANCER PATIENTS

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Introduction: Preoperative cardiorespiratory fitness (CRF) in colorectal cancer patients has been shown to predict postoperative outcome. We have previously shown significant improvements in CRF using high intensity interval training (HIT) in healthy, elderly cohorts. There have been no studies assessing the effect of HIT on CRF within the 31-days available (decision to treat (DTT) to surgery) in cancer patients.

Method: All patients had supervised HIT on stationary cycle ergometers 3 - 4 times each week from DTT until surgery. Exercise intensity during 5x1-minute HIT intervals was set at 100-120% maximum wattage of baseline cardiopulmonary exercise test (CPET). CPET before and after HIT was used to assess CRF. This study was powered to detect a clinically significant difference of 2ml/kg/min in VO2 peak (80% power, 5% significance). Ethical approval was received from East Midlands (Derby) REC (14/EM/1131).

Result: 18 patients (13 males, mean 67 years) completed the study with a mean of 8 HIT sessions (range 6-14) over 19 days (SD 7). There was no significant increase in VO2 peak (23.90 ±7.0 vs. 24.2 ±7.8 ml/kg/min (mean±sd), p=0.58) or AT (13.99 ±3.39 vs. 14.47 ±4.5 ml/kg/min, p>0.05). There was a reduction in systolic blood pressure (152 ±19 vs. 142 ±19 mmHg, p=0.0005) and heart rate at 50% maximum wattage (103 ±19 vs. 98 ±17 bpm, p=0.003).

Conclusion: A pragmatic HIT exercise programme will not improve CRF within the 31-days available from DTT to surgery in an NHS environment. Future direction should explore starting the prehabilitation phase earlier in the patient journey.

Take-home message: A pragmatic HIT exercise programme will not improve CRF within the 31-days available from DTT to surgery in an NHS environment. Future direction should explore starting the prehabilitation phase earlier in the patient journey.

O5 RISK ADJUSTMENT FOR COMORBIDITIES IN AORTIC ANEURYSM SURGERY

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Introduction: The study aimed to improve risk adjustment models for outcomes in aortic aneurysm (AA) surgery, to avoid confounding complications and comorbidities.

Method: All relevant AA surgery episodes were retrieved from Hospital Episode Statistics (HES) between April 2002 and March 2015. Charlon comorbidity categories were modified based on consensus among vascular clinicians. The performance of both the original and the modified version in predicting the impact of comorbidities on in-hospital mortality following aortic aneurysm surgery were examined using regression models.

Result: 83,966 patients had AA repair (6,353 cases (8%) were complex AA). The episodes for these patients were combined to create admission level dataset. 41,298 patients (49.2%) had admissions within 1 year prior to the index admission. Within the index admissions 32% had two or more episodes.
The Consensus group proposed adding four new categories (hypertension, smoking, obesity, dyslipidaemia), combining relevant categories, deleting irrelevant groups (dementia, HIV/AIDS and connective tissue disease) and modifying some groups to avoid counting complications as comorbidities (i.e. coronary artery disease), except where conditions were present in prior admissions for the same patient. The modified categories performed better than the original Charlson categories in regression models. The deleted categories had no impact on predicted in-hospital mortality; the added categories increased the predictive power of the regression model with respect to inpatient mortality.

**Conclusion:** The modified Charlson categories provide an improved method for case-mix adjustment for comorbidities, for comparison of mortality rates derived from routinely collected data.

**Take-home message:** The modified Charlson categories provide an improved method for case-mix adjustment for comorbidities, for comparison of mortality rates derived from routinely collected data.

### O6 GUT HORMONES AFTER OESOPHAGECTOMY: IMPLICATIONS FOR APPETITE, GLYCAEMIA AND NUTRITIONAL STATUS IN SURVIVORSHIP

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**Introduction:** Oesophagectomy is associated with reduced appetite, weight loss and post-prandial hypoglycaemia. However, enteroendocrine mechanisms remain largely unexplored. This study aimed to clarify the pathophysiology of weight loss and post-prandial hypoglycaemia after oesophagectomy.

**Method:** In this prospective study, twelve consecutive patients undergoing oesophagectomy with gastric conduit were studied preoperatively and 10 days, 6, 12, 52 weeks postoperatively (NCT02381249). Serial plasma total fasting ghrelin, and glucagon-like peptide 1 (GLP-1), insulin and glucose responses to a standardised 400kcal mixed meal stimulus were determined. CT-body composition and anthropometry were assessed, and gastrointestinal symptom scores computed using EORTC questionnaires.

**Result:** At one year, 16.7% of patients had post-prandial hypoglycaemia, with loss of body weight (17.1±3.2%; P<0.001), fat mass (-5.5±2.0kg, P=0.01), lean body mass (-4.0±0.9kg, P=0.003) and reduced insulin resistance (HOMA-IR, −0.30±0.09, P=0.008). Fasting ghrelin decreased from postoperative day 10, but recovered by one year postoperatively (621.5±71.7, 415.1±59.8, 309.0±42.0, 415.8±52.1, 547.4±83.2pg/mL, P<0.0001) and did not predict one year weight loss (P=0.12). Post-prandial insulin increased progressively at 10 days, 6, 12 and 52 weeks (insulin AUC-30min, 1.7±0.4, 2.0±0.4, 3.5±0.7 and 4.0±0.8 fold, respectively, P<0.0001). Post-prandial GLP-1 increased from the tenth postoperative day (P=0.01), with a 3.3±1.8 (P<0.0001) fold increase at one year. Peak GLP-1 was inversely associated with post-prandial glucose nadir (P=0.04), while GLP-1 AUC independently predicted weight loss at one year (P=0.003).

**Conclusion** Altered enteroendocrine physiology may contribute to reduced appetite, weight loss, diminished insulin resistance and post-prandial hypoglycaemia post-oesophagectomy, and may represent a therapeutic target to improve body weight and gastrointestinal quality-of-life in survivorship.

**Take-home message:** The exaggerated post-prandial GLP-1 response observed after oesophagectomy may contribute to pancreatic beta cell hypertrophy, with progressively increasing insulin responses to meals. The combination of early reductions in ghrelin and persistent elevations in GLP-1 favour an anorectic state, and progressive loss of fat and lean body mass results in reduced insulin resistance, contributing further to delayed postoperative post-prandial hypoglycaemia.

### O7 THE IMPACT OF MECHANICAL BOWEL PREPARATION IN ELECTIVE COLORECTAL SURGERY: A META-ANALYSIS

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**Introduction:** Mechanical bowel preparation (MBP) has become surgical dogma, despite recent meta-analyses demonstrating mixed results versus no preparation, with many suggesting no significant benefit. MBP is associated with risks of electrolyte disturbance and potentially significant dehydration, however despite lack of evidence of efficacy is still in routine clinical use in many institutions. The aim of this study was to analyse the effect of MBP versus no MBP on postoperative complications in patients undergoing elective colorectal surgery.

**Method:** Meta-analysis of randomised controlled trials and observational studies comparing adult patients receiving MBP versus no MBP, subdivided into those receiving a single rectal enema and those who received no preparation prior to elective colorectal surgery.

**Result:** A total of 36 studies (23 RCTs and 13 observational studies) including 21,568 patients undergoing elective colorectal surgery were included. When all studies were considered, MBP versus no MBP was not associated with any significant difference in anastomotic leak rates (OR 0.90, 95% CI 0.74 to 1.10, P=0.32), SSI, intra-abdominal collection, mortality, reoperation or hospital LOS, nor when
evidence from just RCTs was analysed. A sub-analysis of MBP versus absolutely no preparation or a single rectal enema similarly revealed no differences in clinical outcome measures.

**Conclusion:** In the most comprehensive meta-analysis of MBP in elective colorectal surgery to date, this study has suggested that the use of MBP versus no preparation does not affect the incidence of postoperative complications. Given the significant risk of complications, MBP should not be administered routinely prior to elective colorectal surgery.

**Take-home message:** In the most comprehensive meta-analysis of MBP in elective colorectal surgery to date, this study has suggested that the use of MBP versus no preparation does not affect the incidence of postoperative complications. Given the significant risk of complications, MBP should not be administered routinely prior to elective colorectal surgery.