OC-006 INFLUENCE OF BMI AND ALCOHOL ON LIVER-RELATED MORBIDITY AND MORTALITY IN A COHORT OF 108,000 WOMEN FROM THE GENERAL POPULATION FROM UKCTOCS

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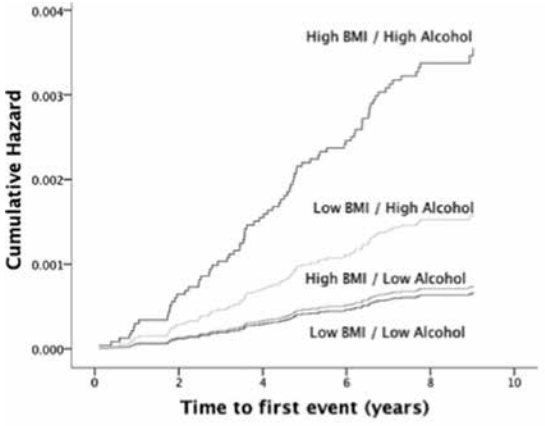
Introduction Alcohol and fat are major causes of chronic liver disease (CLD), however their relative influences are not well understood. We aimed to determine liver-related morbidity and mortality attributable to fat and alcohol by stratifying a cohort of 202,638 women according to BMI and alcohol intake.

Methods 107,742 women participating in the UK Collaborative Trial of Ovarian Cancer Screening where self-reported height, weight and alcohol intake were available were included. First episode related to cirrhosis (ICD-10 codes K70, K73, K74) either from inpatient Hospital Episode Statistics or death certificate was recorded following trial entry. Participants were stratified by low or high BMI (< 25 or ≥25 kg/m^2), low or high alcohol intake (0–15 or over 15 units/week) and combinations of these parameters.

Results Median age at recruitment was 60 years (50–75). Mean BMI was 26.4 kg/m^2. There were 90 events (54 inpatient episodes and 36 deaths). There was no difference in risk of event between the BMI groups, however there was a significant increase in risk in the high alcohol group (Log-Rank < 0.001). Cox proportional hazards regression analysis (covariates age, smoking, BMI and alcohol intake), found that compared to the low BMI/low alcohol group, there was an incremental increase in risk of event in the high BMI/low alcohol, low BMI/high alcohol and high BMI/high alcohol groups respectively. However, only the combination of high BMI and high alcohol reached significance (table and figure).

Abstract OC-006 Table

Group	Number of participants (%)	Exp(B)/HR (p)	95% Confidence intervals
Low BMI/Low Alcohol	46,011 (41.9)	1.0	
High BMI/Low Alcohol	58,432 (53.2)	1.1 (0.65)	0.7 – 1.8
Low BMI/High Alcohol	2,683 (2.4)	2.4 (0.11)	0.8 – 6.9
High BMI/High Alcohol	2,616 (2.4)	5.3 (0.002)	2.5 – 11.4



Abstract OC-006 Figure

Conclusion These data indicate that the combination of high BMI and alcohol intake is associated with a synergistically increased risk of CLD. Alcohol may be the more significant contributing factor. Further work will define thresholds for each risk factor that independently and in combination increase CLD risk.

Disclosure of Interest None Declared

OC-007 OXIDATIVE STRESS RATHER THAN TRIGLYCERIDE ACCUMULATION PERTURBS GLUTATHIONE METABOLISM IN AN IN VITRO MODEL OF CELLULAR STEATOSIS

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Introduction Oxidative stress is the central to molecular events leading to the progression of simple steatosis to steatohepatitis in nonalcoholic fatty liver disease (NAFLD). We have previously shown that an *in vitro* cellular steatosis model using C3A cells treated with energy substrates; lactate (L), pyruvate (P), octanoate (O) and ammonia (N), recapitulates the sequence of events in dietary-induced NAFLD; namely enhanced acute respiration and reactive oxygen species (ROS) formation leading to mitochondrial impairment. In contrast, treatment with oleate results in similar triglyceride accumulation but with relatively low ROS. Using a combined microarray, proteomic and metabolomic approach, we aimed to explore how triglyceride accumulation and enhanced ROS affect glutathione metabolism in our *in vitro* cell model.

Methods C3A cells were treated with either LPON or oleate for 72 hours. Microarray RNA expression was measured using Illumina® Whole Human Genome BeadChip H12 Microarray. For proteomics, peptides were analysed by liquid chromatography (LC) coupled mass spectrometry (MS) (Agilent HPLC/OrbitrapXL). Data were quantified label-free using Progenesis LC-MS and MASCOT. For metabolomics, LC separation was performed using hydrophilic interaction chromatography with a ZIC–HILIC. MS was performed using Orbitrap Exactive with HESI 2 probe. Raw LC/MS data were processed with XCMS Centwave and mzMatch.

Results LPON led to 2-fold downregulation of GCLC (encodes glutamate-cysteine ligase catalytic subunit, the rate limiting enzyme for glutathione synthesis) and upregulation of GPX1 and TXNDC12. Expression of GCLC and TXNDC12 was unchanged with oleate. Metabolomics confirmed that oxidised glutathione, glutathione disulfide, was higher in LPON- than oleate-treated cells. Among glutathione *S*-transferase genes, GSTA1 was unchanged with oleate but was upregulated by LPON (2.4-fold). Similarly, GSTT1, GSTK1 and GSTO1 were significantly increased by LPON. In contrast, MGST2 expression was higher in oleate than LPON-treated cells. Finally, proteomics showed that microsomal glutathione *S*-transferase 2 was downregulated by 2.5-fold by LPON.

Conclusion Our data show that increased ROS formation rather than triglyceride accumulation alters glutathione metabolism. Such alterations may influence susceptibility to further insults, particularly those accelerating glutathione depletion, for example, paracetamol overdose.

Disclosure of Interest None Declared

OC-008 KUPFFER CELLS PLAY A DUAL PRO-INFLAMMATORY AND PROTECTIVE ROLE IN NON-ALCOHOLIC STEATOHEPATITIS

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Introduction Non-alcoholic fatty liver disease (NAFLD) is the leading liver disease in Europe and North America. 30% of patients with NAFLD are estimated to develop inflammatory non-alcoholic steatohepatitis (NASH) with the potential to lead to cirrhosis and hepatocellular carcinoma. Current evidence suggests that gut bacterial products can drive hepatic inflammation by activating specific innate pattern recognition receptors (PRRs) such as TLR4 and the NALP3 inflammasome. Both receptors are expressed by liver resident macrophages, Kupffer cells (KCs).

Methods To determine the role of KCs and interactions with PRRs in NASH, mice were fed a methionine choline deficient (MCD) diet for three weeks to induce NASH. Liposomal clodronate was used to deplete KCs. Serum ALT levels were measured and hepatic inflammatory infiltrates characterised by flow cytometry. Real-time qPCR was used to assess changes in gene expression. Murine findings were correlated with human liver tissue from NASH patients. Groups were compared by one-way ANOVA and significance set at $P < 0.05$.

Results NALP3 KO (knock-out), TLR4 KO or KC deficient WT mice on a MCD diet developed reduced liver damage and decreased T lymphocyte recruitment compared to WT MCD controls. Combined KC depletion and NLRP3 KO however lead to significantly worse liver injury and progressive fibrosis as measured by collagen expression. Further investigation revealed an as yet unrecognised role for KC expressed NALP6 activation which mediated anti-inflammatory responses and modulation of hepatic IL-22 responsiveness to reduce liver injury.

Conclusion

1. KC activation through NALP3 and TLR4 increases hepatic inflammation in the MCD model of NASH.
2. KCs have a dual role in NASH as they also express NALP6 with anti-inflammatory properties and are able to reduce hepatic injury through modulation of IL-22 responsiveness modulation.

Disclosure of Interest None Declared

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OC-009 ENDOSCOPIC THERAPY FOR ZENKER'S DIVERTICULUM – A "BRIDGE" TOO FAR FOR GASTROENTEROLOGISTS?

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Introduction Zenker's diverticulum, caused by dysfunction of the cricopharyngeal (CP) muscle, is a disease of the elderly causing dysphagia. Although rigid endoscopic CP myotomy is the treatment of choice, flexible endoscopic therapy is another technique available. It is performed under sedation without need for anaesthetic or neck extension, a key advantage in elderly patients with significant co-morbidity.

Methods We describe the first UK experience of endoscopic CP myotomy for Zenker's diverticulum.

Results 4 patients (3 male) were referred, aged 74, 73, 60, 80 respectively, with proven Zenker's diverticulum on barium radiology and characteristic symptomatology. Zenker length was 7.0, 4.0, 2.5, 2.5cm respectively. 2 patients were refused surgery due to cardiovascular co-morbidity, 1 due to limited neck extension with 1 case personal preference. The procedure was performed using propofol sedation. The muscle bridge was cut by hook knife electrocautery alone (3) or with Argon (1). A supplementary clip was applied post electrocautery in 1 case. All patients were observed for 24 hours for signs of perforation and then discharged. There were no complications.

At 4 weeks 3 patients had complete resolution of their symptoms, 1 with marked improvement. Follow up time to date 3.4.7.11 months respectively. There was no reported recurrence of symptoms.

Conclusion Diverticulotomy with a flexible endoscope is an effective treatment for Zenker's diverticulum. It is a relatively simple yet under-utilised technique that avoids general anaesthesia in elderly/high-risk patients.

Disclosure of Interest None Declared

OC-010 LARGE COHORT STUDY EVALUATING THE ROLE OF HYBRID ESD (H-ESD) AND CONVENTIONAL PIECEMEAL EMR TECHNIQUE IN THE RESECTION OF LARGE AND CHALLENGING COLONIC POLYPS DEMONSTRATES NO OUTCOME BENEFIT OF H-ESD OVER EMR

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Introduction The learning curve for ESD in the west is very long, so a hybrid technique has been proposed. The impact of Hybrid ESD (H-ESD) technique on clinical outcome is unclear. We aim to compare the outcome benefits of Multi-piece EMR and H-ESD in the resection of challenging colonic polyps.

Methods A Prospective cohort study of endoscopic resection of difficult colonic polyps. Patients were tertiary referrals from experienced endoscopists. EMR was defined as submucosal injection followed by piecemeal snare resection. H-ESD involved submucosal injection before mucosal incision with an ESD knife followed by snare resection of the lesion. Endoscopic follow up was performed. Multiple linear regression analysis was performed using SPSS.

Results 347 flat/sessile polyps > 20 mm were resected between 2007–12. Mean follow-up was 1004 days.

H-ESD Cohort N = 110/347(32%). Mean size was 45mm(range 10–170). 25/110(23%) were salvage procedures for scarred lesions due to failed EMR attempts by other endoscopists. Endoscopic clearance was achieved in 95.5% of procedures. Need for surgery (n = 4): 1 for perforation and 3 for unexpected cancer. 98.6% showed no evidence of recurrence at endoscopic follow up.

EMR cohort N = 237/347(68%). Mean size was 42mm(range 20–150). 11/237(4.6%) were salvage procedures for polyps with

Abstract OC-010 Table

	SIZE		TECHNIQUE		PREV EMR		SITE	
COMPLICATIONS (25)	≤50mm 15/271 (5.5%)	> 50mm 8/76 (10.5%)	ESD 11/110 (10%)	EMR 12/237 (5%)	Yes 3/36 (8%)	No 20/311 (6%)	LC 20/250 (8%)	RC 3/97 (3%)
	P = 0.016		P = 0.11		P = 0.521		P = 0.201	
RECURRENCE (35)	≤50mm 19/271(7%)	> 50mm 16/76(21%)	ESD 12/110 (11%)	EMR 23/237 (10%)	Yes 10/36 (28%)	No 25/311 (8%)	LC 31/250 (12%)	RC 4/97 (4%)
	P = 0.0001		P = 0.156		P = 0.0001		P = 0.105	