Dansk Selskab for
Gastroenterologi og Hepatologi

Danish Society for Gastroenterology and Hepatology

7. årsmøde

30-31/8 2019

på

Hotel Nyborg Strand
Østerøvej 2, 5800 Nyborg

Indholdsfortegnelse

Årsmøde 30-31/8 2019

Tidspunkt	DSGH-årsmøde - Fredag 30. august 2019
09.30-10.00	**Registrering og kaffe**
10.00-10.15	**Velkomst, æresmedlem og legat** *Formand Henning Glerup*
10.15–10.40	**Legater** *Sidste års tre modtagere fortæller (Trine Boysen, Christian Borup, Mette Munk Lauridsen)* *Afsløring af de tre nye modtagere*
10.40-11.25	**IBD-tema** **Behandling af fistler ved morbus Crohn** Kirurg og mediciner: Helene Tarri Hougaard og Jørgen Agnholt *Chair: Jakob Seidelin*
11.25-12.00	**ePosterpræsentation (talk-no-walk á 2 min)** *Chairs: Signe Wildt & Anne-Mette Haase*
12.00-12.45	**Guideline og nyt fra leverinteressegruppen: Primær profylakse af øsofagus varicer** Lise Hobolt *Chair: Jane Møller Hansen*
12.45-13.45	**Frokost og besøg på udstilling**
13.45-14.30	**Guideline og nyt fra leverinteressegruppen: ernæring af leverpatient** Peter Holland-Fischer *Chair: Anders Neumann*
14.30-15.00	**ePosterpræsentation (talk-no-walk á 2 min)** *Chair: Mark Ainsworth & Nina Kimer*
15.00-15.45	**Eosinophilic esophagitis anno 2019** Prof. Dr.med. Alex Straumann *Chair: Anne Lund Krarup*
15.45-16.15	**Kaffe og besøg på udstilling**
16.15-17.45	**Foredragskonkurrence** *Chairs: Henning Grønbæk & Søren Schou Olesen*
17.45-18.00	**DSGH generalforsamling**
19.00- ….	**Festmiddag med partybandet Tråd**
	DSGH-årsmøde - Lørdag 31. august 2019
9.15-10.00	**Levertema: Cases fra DK med afstemninger** Case 1: Sunganya Jacobsen Case 2: Peter Ott Case 3: Anders E Junker Case 4: Mette Munk Lauridsen *Chair: Henning Grønbæk*
10.00-10.45	**NKR: NAFLD/NASH** Lise Lotte Gluud *Chair: Niels Kristian Aagaard*
10.45 – 11.15	**Kaffe og Pause**
11.15 – 11.35	**IBD interesse-gruppen, en kort orientering** Henning Glerup *Chair: Jakob Seidelin*
11.35–11.45	**Opdatering af IBD graviditet og amning inkl. patientinformation** Klaus Theede *Chairs: Amer Hadi & Inge Nordgaard-Lassen*
11.45–12.15	**Nyt kort emne: Ultralydsuddannelse for det gastro-hepatologiske speciale: Hvordan ser fremtiden ud?"** Maja Thiele *Chair: Jakob Seidelin*
12.15–14.00	**Sandwich to go**

Abstract oversigt

	FOREDRAG	
Nr.	**Navn**	**Titel**
1	Bjørn Stæhr Madsen	Prediction of liver fibrosis severity in alcoholic liver disease by human microfibrillar-associated protein 4
2	Julie Steen Pedersen	Non-alcoholic steatohepatitis (NASH) is associated with decreased mitochondrial oxidative phosphorylation in visceral adipose tissue (VAT)
3	Anne Rode Olsen	Treatment of recurrent Clostridium difficile infection with a 12-strain consortium of gut bacteria, faecal microbiota transplantation or oral vancomycin: results from an open-label multicentre randomised controlled trial
4	Thomas Damgaard Sandahl	Evaluation of human copper metabolism and diagnosis of Wilson disease by 64CuCl2 positron emission tomography
5	Mads Israelsen	Dobutamine reverses the cardio-suppressive effects of terlipressin without improving GFR in decompensated cirrhosis: An RCT
6	Josephine Grandt	Inflammasome activation predisposes for acute-on-chronic liver failure in compensated and recompensated cirrhosis
7	Christian Borup	Towards the biochemical diagnosis of bile acid diarrhoea
8	Tea Lund Laursen	Normalization of decreased capacity for ureagenesis after successful direct-acting antiviral therapy in patients with hepatitis C cirrhosis
	POSTER + FLASH TALK	
9	Peter Lykke Eriksen	Non-alcoholic steatohepatitis, but not simple steatosis, disturbs the functional homogeneity of the liver – a human galactose positron emission tomography study
10	Jakob Seidelin	Defining the Minimal Medium for Culturing Human Colonic Stem Cells
11	Jakob Seidelin	Tracking intestinal epithelial cells with fluorescent dyes
12	Alicia Meli	Positive Results from REGENERATE: A Phase 3 International, Randomized, Placebo-Controlled Study Evaluating Obeticholic Acid Treatment for NASH
13	Alicia Meli	From guidelines to uniform pan-healthcare professional practice: development of an international consensus Care Pathway for the diagnosis and management of Primary Biliary Cholangitis
14	Sara Heebøll	Serum lumican as a biomarker for the identification of hepatic fibrosis
15	Lisbet Grønbæk	Is smoking a risk factor for autoimmune hepatitis? An English registry-based matched case-control study
16	Morten Daniel Jensen	Alanine-aminotransferase and 20-year risk of major chronic diseases and death in a healthy cohort aged 30 to 49 years
17	Sabina Volmar	Administration and monitoring of biologic therapy in patients with inflammatory bowel disease – A national Danish survey
18	Kristoffer Kjærgaard	Biodistrubtion and radiation dosimetry of [64Cu]copper dichloride PET by intravenous and oral administration in healthy humans
19	Bobby Lo	High incidence and infrequent evaluation of osteoporosis among patients with inflammatory bowel disease; 10 years of follow-up in a Danish population-based inception cohort
20	Luise Aamann	The gut microbiota is not affected by twelve weeks of muscle-strengthening resistance training in patients with cirrhosis
21	Frederik Kraglund	Decreasing incidence of alcoholic liver disease in Denmark: a nationwide study
22	Julie Steen Pedersen	Prevalence of non-alcoholic steatohepatitis (NASH) and liver fibrosis in a Danish obese cohort before and 12 months after surgically induced weight loss
23	Pernille Glahn Wernlund	Casein glycomacropeptide is well tolerated in healthy adults and changes neither gut microbiota nor fecal butyrate: a randomized trial
24	Andreas Bartholdy	Long-term follow up in patients with walled-off pancreatic necrosis treated with endoscopic

		transmural drainage and necrosectomy
25	Signe Wiese	Increased cardiac and hepatic extracellular volume reflect augmented collagen metabolism and inflammation in liver cirrhosis
26	Marte Opseth Rygg	No clear evidence of a disrupted liver-alpha cell axis in patients with NASH and fibrosis
27	Maja Thiele	Serial testing with the enhanced liver fibrosis test and liver stiffness is cost-effective for detection of advanced alcoholic liver fibrosis in primary care
28	Emilie Glavind	The macrophage activation marker soluble CD163 is elevated and associated with liver disease phenotype in patients with Wilson's disease
29	Mia Bendix Rasch	Seven weeks high-dose vitamin D treatment in Crohn's disease reduces the need for intensified infliximab treatment during 52 weeks follow up
30	Konstantin Kazankov	QT interval is not associated with mortality in patients with cirrhosis and ascites
31	Konstantin Kazankov	Macrophage activation marker soluble CD163 is associated with improvement in liver injury and hepatic insulin sensitivity in obese patients following bariatric surgery
32	Nikolaj Worm Ørntoft	Postprandial changes in the hepatic bile acid transport in healthy human subjects measured by 11C-CSar PET/CT
33	Jane Møller Hansen	How Dyspepsia, Gastroesophageal Reflux Symptoms and Overlapping Symptoms Affect Quality of Life and use of Health Care and Medication - A Long-term Population Based Cohort Study
34	Ming Tan	Gene co-expression network analysis of precursor lesions in familial pancreatic cancer
35	Stine Karlsen	TERT mutation is detectable in plasma in nearly half of Danish patients with hepatocellular carcinoma and predicts poor prognosis
36	Lotte Lindgreen Eriksen	The Role and Modulation of T-lymphocyte 4-1BB in alcoholic hepatitis
37	Ditlev Nytoft Rasmussen	Non-invasive markers Accurately Predict Liver-Related Outcomes in Compensated Alcoholic Liver Disease
38	Stine Johansen	Development of advanced alcoholic liver fibrosis involves intensive remodelling of a wide range of extracellular matrix proteins and is characterised by imbalance between collagen formation and -degradation
39	Line Godskesen	Remote ischaemic conditioning in active ulcerative colitis: An explorative randomised clinical trial
40	Tea Lund Laursen	Effects of direct-acting antiviral therapy on markers of type III and IV collagen formation and degradation in the course of chronic hepatitis C viral eradication and follow-up

Abstracts 2019

Foredrag - Abstract nummer 1-8:

1)

Prediction of liver fibrosis severity in alcoholic liver disease by human microfibrillar-associated protein 4

Bjørn Stæhr Madsen[1,2], Maja Thiele[1,], Sönke Detlefsen[3,4], Maria Kjærgaard[1], Linda Sevelsted Møller[1], Ditlev Nytoft Rasmussen[1], Anders Schlosser[5], Uffe Holmskov[5], Jonel Trebicka[4,6,7,8], Grith Lykke Sorensen[5], Aleksander Krag[1] on behalf of the GALAXY consortium

[1]Department of Gastroenterology and Hepatology, Odense University Hospital, Denmark ; [2]OPEN, Odense Patient Data Exploratory Network, Odense University Hospital, Odense, Denmark; [3]Department of Pathology, Odense University Hospital, Odense, Denmark; [4]Institute of Clinical Research, University of Southern Denmark, Odense, Denmark; [5]Institute of Molecular Medicine, University of Southern Denmark, Odense, Denmark; [6]Department of Internal Medicine, University Clinic Frankfurt, Frankfurt, Germany; [7]European Foundation for the Study of Chronic Liver Failure - EF Clif, Barcelona, Spain; [8]Institute for Bioengineering of Catalonia, Barcelona, Spain

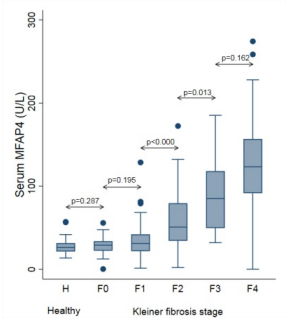
Background and Aims: Early detection of fibrosis, ideally in the pre-cirrhotic stage, is a key strategy for preventing progression to cirrhosis in Alcoholic Liver Disease (ALD). We investigated the utility of human microfibrillar-associated protein 4 (MFAP4) as a serological biomarker to detect ALD-related fibrosis.

Method: We performed a prospective liver biopsy-controlled study involving 266 patients with prior or current alcohol overuse. All patients were evaluated with a) liver biopsy, b) transient elastography (TE), c) Enhanced Liver Fibrosis test (ELF) and d) serum MFAP4 level. Patients were split into a training (n= 153) and a validation (n= 113) cohort. MFAP4 expression in liver biopsies was evaluated by immunostaining of MFAP4 in 116 liver biopsies.

Results: The distribution of Kleiner fibrosis stage in the cohort was F0= 32; F1= 93; F2= 79; F3= 17; F4= 45. MFAP4 expression in liver tissue and serum MFAP4 levels increased with fibrosis stage (Spearman's $\rho = 0.66$, $P < .000$). The area under the receiver operating characteristic curve (AUROC) for detection of advanced fibrosis was 0.88 (95% CI 0.81-0.94) in the training cohort and 0.92 (95% CI 0.83-1.00) in the validation cohort. The sensitivity was 76% and specificity was 90% for the detection of advanced fibrosis in the test cohort. The diagnostic accuracy did not differ between MFAP4 and the ELF test or TE in an intention-to-diagnose analysis.

Conclusion: MFAP4 is a novel serological biomarker that can detect ALD-related liver fibrosis with high accuracy.

Figure: Serum concentration of MFAP4 in the healthy population group and in the cohort of patients with current or prior alcohol overuse distributed according to the Kleiner fibrosis stage.



2)

Non-alcoholic steatohepatitis (NASH) is associated with decreased mitochondrial oxidative phosphorylation in visceral adipose tissue (VAT)

Julie Steen Pedersen[1], Marte Opseth Rygg[1], Steen Larsen[2], Karoline Chrøis[2], Viggo Kristiansen[3], Astrid Bruun Boilesen[3], Maria Franzmann[4], Reza Serizawa[4], Sten Madsbad[5] Lise Lotte Gluud[1], Flemming Dela[2], Flemming Bendtsen[1]

[1] Gastrounit, Medical Division, Copenhagen University Hospital Hvidovre; [2] Center for Healthy Ageing, Department of Biomedical Sciences, University of Copenhagen; [3] Gastrounit, Surgical Division, Copenhagen University Hospital Hvidovre; [4] Department of Pathology, Copenhagen University Hospital Hvidovre; [5] Department of Endocrinology, Copenhagen University Hospital Hvidovre

Background: NASH is associated with impaired hepatic mitochondrial function and subsequently augmented necrosis and apoptosis signaling. The same could apply for adipose tissue in NASH patients, but human data are non-existing. We studied liver, VAT and subcutaneous adipose tissue (SAT) mitochondrial function using high-resolution respirometry (HRR) by measuring the oxygen consumption rate during maximum ATP production (OXPHOS capacity).

Methods: We prospectively enrolled 55 patients with obesity undergoing bariatric surgery. Liver and VAT biopsies were collected during surgery. Tissue was placed in tubes with icecold preservation buffer and underwent HRR analysis in an Oxygraph. Histopathological evaluation of NASH was assessed using the NAFLD Activity score (NAS). A NAS of ≥ 5 was considered 'NASH'.

Results: In total, 22 patients had definite NASH with a NAS of ≥ 5 ('NASH' group) and 33 had a NAS score of <5 ('non-NASH' group). Median (IQR) liver OXPHOS capacity was 30 (23.5-38.2) pmol O^2/mg/s in the NASH group and 33 (24,4-40,1) pmol O^2/mg/s in the 'non-NASH' group (p=0,465). Median VAT OXPHOS capacity was significantly (p = 0.020) decreased in the NASH group 0.96 (0.68-1.22) vs 1.51 (0.92-1.78) pmol O^2/mg/s. In a multiple linear regression model HOMA-IR was a borderline significant predictor (p=0.050) of low VAT OXPHOS (β = -0,069 (95% CI -0,137; 0,000).

Conclusion: The VAT but not the liver OXPHOS capacity is decreased in patients with NASH. Our data support the hypothesis that VAT dysfunction is closely linked to metabolic deterioration and could play a significant and independent role in NASH pathophysiology.

3)

Treatment of recurrent *Clostridium difficile* infection with a 12-strain consortium of gut bacteria, faecal microbiota transplantation or oral vancomycin: results from an open-label multicentre randomised controlled trial

Anne A. Rode1,2; Mahtab Chehri2,3,4; Laura Krogsgaard1; Morten Helms2,3; Jørgen Engberg5; Kristian Schønning2,4; Michael Tvede6; Christian Østergaard Andersen4; Ulrich Stab Jensen5; Andreas Munk Petersen2,4,7; Peter Bytzer1,2

1 Department of Medicine, Zealand University Hospital Køge, Denmark; 2 Department of Clinical Medicine, University of Copenhagen, Denmark; 3 Department of Infectious Diseases, Hvidovre University Hospital, Denmark; 4 Department of Clinical Microbiology, Hvidovre University Hospital, Denmark; 5 Department of Clinical Microbiology, Slagelse Hospital, Denmark;6 MT MicroSearch by Michael Tvede, COBIS, Copenhagen, Denmark; 7 Department of Gastroenterology, Hvidovre University Hospital, Denmark

Background: A well-characterized bacterial consortium could be a safer alternative to faecal microbiota transplantation (FMT) for recurrent *Clostridium difficile* infection (rCDI). Therefore, we compared the efficacy of a 12-strain bacterial consortium (rectal bacteriotherapy, RBT) with FMT and oral vancomycin for rCDI in an open-label multicentre RCT.
Methods: All consecutive individuals with a positive test for *Clostridium difficile* in the Capital Region and Region Zealand was screened for eligibility May 2017 - March 2019.
We pre-treated FMT and RBT groups with vancomycin for 7-14 days. We applied RBT rectally on three consecutive days and FMT rectally once with possibility of repetition. The vancomycin-group was treated for 14 days with additional tapering for five weeks for participants with multiple recurrences.
The primary outcome was clinical cure during 90 days, while a secondary outcome was 180-day mortality.
Results: Participants in the FMT-group (n=34) was cured more often than participants in the vancomycin-group (n=31), 76 vs. 45%, OR 3.9 (1.3 – 11.3), p = 0.02, NNT 3. FMT seemed more effective than RBT (n=31), 76 vs. 52%, OR 3.2 (1.1 – 9.4), p = 0.06, while RBT and vancomycin performed similarly.
Mortality ranged from 6% in the FMT-group to 23% in the vancomycin-group. Thus, FMT tended to reduce mortality compared with vancomycin, OR 0.2 (0.04 – 1.12), p = 0.07, NNT 6.
Conclusion: Rectally applied FMT is superior to oral vancomycin for treating rCDI and also might reduce mortality. Rectal bacteriotherapy appears as effective as vancomycin and the potential role for this 12-strain consortium is unclear.

4)

Evaluation of human copper metabolism and diagnosis of Wilson disease by $^{64}CuCl_2$ positron emission tomography

Thomas D Sandahl[1], Lars C Gormsen[2], Ole L Munk[2], Kristoffer Kærgaard[1,2] Dirk Bender[2], Karina H Vase[2], Kim Frisch[2], Hendrik Vilstrup[1], Susanne Keiding[1,2], Peter Ott[1]
1. Department of Hepatology & Gastroenterology, Aarhus University Hospital, Denmark. 2. Department of Nuclear Medicine & PET Centre, Aarhus University Hospital, Denmark.

Background: Wilson disease (WD) is a rare genetic defect in copper metabolism leading to toxic copper accumulation in different organs, especially in the liver and brain. The underlying defect in copper transport kinetics is only partly understood, and the diagnosis of WD is challenging. Copper-64 (64Cu) is a positron emitting isotope of copper with a half-life of 12,7 hours making it ideal for long term positron emission tomography (PET) studies.
Aims: 1) To evaluate possible differences in hepatic copper metabolism using PET/CT with $^{64}CuCl_2$ in healthy subjects (controls), healthy but heterozygote (heterozygote) subjects, and patients with Wilson disease. 2) To evaluate the diagnostic potential of $^{64}CuCl_2$ PET/CT for Wilson disease.
Methods: 8 healthy participants, 5 heterozygote participants and 9 patients with Wilson disease were enrolled in the study. All subjects underwent $^{64}CuCl_2$ dynamic PET/CT of the liver 0-90 minutes after intravenous tracer injection, followed by static whole-body PET/CT after 20 hours. Hepatic copper uptake (0-90 after tracer administration) was quantified by steady-state clearance (Gjedde-Patlak analysis) and the subsequent hepatic copper excretion and redistribution was evaluated semiquantitatively by static PET/CT images 90 minutes and 20 hours after tracer administration using the standardized uptake value (SUV). The ratio between mean SUV values (SUV-R) at 90 minutes and 20 hours was evaluated for diagnostic potential of WD.

Results: Hepatic copper uptake from blood was similar in all groups as assessed by the Gjedde-Patlak clearance. The 20 hour SUVs differed significantly between groups (see figure 1) with increasing hepatic radioactivity in the Wilson patients and decreasing activity in both controls and heterozygotes (P<0.001, repeated measures ANOVA). Interestingly, no maximal ^{64}Cu activity was reached in the Wilson patients during the 20-hour study indicating an ongoing redistribution from other tissues towards the liver. This was reflected in a significantly higher SUV-R in Wilson patients compared with the other groups (ANOVA p<0.0001)(figure 2). In fact, the SUV-R correctly identified Wilson patients with 100% sensitivity and 100% specificity using a cut-off of 1.33.

Conclusions: $^{64}CuCl_2$ PET/CT demonstrated increasing hepatic copper accumulation over a 20-hour period in patients with Wilsons disease compared to healthy and heterozygote controls. Using a simple ratio of mean hepatic SUV at 90 minutes and 20 hours, $^{64}CuCl_2$ PET/CT accurately diagnosed Wilson patients with 100% accuracy and thus holds great promise as a diagnostic tool.

Figure 1:

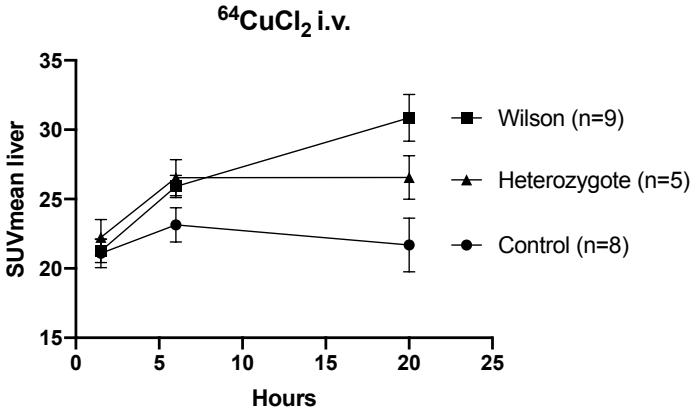
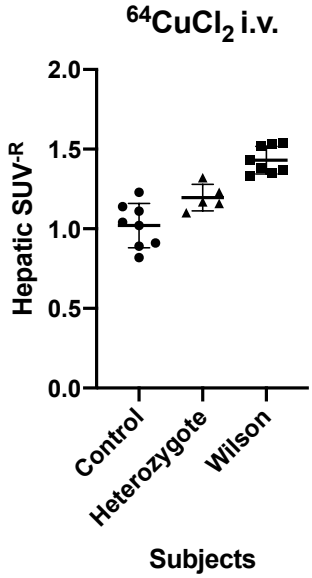


Figure 2:



5)

Dobutamine reverses the cardio-suppressive effects of terlipressin without improving GFR in decompensated cirrhosis: An RCT

Mads Israelsen[1,2], Emilie Dahl[1], Bjørn Stæhr Madsen[1,2], Signe Wiese[3,4], Flemming Bendtsen[3], Søren Møller[4], Annette Dam Fialla[1], Boye L. Jensen[5], Aleksander Krag[1,2]

1: Department of Gastroenterology and Hepatology, Odense University Hospital, Odense, Denmark; 2: University of Southern Denmark, Department of Clinical Research, Odense, Denmark; 3: Gastro Unit, Copenhagen University Hospital Hvidovre, Hvidovre, Denmark; 4: Department of Clinical Physiology and Nuclear Medicine, 260 Center for Functional and Diagnostic Imaging and Research, Faculty of Health Sciences Hvidovre Hospital, University of Copenhagen, Denmark; 5: Department of Cardiovascular and Renal Research, Institute of Molecular Medicine, University of Southern Denmark, Odense, Denmark.

Background and Aims: Acute kidney injury and hepatorenal syndrome (HRS) are frequent complications in patients with cirrhosis and ascites. First-line treatment is terlipressin, which reverses HRS in approximately 40% of patients but also lowers cardiac output (CO). We hypothesised that reversing the cardio-suppressive effect of terlipressin with the β-adrenoceptor agonist dobutamine would increase CO and thereby the glomerular filtration rate (GFR).

Methods: We randomised twenty-five patients with cirrhosis, ascites and impaired renal function (2:2:1): Group A received terlipressin followed by dobutamine, Group B received dobutamine followed by terlipressin and Group C received placebo. Renal and cardiac functions were assessed during 8 clearance periods of 30 minutes, and concentrations of vasoactive hormones were measured in plasma.
Results: Dobutamine as a monotherapy increased CO (1.03 L/min, P<0.01) but had no significant effects on GFR. Renin (P<.05), angiotensin II (P<.005) and aldosterone (P<.05) increased after dobutamine infusion. Terlipressin as a monotherapy improved GFR (18.9 ml/min/m^2, p=.005) and mean arterial pressure (MAP) (14 mmHg, P=.001) but reduced CO (-0.92 L/min, P<.005) and renin (P<.005). A combined treatment of dobutamine and terlipressin had a positive effect on CO (1.19 L/min, P<.05) and increased renin (P<.005), angiotensin II (P<.005) and aldosterone (P<.05), but it had no significant effects on MAP or GFR.
Conclusion: Dobutamine reversed the cardio-suppressive effect of terlipressin in cirrhosis, ascites and impaired renal function. Dobutamine reduced peripheral vascular resistance, activated RAAS and did not improve GFR compared to terlipressin as a monotherapy and therefore cannot be recommended in patients with cirrhosis and ascites.

6)

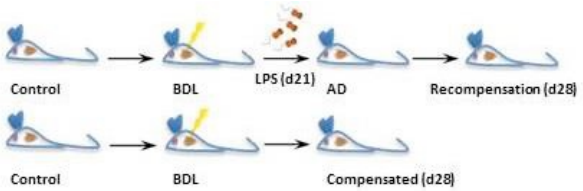
Inflammasome activation predisposes for acute-on-chronic liver failure in compensated and recompensated cirrhosis

Josephine Grandt 1*, Sofia Monteiro,2,3*, Frank Uschner4*, Robert Schierwagen4, Sabine Klein4, Joan Clària5,6, Vicente Arroyo5, Richard Moreau7, Javier Fernández5,6, Flemming Bendtsen1, Søren Møller8, Michael Praktiknjo2#, Jonel Trebicka2,4,5,9,10#, Lise Lotte Gluud1#
1 Gastrounit Medical Division, Hvidovre Hospital, University of Copenhagen, Copenhagen, Denmark; 2Department of Internal Medicine I, University of Bonn, Bonn, Germany; 3 Department of Medicine, Hospital Pedro Hispano, Matosinhos, Portugal;4 Department of Internal Medicine I, J.W.Goethe University Hospital, Frankfurt, Germany ; 5European Foundation for Study of Chronic Liver Failure, Barcelona, Spain; 6 Hospital Clínic, IDIBAPS and CIBERehd, Barcelona, Spain; 7Assistance Publique-Hôpitaux de Paris, Hôpital Beaujon, Département Hospitalo-Universitaire UNITY, Service d'Hépatologie, Clichy, France; Institut National de la Santé et de la Recherche Médicale and Université Paris Diderot, Centre de Recherche sur l'Inflammation, Unité Mixte de Recherche 1149, Paris, France; 8 Department of Clinical Physiology and Nuclear Medicine, 239 Center for Functional and Diagnostic Imaging and Research, Faculty of Health Sciences Hvidovre Hospital, University of Copenhagen, Denmark; 9 Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark; 10 Institute of Bioengineering Catalunya, Barcelona, Spain'

Background: While Acute Decompensation (AD) in cirrhosis can be successfully treated in many patients, Acute-on-chronic liver failure (ACLF) is associated with high mortality. This study evaluates the association between proinflammatory states and development of ACLF in patients with compensated cirrhosis and previous decompensation (recompensated cirrhosis)
Methods: 249 patients with compensated and recompensated cirrhosis were electively evaluated and blood was collected. Patients were followed prospectively for fatal ACLF development (mean duration of follow up was 3 years). Systemic Inflammation (SI) was assessed by levels of inflammasome-driving IL-1α (Caspase-4/11 dependent) and IL-1β (Caspase-1 dependent) in patients and in an animal model of bile duct ligated rats (figure 1).
Results: All 52 patients developing fatal ACLF showed significantly higher baseline levels of proinflammatory ILs. The proportion with fatal ACLF was 11% among compensated and 31% among

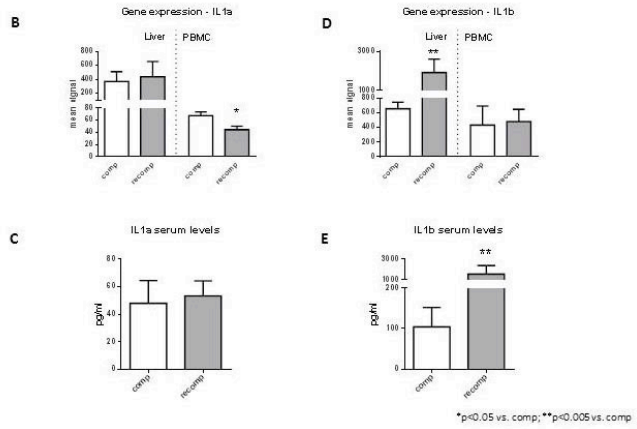
re-compensated patients (P<0.05). In multivariable analysis, albumin (HR 0.872, p=0.010) and IL-1α (HR 1.248, p=0.013) were independent predictors of fatal ACLF in compensated cirrhosis; CLIF-C AD score (HR 1.079, p=0.006) and IL-1β (HR 1.184, p=0.011) in recompensated patients. Animal data showed significantly lower IL-1α gene expression in peripheral blood mononuclear cells and higher levels of and IL-1β with higher gene expression in the liver of recompensated compared with compensated animals (figure 2).
Conclusion: Inflammasone activation is associated with the risk of fatal ACLF; IL-1α predicts fatal ACLF in compensated and IL-1β in recompensated patients.

Figure 1: Animal model of bile duct ligated rats



Abbreviations: AD, acute decompensation ; BDL, bile duct ligation ; LPS, Lipopolysaccharides

Figure 2 Gene expression and IL1a and IL1b serum levels in animal model



7)

Towards the biochemical diagnosis of bile acid diarrhoea

Christian Borup (1), Signe Wildt (1,7), Jüri J. Rumessen (2), Jesper Graff (3), Trine B. Andersen (4), Anna Zaremba (4), Lars Vinter-Jensen (4), Camilla Nøjgaard (3), Hans B. Timm (3), Tine Gregersen (5), Søren P. G. Jørgensen (5), Pierre N. Bouchelouche (1), Dominique Rainteau (6), Lars K. Munck (1,7)

1: Zealand University Hospital, Koege-DK. 2: Herlev and Gentofte University Hospital, Hellerup-DK. 3: Hvidovre University Hospital, Hvidovre-DK. 4: Aalborg University Hospital, Aalborg-DK. 5: Aarhus University Hospital, Aarhus-DK. 6: Faculté de Médecine, Sorbonne Université, Paris-FR, 7: Department of Clinical Medicine, University of Copenhagen.

Background: Missed diagnosis of bile acid diarrhoea (BAD) is common because availability of the 75Seleno-taurohomocholic acid retention test (SeHCAT) is limited. The biomarkers 7α-hydroxy-4-cholesten-3-one (C4) and fibroblast growth factor-19 (FGF19) are proposed alternatives and we previously reported the initial comparison. We now explore possible improvements to the diagnostic precision (NCT03059537).

Methods: We prospectively recruited patients referred for SeHCAT for fasting blood samples. SeHCAT ≤10% defined BAD and >10% defined idiopathic diarrhoea. We analysed plasma C4 and bile acid species with high-performance liquid chromatography tandem mass-spectrometry. We analysed receiver operating characteristics (ROC), compared groups with the Mann Whitney U-test, and did explorative multivariate logistic regression.
Results: Twenty-six of 71 patients had BAD. The plasma bile acid profile for patients with BAD showed less secondary (p=0.008) and sulfonate conjugated species (p=0.001) and a higher taurine to glycine conjugated bile acid species ratio (p=0.041). C4 >15 ng/mL had 0.83 (0.72–0.93) area under the ROC curve (ROCAUC) with 77% sensitivity and 76% specificity which classified 54/71 patients correctly as true positive/true negative. A logistic regression model with the covariates C4, age and mean stools/day achieved ROCAUC 0.88 (0.79–0.96) and correctly classified 58/71 patients. With FGF19 added to the model gave ROCAUC 0.91 (0.84–0.98) classifying 61/71 correctly.
Conclusion: Biochemical diagnosis of BAD with C4 compares well with SeHCAT. It is feasible and clinically relevant. The plasma bile acid profile reflects an increased intestinal bile acid loss and decreased renal excretion. The logistic model covariates may increase the diagnostic precision but need validation.

8)

Normalization of decreased capacity for ureagenesis after successful direct-acting antiviral therapy in patients with hepatitis C cirrhosis

Tea Lund Laursen[1], Thomas Damgaard Sandahl[1], Konstantin Kazankov[1], Peter Lykke Eriksen[1], Holger Jon Møller[2], Lena Hagelskjær Kristensen[3], Charlotte Henneberg Holmboe [4], Christina Sølund[5], Hanne Arildsen[6], Alex Lund Laursen[6], Hendrik Vilstrup[1], Henning Grønbæk[1].
1. Department of Hepatology & Gastroenterology, Aarhus University Hospital, Aarhus, Denmark; 2. Department of Clinical Biochemistry, Aarhus University Hospital, Aarhus, Denmark; 3. Department of Medicine, Viborg Regional Hospital, Viborg, Denmark; 4. Department of Gastroenterology and Hepatology, Aalborg University Hospital, Aalborg, Denmark; 5. Department of Infectious Diseases, Hvidovre Hospital, Hvidovre, Denmark; 6. Department of Infectious Diseases, Aarhus University Hospital, Aarhus, Denmark

Background: The effect of direct-acting antiviral (DAA)-treatment of chronic hepatitis C (CHC) cirrhosis on metabolic liver function is unknown but of importance for the patients' prospects. Ureagenesis is an essential liver function involved in whole-body nitrogen homeostasis. We aimed to measure the ureagenesis capacity before and after DAA-treatment and relate the findings to hepatic inflammation and structural liver changes.
Methods: The ureagenesis capacity was quantified by the functional hepatic nitrogen clearance (FHNC) in nine CHC cirrhotics and ten healthy volunteers. Hepatic inflammation was evaluated by ALT and the hepatic macrophage activation markers sCD163 and sMR. Structural changes were estimated as liver stiffness and by portal hypertension as the hepatic venous pressure gradient (HVPG).
Results: Prior to treatment, the FHNC in the patients was half of the controls (16.4 L/hour (8.2-24.5) vs. 33.4 (29.2-37.6), p=0.0004); after successful DAA-treatment it normalized (28.4 (15.9-40.9), p=0.008). The treatment normalized ALT (p<0.0001), decreased the elevated sCD163 from 5.6 to 3.4 (p<0.001) and slightly decreased the sMR from 0.35 to 0.31 (p<0.01). The patients had a liver stiffness of 24.1 kPa, which fell to 15.2 kPa (p<0.05), and clinically significant portal hypertension (HVPG:11 mmHg), which did not improve (p=0.59).

Conclusion: DAA-treatment rapidly restored the severely reduced ureagenesis capacity, along with amelioration of hepatic inflammation and without normalization of other cirrhosis characteristics. Our findings indicate that the anti-inflammatory effect of virus eradication independent of hepatic structural effects rapidly improves the metabolic dysfunction. We suggest this effect to be an important part of the expected clinical treatment benefit.

Poster – abstract 9-40

9)

Non-alcoholic steatohepatitis, but not simple steatosis, disturbs the functional homogeneity of the liver – a human galactose positron emission tomography study

Peter Lykke Eriksen[1], Karen Louise Thomsen[1], Lars Peter Larsen[2], Henning Grønbæk[1], Hendrik Vilstrup[1], Michael Sørensen[1,3]

1: Department of Hepatology and Gastroenterology, Aarhus University Hospital, Denmark; 2: Department of Radiology, Aarhus University Hospital, Denmark; 3: Department of Nuclear Medicine & PET-Centre, Aarhus University Hospital, Denmark

Background: The disease severity of non-alcoholic fatty liver disease (NAFLD) and the distinction between simple steatosis and non-alcoholic steatohepatitis (NASH) are based on the pathohistological presence of steatosis, inflammation, ballooning, and fibrosis. However, little is known about the relation between such structural changes and the function of the afflicted liver. We investigated *in vivo* effects of hepatic fat fraction, ballooning, and fibrosis on regional and whole liver metabolic function assessed by galactose elimination in NASH and simple steatosis.

Methods: Twenty-five biopsy-proven, non-diabetic patients with NAFLD (13 NASH with low-grade fibrosis, 12 simple steatosis with no fibrosis) underwent 2-[^{18}F]fluoro-2-deoxy-D-galactose positron emission tomography and magnetic resonance imaging-derived proton density fat fraction of the liver. Nine healthy persons were included as controls.

Results: In the NASH patients, the standardised hepatic uptake of 2-[^{18}F]fluoro-2-deoxy-D-galactose was reduced to 13.5 (95% confidence interval, 12.1–14.9) as compared with both simple steatosis and controls (16.4 (15.6–17.1), $p<0.001$). Thus, the NASH patients had reduced regional metabolic liver function. The liver fat fraction diluted the standardised uptake equally in NASH and simple steatosis but the fibrosis and ballooning of NASH were associated with a further decrease. Moreover, the NASH livers exhibited increased variation in their standardised uptake values (coefficient of variation 13.8% vs. 11.6% in simple steatosis and 10.2% in controls, $p=0.02$), reflecting an increased functional heterogeneity.

Conclusions: In NASH, the regional metabolic liver function was lower and more heterogeneous than in both simple steatosis and healthy controls. Thus, NASH disturbs the normal homogeneous metabolic function of the liver.

10)

Defining the Minimal Medium for Culturing Human Colonic Stem Cells

Fredrik EO Holmberg, Jakob B Seidelin, Ole H Nielsen

Department of Gastroenterology, Herlev Hospital, University of Copenhagen, Denmark

Background: Numerous protocols have been developed to culture human intestinal *LGR5*$^{+}$ stem cells *in vitro*, giving rise to organoid structures that efficiently recapitulate the intestinal epithelium *in vivo.*

Aim: To define the minimal medium composition required.

Methods: Human colonic stem cells were cultured in Matrigel as organoids for 7 days, and different growth media compositions were screened, by excluding one component at a time (Table 1) and by subsequent omission of several dispensable growth factors. Organoids were seeded and RNA was harvested at day 7. *LGR5* expression was quantified using RT-PCR. Seeding efficiency was determined at day 10, defined as organoid forming capacity after single cell passaging.

Results: N2 and nicotinamide could be omitted without observing decreased seeding efficiency or *LGR5* expression ($p>0,05$). Leaving out Wnt3a or Rspo1 resulted in a near complete loss of stem cell

yield. Without EGF or Noggin, seeding efficiency were reduced by 93 and 94% respectively, and LGR5 expression by 57-62%. Withholding nAC, SB202190 or A8301, only marginally affected the seeding efficiency, but decreased *LGR5* expression by 25-70%. Omitting A8301, however, generated massive organoids with a cystic morphology.

Conclusions: N2 and nicotinamide can be omitted, whereas the components marked in Table 1 were found to be pivotal or even indispensable for normal stem cell yield. Nonetheless, functional organoids were successfully grown in medium only containing PGE_2 (0.02 µM), Rspo1, nAC, B27, albeit at the cost of a negligible stem cell yield after passaging.

Table 1: Growth Factors and Small Molecules (Volume or Concentration) ** Indispensable * Decreased Stem Cell Yield
**** Wnt3a conditioned medium (50 % of the total volume)**
**** Rspo1, conditioned medium (10 % of the total volume)**
**** EGF (50 ng/ml)**
**** Noggin (100 ng/ml)**
****/* B27 Supplement (2 % of the total volume)**
*** n–Acetylcysteine/nAC (1 mM)**
*** A83-01 (0,5 µM)**
*** SB202190 (10 µM)**
N2 Supplement (1 % of the total volume)
Nicotinamide (1 % of the total volume)

11)

Tracking intestinal epithelial cells with fluorescent dyes

Jakob Benedict Seidelin, Fredrik Holmberg Bergenheim, Ole Haagen Nielsen

Background: Enteroids have been shown to be able to engraft onto injured intestinal mucosa in murine experimental colitis models. This observation may provide an innovative approach to accomplish mucosal healing in patients with inflammatory bowel disease. Nevertheless, there are several issues to be resolved before this approach can be attempted in humans. One such issue is how to label and track transplanted cells. Hence, we investigated the applicability of a panel of non-gene modifying fluorescent dyes and nanoparticles, and whether labeled enteroids could be visualized using the clinically approved imaging modality, confocal laser endomicroscopy.

Methods: Intestinal biopsies were harvested from healthy human colonic mucosa, and enteroids were established using standard protocols. Enteroids were then attempted stained with fluorescein, a carbocyanine dye (*CellBrite*™), an inert membrane permeable dye, 5-chloromethylfluorescein diacetate (CMFDA; *CellTracker™),* quantum dots (QTracker™) and PLGA nanoparticles. Only 5-25 µM of CMFDA was found suitable, and staining homogeneity, durability, cell viability and organoid forming capacity following single cell seeding were evaluated, together with visualization of stained enteroids *in vitro* over time using endoscope-based confocal laser endomicroscopy.

Results: CMFDA efficiently and homogeneously stained all enteroids (Fig. 1a). The viability and enteroid growth appeared to be unaffected by CMFDA staining (Fig. 2a, b), whereas single cell seeding revealed a significant reduction in organoid forming capacity with increasing dye concentration (Fig. 2 c). No transfer of dye to unstained enteroids in co-cultures was observed. The CMFDA-derived fluorescent intensity of stained cells decreased in a linear fashion, with a $t_{1/2}$ of approximately 24 h, and approached the background signal intensity after approximately seven days. Further, stained enteroids were easily identified *in vitro* using confocal laser endomicroscopy for a duration of at least three days (Fig. 1b).
Conclusion: It is plausible to track human intestinal organoids using common fluorescent dyes (e.g., CMFDA) and confocal laser endomicroscopy. This type of approach might clearly be limited to short-term tracking, which, however, may be sufficient to allow for confirmation of engraftment following transplantation.

12)

Positive Results from REGENERATE: A Phase 3 International, Randomized, Placebo-Controlled Study Evaluating Obeticholic Acid Treatment for NASH

Zobair Younossi[1], Vlad Ratziu[2], Rohit Loomba[3], Mary Rinella[4], Quentin M. Anstee[5], Zachary Goodman[1], Pierre Bedossa[6], Andreas Geier[7], Susanne Beckebaum[8], Philip Newsome[9], David Sheridan[10], James Trotter[11], Whitfield Knapple[12], Eric Lawitz[13], Kris Kowdley[14], Aldo Montano-Loza[15], Jerome Boursier[16], Philippe Mathurin[17], Elisabetta Bugianesi[18], Giuseppe Mazzella[19], Antonio Olveira[20], Helena Cortez-Pinto[21], Isabel Graupera[22], David Orr[23], Lise Lotte Gluud[24], Jean-Francois Dufour[25], David Shapiro[26], Jason Campagna[26], Luna Zaru[26], Leigh MacConell[26], Reshma Shringarpure[26], Stephen Harrison[27], Arun J. Sanyal[28] on behalf of the REGENERATE Study Investigators

1. Betty and Guy Beatty Center for Integrated Research, Inova Health System, Falls Church, United States; 2. Sorbonne Université, Hôpital Pitié – Salpêtrière, Paris, France; 3. University of California, San Diego, San Diego, United States; 4. Feinberg School of Medicine, Northwestern University, Chicago, United States; 5. Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle Upon Tyne, United Kingdom; 6. Service d'Anatomie Pathologique, Hôpital Beaujon, Assistance Publique-Hôpitaux de Paris, Paris, France; 7. University of Wuerzburg, Wuerzburg, Germany; 8. St. Josef-Krankenhaus Kupferdreh, Essen, Germany; 9. University of Birmingham, Birmingham, United Kingdom; 10. Derriford Hospital, Plymouth, United Kingdom; 11. Baylor Health, Liver Consultants of Texas, Dallas, United States; 12. Arkansas Gastroenterology, North Little Rock, United States; 13. Texas Liver Institute, University of Texas Health San Antonio, San Antonio, United States; 14. Swedish Liver Center, Seattle, United States; 15. Division of Gastroenterology and Liver Unit, University of Alberta, Edmonton, Canada; 16. Angers University Hospital, Angers, France; 17. Hepato-gastroenterology, CHU Lille, Lille, France; 18. University of Turin, Turin, Italy; 19. University of Bologna, Bologna, Italy; 20. Hospital Universitario La Paz, Madrid, Spain; 21. Centro Hospitalar Lisboa, Lisbon, Portugal; 22. Hospital Clinic de Barcelona, Barcelona, Spain; 23. Auckland City Hospital, Auckland, New Zealand; 24. Copenhagen University Hospital Hvidovre, Hvidovre, Denmark; 25. University of Bern, Bern, Switzerland; 26. Intercept Pharmaceuticals, San Diego, United States; 27. Pinnacle Clinical Research Center, San Antonio, United States; 28. Virginia Commonwealth University, Richmond, United States

Background: This Month 18 pre-specified interim analysis of the ongoing Ph3 REGENERATE study evaluated the effect of OCA on liver histology in patients with biopsy-confirmed NASH.

Methods: Patients with NASH and fibrosis stages F2-3 (ITT), and an exploratory group of F1 pts with metabolic syndrome, were randomized to placebo, OCA 10mg, or OCA 25mg QD. Primary endpoints were fibrosis improvement (≥1 stage) with no worsening of NASH, or NASH resolution with no worsening of liver fibrosis per liver biopsy. The safety population included all randomized and dosed patients (F1-3, N=1968). Clinical outcomes will be evaluated at the end-of-study.
Results: The ITT population included 931 patients (placebo [n=311], OCA 10mg [n=312] or OCA 25mg [n=308]), comprised of 44% F2 and 56% F3. The primary fibrosis endpoint was met by 11.9% placebo, 17.6% OCA 10mg (p=0.0446), and 23.1% OCA 25mg (p=0.0002) patients. The primary NASH endpoint was not statistically significant. More patients on OCA 25mg showed improvements in hepatocellular ballooning and lobular inflammation. Pruritus was the most common AE (19% placebo, 28% OCA 10mg, 51% OCA 25mg) and was predominantly mild to moderate in severity (severe pruritus: <1% placebo, <1% OCA 10mg, 5% OCA 25mg). SAEs occurred in 11% placebo, 11% OCA 10mg and 14% OCA 25mg pts. Three deaths occurred; none were considered treatment-related (placebo n=2; OCA 25mg n=1).
Conclusion: Treatment with OCA 25mg improved liver fibrosis, key histologic features of steatohepatitis and liver biochemistry, demonstrating consistent efficacy with an overall AE profile similar to previous studies.

	Placebo	**OCA 10 mg**	**OCA 25 mg**
Primary: ITT Population (F2 + F3)	**n=311**	**n=312**	**n=308**
Fibrosis improvement + no worsening of NASH	11.9%	17.6% p=0.0446	23.1% p=0.0002
NASH resolution + no worsening of fibrosis	8.0%	11.2% p=0.1814	11.7% p=0.1268
Improvement in hepatocellular ballooning	23.2%	27.2% p=0.2423	35.1% p=0.0011
Improvement in lobular inflammation	35.7%	39.1% p=0.3380	44.2% p=0.0322

Overall study discontinuations (ITT): 16% PBO, 17% OCA 10 mg, 15% OCA 25 mg.

13)

From guidelines to uniform pan-healthcare professional practice: development of an international consensus Care Pathway for the diagnosis and management of Primary Biliary Cholangitis

Gideon M Hirschfield, Marco Carbone, Helena Cortez-Pinto, Guilherme Macedo, Victor de Lédinghen, Olivier Chazouilleres, Femi Adekunle

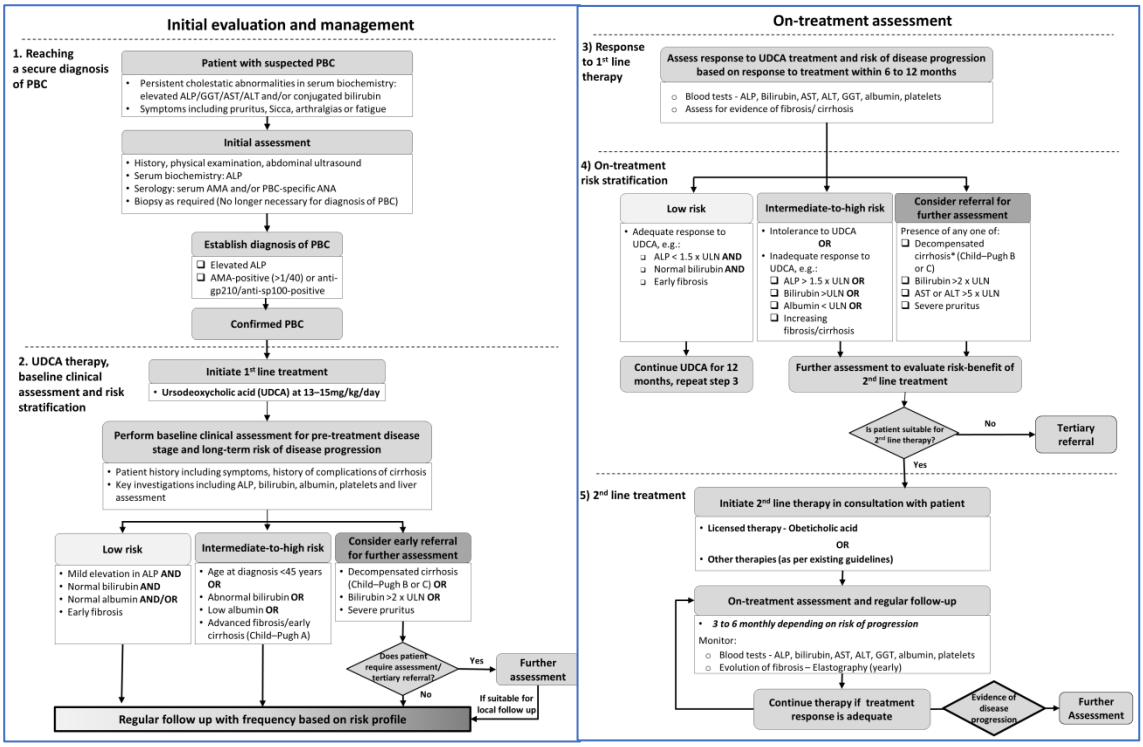
Background: Primary biliary cholangitis (PBC) is a chronic, rare, autoimmune cholestatic liver disease that leads to liver fibrosis, cirrhosis and, ultimately, the need for liver transplantation. Its clinical course is heterogeneous, making it difficult for clinicians to diagnose and stratify patients with confidence and patient management is frequently shared across specialities. The objective of this exercise was to leverage clinical expertise to translate European treatment guidelines into a patient Care Pathway.
Methods: Twelve PBC specialists convened (with transparent financial support from industry) with the aim of drafting a Care Pathway to support clinicians in the day-to-day management of patients with PBC. The Care Pathway should give practical advice on: confirming PBC diagnosis, performing

baseline clinical and risk assessments, initiating first-line treatment, performing on-treatment risk stratification at 6–12 months based on response to first-line treatment, and identifying patients who require second-line treatment and/or further assessments.

Results: Based on the consensus, a working group of six experts developed and completed the Care Pathway. The working group reached added-consensus on a five-part structure and content for the Care Pathway based on EASL guidelines alongside their clinical experience (**Figure 1**).

Conclusions: As an exemplar for all clinicians involved in the care of patients with chronic liver disease, this consensus PBC Care Pathway, builds on guidelines to support patient care. It provides an opportunity for more uniform practice, and for safe and timely adoption of varied models of care provision to patients with PBC, which go beyond classical physician-lead only management.

Figure 1. Consensus Care Pathway for the Diagnosis and Management of PBC



Disclosures: The development meeting and production of the Care Pathway have been organized and funded by Intercept Pharma Europe Ltd.

14)

Serum lumican as a biomarker for the identification of hepatic fibrosis

S Heebøll[1,2,3], KW Antonsen[2], NK Aagaard[1], H Grønbæk[1], HJ Møller[2]

1. Department of Hepatology and Gastroenterology; 2. Department of Clinical Biochemistry, 3. Department of Endocrinology and Internal Medicine; Aarhus University Hospital and Department of Clinical Medicine, Aarhus University

Background and Aims: Lumican, a proteoglycan involved in fibrogenesis, can be measured in circulation. We aimed to study serum levels in healthy subjects, and in patients with non-alcoholic fatty liver disease (NAFLD) or liver cirrhosis to investigate a potential biomarker for fibrotic liver disease.

Methods: We verified lumican in serum using Western blotting and established a lumican reference interval in blood donors using a commercial enzyme-linked immunosorbent assay. In a retrospective,

observational study, we measured lumican in 24 subjects with no fibrotic liver disease; 28 NAFLD patients without fibrosis; and 143 patients with cirrhosis, including 14 with NAFLD cirrhosis.
Results: Lumican was present in serum in high concentrations. In blood donors, median lumican concentration was 5.9 μg/mL (95% reference range 3.2−8.9). In cirrhosis patients, median lumican was 9.3 μg/mL (range 2.3−22.0), which was significantly higher than in blood donors, and subjects with no fibrotic disease (5.0 μg/mL, 2.8−9.3) (for all, $P < 0.01$). Lumican levels in patients with NAFLD cirrhosis were 9.3 μg/mL, in contrast to the normal levels of NAFLD patients without fibrosis (5.7 μg/mL, 4.0−9.8, $P < 0.01$). Lumican was positively correlated with hepatic vein pressure gradient ($r = 0.49$, $P < 0.01$) and transient elastography ($r_s = 0.58$, $P < 0.01$).
Conclusions: High levels of lumican are present in the human circulation and lumican is a promising marker of severe hepatic fibrosis, including NAFLD cirrhosis. Our results need confirmation in a prospective cohort of patients that includes all levels of fibrosis.

15)

Is smoking a risk factor for autoimmune hepatitis? An English registry-based matched case-control study

Lisbet Grønbæk[1, 2, 3]: Harmony Otete[3, 4]: Lu Ban[5, 6]: Colin Crooks[3, 5]: Timothy Card[3, 5]: Peter Jepsen[1, 2, 3]: Joe West[3, 5]

1. *Department of Hepatology and Gastroenterology, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, 8200 Aarhus N, Denmark.; Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Allé 43-45, 8200 Aarhus N, Denmark.*
2. *Division of Epidemiology and Public Health, School of Medicine, University of Nottingham, Nottingham NG7 2UH, United Kingdom.*
3. *School of Medicine and Dentistry, University of Central Lancashire, Preston, Lancashire PR1 2HE, United Kingdom.*
4. *National Institute for Health Research (NIHR) Nottingham Biomedical Research Centre, the Nottingham University Hospitals NHS Trust and University of Nottingham, Nottingham NG7 2UH, United Kingdom.*
5. *Nottingham Digestive Diseases Centre, School of Medicine, University of Nottingham, Nottingham, NG7 2UK, United Kingdom*

Background and Aims: It is assumed that autoimmune hepatitis (AIH) develops as a result of a complex interplay between genetic predisposition and exposure to unknown risk factors. Smoking is a known risk factor for some autoimmune diseases, but the association with AIH has never been evaluated. We conducted a population-based matched case-control study to examine the association between cigarette smoking and the risk of AIH in England.
Methods: From the Clinical Practice Research Datalink, 2005-2017, we included 987 cases diagnosed with AIH after age 18 years and up to 10 frequency-matched population controls per case. We defined 'ever-smokers' as patients recorded with indicators of current or previous cigarette smoking and 'never-smokers' as patients recorded as non-smokers. We used multiple logistic regression to estimate the odds ratio of AIH in 'ever-smokers' versus 'never-smokers', adjusting for sex, age, general practice, calendar time of registration with the general practice, and socioeconomic status.
Results: The cases with AIH had a median age of 60 years (Interquartile Range 47-71), and 78% were women. The cases were more likely to be ever-smokers than the controls (44% versus 37%). The 'ever-smokers' had an increased risk of AIH compared with the 'never-smokers' (adjusted odds

ratio = 1.20, 95% confidence interval 1.03-1.40). The association between AIH and smoking was the same across all layers of socioeconomic status.
Conclusion: A current or previous history of smoking was associated with an increased risk of having an AIH diagnosis. Interventions to stop cigarette smoking could potentially help preventing AIH in the future.

16)

Alanine-aminotransferase and 20-year risk of major chronic diseases and death in a healthy cohort aged 30 to 49 years

Morten Daniel Jensen[1], Torsten Lauritzen[2], Hendrik Vilstrup[1], Henrik Toft Sørensen[3], Peter Jepsen[1,3]
1. *Department of Hepatology and Gastroenterology, Aarhus University Hospital, Aarhus, Denmark*
2. *University of Aarhus, Department of Public Health, Research group for General Practice, Aarhus, Denmark*
3. *Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark*

Background and Aims: Alanine-aminotransferase (ALT) is the most frequently used marker of liver cell injury. We examined the association between ALT levels and long-term absolute risks of morbidity and mortality in healthy Danish people aged 30-49 years.
Methods: We divided 671 healthy participants from the Ebeltoft Health Promotion Project into four categories based on their baseline ALT values: low (≤10U/l), medium-low (men: 11–34U/l, women: 11–22U/l), medium-high (men: 35–69U/l, women: 23–44U/l) and high (men: ≥70U/l, women: ≥45U/l), and followed them through Danish healthcare registries for up to 20 years. We examined mortality and absolute risks of liver disease, overall cancer, ischemic heart disease, and diabetes.
Results: The risk of any cancer was highest for participants with 'low ALT' or 'high ALT' (20-year risk: 17.2% [95% confidence interval (CI): 6.3%-32.7%] and 18.2% [95% CI: 5.7%-36.3%], respectively). The risk of diabetes was highest for 'medium-high ALT' or 'high ALT' participants (20-year risk: 12.1% [95% CI: 7.3%-18.3%] and 9.1% [95% CI: 1.6%-25.1%], respectively). The 'high ALT' participants had the highest 20-year risk of liver disease (20-year risk: 13.6% [95% CI: 3.4%-30.9%], while it was 1.0% or less for all others). The chance of being alive after 20 years without having been diagnosed with liver disease, cancer, ischemic heart disease, or diabetes was lowest in the 'high ALT' group (50% [95% CI: 28%-68%]) and 72%-79% in the other groups.
Conclusions: Our findings suggest that persons with high or abnormally low ALT measurements are at increased long-term risk of several chronic diseases.

17)

Administration and monitoring of biologic therapy in patients with inflammatory bowel disease – A national Danish survey

Sabina Volmar[a], Signe Wildt[a,b], Lars Kristian Munck[a,b]
[a]Section of Gastroenterology, Department of Internal Medicine, Zealand University Hospital Køge, DK-4600 Køge, Denmark; [b]Department of Clinical Medicine, University of Copenhagen, Blegdamsvej 3B, 2200 Copenhagen, Denmark

Objective: There are no national guidelines on administration and monitoring of biologic therapy to patients with inflammatory bowel disease (IBD). We investigated the organization, administration and monitoring of immunosuppressive treatment of IBD patients in Denmark and relate this to the published evidence.

Material and method: A online survey was send to all outpatient clinics administering biologic treatment to IBD patients in Denmark focusing on infusion time, observation and biochemical control of treatment with biologic drugs, methotrexate and thiopurines. A systematic literature search was performed.
Results: 21 of 23 clinics completed the survey. Infliximab infusion time was reduced to 30 minutes in 60 % of the clinics starting from the 4^{th} to 11^{th} infusion while it was 30 min from start of vedolizumab. The majority of clinics discharged patients immediately after injection of biologic therapy. Observation time after intravenously administered biologics varied considerably. The majority performed biochemical control before every infusion with vedolizumab and infliximab, every second to third month with ustekinumab, golimumab and adalimumab, and every third month with thiopurines and methotrexate. Only six clinics screened for infectious diseases before initiating treatment with thiopurines and methotrexate. The systematic literature search identified 27 relevant articles. These showed that infliximab infusion time of 30 minutes is safe and questioned the necessity of post infusion observation.
Conclusions: Infusion time, post infusion observation, and monitoring varied considerably between centers. national guideline on administration and monitoring of immunosuppressive therapy to patients with IBD is warranted and in some outpatient clinics liberate staff and patient resources.

18)

Biodistrubtion and radiation dosimetry of [^{64}Cu]copper dichloride PET by intravenous and oral administration in healthy humans.

Kristoffer Kjærgaard[1,2], Thomas Sandahl[1], Kim Frisch[2], Susanne Keiding[1,2], Hendrik Vilstrup[1], Peter Ott[1], Lars Christian Gormsen[2], Ole Lajord Munk[2].
[1]Department of Hepatology and Gastroenterology, Aarhus University Hospital, Aarhus, Denmark; [2]Department of Nuclear Medicine & PET-Centre, Aarhus University Hospital, Aarhus, Denmark.

Background & Aim: Copper is absorbed through the diet, deposited in the liver and excreted into bile, while disturbances in copper homeostasis can lead to critical illness, involving the liver and brain. $^{64}CuCl_2$ computed positron emission tomography (PET/CT) is a potential method to study copper metabolism in humans. We determined the hepatic handling, biodistribution and radiation dosimetry of $^{64}CuCl_2$ after intravenous and oral administration in healthy humans using PET/CT.
Methods: In six healthy participants, $^{64}CuCl_2$ was administered intravenously or orally (intravenous/oral: 4/2), immediately followed by a dynamic PET scan of 90 minutes and three consecutive whole body PET/CT scans performed at 1.5, 6 and 20 hours. Organs accumulating $^{64}CuCl_2$ were identified as source organs on the fused PET/CT data and used to estimate absorbed and effective radiation doses.
Results: For intravenously administered $^{64}CuCl_2$, uptake was highest in the liver, intestinal walls and kidneys. For oral administration, $^{64}CuCl_2$ was present primarily in the liver and in the gastrointestinal tract. Hepatic uptake was at maximum after 6 hours for both administration forms with 46% and 34% of administered dose, respectively, and excretion to the gallbladder was insignificant. For intravenous and oral administration respectively, the most critical organs were the liver and right lower intestine (mean 448.0 and 738.5 µGy/MBq), while the mean effective doses were 61.9 and 110.5 µSv/MBq.
Conclusion: $^{64}CuCl_2$ is primarily taken up by the liver and is rapidly absorbed from the gastrointestinal tract when swallowed. Oral administration of $^{64}CuCl_2$ was associated with the highest effective radiation dose because of widespread radiation exposure to the intestines.

19)

High incidence and infrequent evaluation of osteoporosis among patients with inflammatory bowel disease; 10 years of follow-up in a Danish population-based inception cohort

Lo B[1], Holm JP[3], Vester-Andersen MK[1,2], Bendtsen F[1], Vind I[1], Burisch J[1]

[1]*Gastrounit, Medical Division, Copenhagen University Hospital Hvidovre, Hvidovre, Denmark*

[2]*Medical Department, Zealand University Hospital, Koege, Denmark*

[3]*Deparment of Endocrinology, Copenhagen University Hospital Herlev, Herlev, Denmark*

Background: Patients with Crohn's disease (CD) and ulcerative colitis (UC) are at risk of developing metabolic bone disease. The aims of the present study were to investigate the screening strategy, incidence and risk factors of osteoporosis in a well-defined prospective population-based inception cohort.

Method: Between 2003 and 2004 all incident patients diagnosed with CD and UC in a well-defined Copenhagen area were included and followed until 2015. Data were compared with a control population (1:20). Regression models were performed with several covariates.

Results: A total of 513 patients with IBD were included (213 CD, 300 UC). Overall, 338 (66%, CD: 164 [77%], UC: 174 [58%], $p<0.001$) patients received ≥ 500 mg steroids within a year, resulting in 781 patient years at risk of osteoporosis. Of those, only 83 (10.6%) patient years were followed by a Dual-energy X-ray absorptiometry scan within the same or the following 2 years.

Overall, 73 (14.2%) IBD patients (CD: 31 [14.6%], UC: 42 [14%]) and 680 (6.6%, $p<0.001$) controls were diagnosed with osteoporosis during follow-up. The risk of osteoporosis was increased compared to the control population (OR: CD: 2.9 [CI95%: 2.0-4.1], UC: 2.8 [2.1-3.9]).

Conclusion: In this population-based inception cohort the incidence of osteoporosis is significant higher compared to a control population. Follow-up with measurement of bone mass density is limited, especially in patient at high-risk of developing osteoporosis. These results demonstrate the need of increased focus regarding osteoporosis and osteoporotic complications in CD and UC patients among gastroenterologists.

20)

The gut microbiota is not affected by twelve weeks of muscle-strengthening resistance training in patients with cirrhosis

Luise Aamann[1]; Gitte Dam[1]; Hendrik Vilstrup[1]; Niels Kristian Aagaard[1].

1) Department of Hepatology and Gastroenterology, Aarhus University Hospital.

Background and Aims: Physical activity modulates the gut microbiota composition and stimulates a health-promoting effect in healthy individuals and in patients with chronic diseases e.g. diabetes. In cirrhosis, changes of the gut microbiota affect disease severity and complications, including higher relative abundance of gram-negative proteobacteria. We examined if 12 weeks of resistance training could alter the microbiota in cirrhotic patients.

Method: 39 patients with cirrhosis Child Pugh A/B were randomized 1:1 to either an exercising group performing 12 weeks of progressive resistance training three times per week or a non-exercising control group. Diet was protein-rich Northern European. Stool samples were collected at week 0 and 12 using 16S rRNA sequencing. Microbial taxa at the family level were studied between and within groups at baseline and study-end.

Results: Resistance training increased muscle strength. Diet, use of antibiotics and hepatic encephalopathy treatment were equal among groups (17 exercisers and 14 controls). There were no changes in Shannon diversity or UniFrac between groups at baseline and study-end.

Two exercisers did not improve their muscle strength. These patients had a higher relative abundance of Proteobacteria compared to those who improved muscle strength. Interestingly, Proteobacteria were higher in these patients at baseline as well.
Conclusion: Although based on a secondary randomized clinical trial outcome, our findings lend no support to the hypothesis that physical activity affect gut microbiota.
Yet, the microbiota may affect the results of resistance training and exercise-improved muscle strength may be associated with lower Proteobacteria constituents at baseline and study-end.

21)

Decreasing incidence of alcoholic liver disease in Denmark: a nationwide study

Frederik Kraglund a, Thomas Deleuran a, b, Gro Askgaard c, Peter Jepsen a, d
a Department of Hepatology and Gastroenterology, Aarhus University Hospital, Aarhus, Denmark; b Department of Medicine, Randers Regional Hospital, Randers, Denmark; c Department of Internal Medicine, Zealand University Hospital, Køge, Denmark; d Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark

Background and aims: Alcohol exposure has decreased in Denmark since 1994. We undertook this study to describe the recent developments in the national epidemiology of alcoholic liver disease.
Methods: We identified all Danish patients with a first-time diagnosis of alcoholic cirrhosis, hepatitis, steatosis or unspecified liver disease from 1977-2017. We computed standardised incidence rates, prevalence, hospitalisation rates, and survival for the period 1994–2017 by age and gender. Moreover, we computed incidence rates by 5-year birth cohorts (1950-1979). We used publicly available data to contrast our findings to per capita alcohol consumption.
Results: The overall standardized incidence rate of alcoholic liver diseasewas stable until 2009 but decreased from 362 (95% CI: 346-378) to 258 (95% CI: 245-271) per 1,000,000 population per year from 2009 to 2017. This decrease was most pronounced in men aged 15-44 and women aged 45-64. The 1950-1959 birth cohorts had the highest age-specific incidence rates, and the rates decreased sequentially with each following birth cohort. Both prevalence of alcoholic liver disease (0.22%) and hospitalisation rate of patients with alcoholic liver disease (0.4 per patient per year) was stable from 2012 onwards. The 5-year survival after first-time diagnosis for alcoholic liver diseasewas 44.9% (95% CI: 44.3-45.4%) for men and 51.8% (95% CI: 51.1-52.6%) for women.
Conclusions: Incidence of alcoholic liver disease has decreased since 2009 in Denmark, mainly caused bya lower incidence rate in the population born after 1960.Yet, the prevalence of alcoholic liver disease is unchanged, and the overall survival is poor.

22)

Prevalence of non-alcoholic steatohepatitis (NASH) and liver fibrosis in a Danish obese cohort before and 12 months after surgically induced weight loss

Julie Steen Pedersen[1], Marte Opseth Rygg[1], Astrid Bruun Boilesen[2], Maria Franzmann[4], Reza Serizawa[4], Beth Hærsted Olsen[3], Sten Madsbad, Lise Lotte Gluud[1], Flemming Bendtsen[1]
[1] Gastrounit, Medical Division, Copenhagen University Hospital Hvidovre; [2] Gastrounit, Surgical Division, Copenhagen University Hospital Hvidovre; [3] Center for Functional and Diagnostic Imaging, Ultrasound Section, Copenhagen University Hospital Hvidovre; [4] Department of Pathology, Copenhagen University Hospital Hvidovre

Background: In morbidly obese patients (BMI>40 kg/m^2) the prevalence of fatty liver has previously been estimated to be as high as 90 %. Reportedly, half of these patients have NASH and various degrees of liver fibrosis. However, data are sparse in Danish obese patients.
Methods: 65 patients were prospectively enrolled and underwent laparoscopic Roux-en-Y gastric bypass or sleeve gastrectomy. During surgery a baseline wedge liver biopsy was sampled. Till date 25 patients with NAFLD Activity Score (NAS) ≥3 and/or liver fibrosis ≥ 1 have participated in a follow-up protocol involving TRU-cut liver biopsy 12 months after surgery. All samples underwent histopathological assessment using the NAFLD Activity score (NAS) and Kleiner fibrosis score.
Results: At baseline (n=65) mean (SD) age was 42 years (8,6) and mean BMI was 42 kg/m^2 (9,2). ALT, AST and GGT were all within normal range. Mean NAS was 4,0 (1,3) and mean fibrosis score was 1,42 (. 26 patients (40,1%) had a diagnosis of 'definite NASH' and 60 patients (92,3 %) had liver fibrosis grade of 1 or above.
12 months after surgery (n=25) both NAS and fibrosis score were significantly reduced compared to baseline in this group. NAS: 3,8 vs 2,2 (p= 0,000). Fibrosis: 1,4 vs 0,8 (p=0,018).
Conclusion: Despite normal liver biochemistry prevalence of NASH and liver fibrosis is high and similar to the globally reported prevalence in this patient group. Weight loss is associated with a significant decrease in NASH and fibrosis prevalence and cements the importance of weight loss in treatment of NAFLD.

23)

Casein glycomacropeptide is well tolerated in healthy adults and changes neither gut microbiota nor fecal butyrate: a randomized trial

Pernille G Wernlund,1,2 Christian L Hvas,1 Jens F Dahlerup,1 Martin I Bahl,3 Tine R Licht,3 Knud Erik B Knudsen,4 and Jørgen S Agnholt,1
1 Department of Hepatology and Gastroenterology, Aarhus University Hospital, Aarhus, Denmark; 2 Department of Clinical Medicine, Aarhus University, Aarhus, Denmark; 3 National Food Institute, Technical University of Denmark, Denmark; 4 Department of Animal Science, Aarhus University, Tjele, Denmark

Background: Casein glycomacropeptide (CGMP) is a bioactive milk-derived peptide with potential anti-inflammatory effects. Its effects on intestinal microbiota and metabolites are unknown.
Objective: The objective was to assess both the intestinal and systemic immunomodulatory effects of orally ingested CGMP in healthy adults as well as the participants' intestinal symptoms and overall well-being.
Design: In a single-center randomized, double-blinded, placebo-controlled study, we compared the effects of a four-week intervention of either 25 grams of oral powder-based chocolateflavored CGMP or placebo. Placebo consists of skimmed milk powder and flavoring.
Results: We included 24 healthy adults who all completed the study. CGMP had no systemic or intestinal immunomodulatory effects compared with placebo, either with regard to C-reactive protein, fecal calprotectin level, fecal microbiota composition or fecal short-chain fatty acid content. CGMP ingestion did not affect satiety or body weight, and it caused no severe adverse events. The palatability of CGMP was acceptable and adherence was high. CGMP did not induce or change gastrointestinal symptoms.
Conclusions: In healthy adults, oral ingestion of 25 grams of CGMP during four weeks was safe, well tolerated, had acceptable palatability, and was without any effects on body weight. We found no immunomodulatory effects of CGMP in healthy adults.

24)

Long-term follow up in patients with walled-off pancreatic necrosis treated with endoscopic transmural drainage and necrosectomy

Andreas Bartholdy, Amer Hadi, Mikkel Werge, Anders Borch, Camilla Nøjgaard, Palle Nordblad Schmidt, Erik Feldager, Lise Lotte Gluud, Srdan Novovic

Department of Gastroenterology and Gastrointestinal Surgery, Medical division, Hvidovre Hospital, Hvidovre, Denmark

Objectives: Although endoscopy is a cornerstone in treatment of walled-off pancreatic necrosis (WON), long term outcomes are unclear. We performed a retrospective cohort study of patients with WON treated with transgastric drainage and necrosectomy (ETDN) in a tertiary referral center.

Methods: From 2010 to 2018, 215 patients with WON underwent ETDN in our center. Patients with index EDTN more than 90 days from onset of AP, chronic pancreatitis, death during admission or follow-up were excluded from main analysis. Main outcomes were development of exocrine and endocrine insufficiency (defined as enzyme replacement therapy and antidiabetic use respectively), use of analgesics and need for endoscopic therapy on main pancreatic duct (MPD) during follow-up. Median follow-up time was 4.3 years.

Results: We included 125 patients. During follow-up, 22 (18%) patients developed exocrine insufficiency,33 (27%) developed endocrine insufficiency, 11 patients (8%) needed potent opioids and 10 patients needed mild opioids.

Endoscopic therapy on MPD predicted development of exocrine insufficiency in multivariate analysis (OR 6.20; 95% CI, 2.54-15.10; p<0.001). CTSI (OR 1.61; 95% CI, 1.24-2.09; p<0.001) and modified CTSI (OR 1.52; 95% CI, 1.14-2.02; p=0.004) predicted development of endocrine insufficiency in multivariate analysis.

Conclusion: With a median follow-up of 4.3 years and a sizable number of patients, this study provides robust data on long-term outcome of patients with WON treated with ETDN. The proportion of patients with endo- or exocrine insufficiency was small, as was the proportion with opioid requiring pain. Our results support current recommendations of ETDN being the treatment of choice for WON.

25)

Increased cardiac and hepatic extracellular volume reflect augmented collagen metabolism and inflammation in liver cirrhosis

Signe Wiese[1, 2], Andrei Voiosu[1,3], Jens D. Hove[4], Karen V. Danielsen[1, 2],
Henning Grønbæk[5], Holger Jon Møller[6], Federica Genovese[7], Alexander Lynge Reese-Petersen[7],
Rajeshwar P. Mookerjee[8], Jens Otto Clemmesen[9], Jens Peter Gøtze[10], Ove Andersen[11],
Flemming Bendtsen[2], Søren Møller[1]

[1] Department of Clinical Physiology and Nuclear Medicine, Hvidovre Hospital, Denmark.; [2] Gastro Unit, Medical division, Hvidovre Hospital, Denmark.; [3] Gastroenterology and Hepatology Department, Colentina Clinical Hospital, Romania. ; [4] Department of Cardiology, Hvidovre Hospital, Denmark.;[5] Department of Hepatology and Gastroenterology, Aarhus University Hospital, Denmark.

[6] Department of Clinical Biochemistry, Aarhus University Hospital, Denmark. [7] Nordic Bioscience Biomarkers & Research A/S, Herlev, Denmark. [8] Liver Failure Group, UCL Institute for Liver and Digestive Health, Royal Free Hospital, United Kingdom; [9] Department of Hepatology, Rigshospitalet, Denmark; [10] Department of Clinical Biochemistry, Rigshospitalet, Denmark; [11] Clinical Research Centre, Hvidovre Hospital, Denmark.

Background & aims: Fibrotic remodeling of the extracellular matrix and ongoing low-grade inflammation contribute to the development and progression of liver cirrhosis. The same processes seem to underlie cardiac dysfunction in cirrhosis. We investigated the relation between myocardial and hepatic extracellular volume (ECV) in cirrhotic patients and the role of collagen turnover and systemic inflammation.
Methods: We prospectively included 52 cirrhotic patients and 14 healthy controls. All patients underwent contrast-enhanced MRI with T1-mapping and quantification of myocardial and hepatic ECV, biochemical assessments of collagen turnover (PRO-C3, PRO-C5, PRO-C6, C4M, C5M, LG1M), macrophage activation (sCD163, sMR) and inflammation (TNFα, IL-1β, IL-6, IL-8, IL-18, SDF1α).
Results: Myocardial and hepatic and ECV were increased in patients compared with healthy controls (myocardial ECV 31.2±5.5% vs. 27.4±2.9%, p=0.037; hepatic ECV 44.1±9.6% vs. 33.7±6.7%, p<0.001). Myocardial ECV correlated with collagen and inflammatory biomarkers: PRO-C6 (r=0.40, p=0.004), PRO-C3 (r=0.43, p=0.002), IL-6 (r=0.46, p=0.001), sMR (r=0.43, p=0.002), sCD163 (r=0.34, p=0.014). Hepatic ECV correlated with myocardial ECV (r=0.48, p=0.001) and collagen biomarkers: PRO-C3 (r=0.62, p<0.001), PRO-C6 (r=0.52, p<0.001) and inflammatory biomarkers: SDF1α (r=0.54, p<0.001), IL-6 (r=0.46, p<0.001), sMR (r=0.43, p=0.002). In a multivariate analysis, hepatic ECV was predicted by PRO-C3 and PRO-C6, whereas PRO-C6, IL-6 and sMR were the strongest predictors of myocardial ECV.
Conclusions: Myocardial ECV and hepatic ECV are significantly increased and closely interrelated in cirrhotic patients. They also strongly correlate with biomarkers of collagen formation, macrophage activation and inflammation thus supporting the role of inflammation and fibrogenesis in the development of cirrhosis towards multi-organ failure.

26)

No clear evidence of a disrupted liver-alpha cell axis in patients with NASH and fibrosis

Marte Opseth Rygg1, Julie Steen Pedersen1, Nicolai J. Wewer Albrechtsen2,3, Lise Lotte Gluud1 and Flemming Bendtsen1
1 Gastrounit, Medical Division, Copenhagen University Hospital Hvidovre, DK-2650 Hvidovre, Denmark. 2 Department of Clinical Biochemistry, Copenhagen University Hospital Rigshospitalet, DK-2100 Copenhagen, Denmark.; 3 Novo Nordisk Foundation Center for Protein Research, Faculty of Health and Medical; Sciences, University of Copenhagen, DK-2200 Copenhagen, Denmark.

Background: Emerging data indicate that the recently described liver-alpha cell axis is disrupted in patients with nonalcoholic fatty liver disease (NAFLD). Glucagon regulates hepatic amino acid (AA) metabolism by stimulating ureagenesis. Hepatic steatosis has been hypothesized to impair glucagon's action on hepatic AA turnover leading to increased plasma amino acids (PAA), which in feedback manner stimulates the secretion of glucagon. However, these data are obtained in patients with mild NAFLD. It is not known if and to what degree nonalcoholic steatohepatitis (NASH) and fibrosis affect the liver-alpha cell axis. Consequently, we evaluated PAA and glucagon in patients with NAFLD with and without NASH and hypothesized that NASH patients would have increased concentrations of PAA and glucagon compared to 'non-NASH' patients.
Methods: We quantified total PAA and plasma glucagon concentrations in 46 prospectively enrolled obese patients undergoing Roux-en-Y gastric bypass or sleeve gastrectomy. During surgery a wedge liver biopsy was obtained. Histopathological evaluation of NASH was

assessed using the NAFLD Activity Score (NAS). NAS≥5 was considered NASH. Fibrosis grade≥2 was considered significant fibrosis.
Results: Median PAA concentration was increased in patients with NASH (n=18) versus 'non-NASH' (n=28) (1888; IQR 1762-2246 versus 1766; IQR 1497-1908 μmol/L, P=0.024). Glucagon concentration did not differ between the groups (P=0.38). PAA and glucagon were similar in patients with mild (n=24) and significant (n=22) fibrosis.
Conclusion: Our study found no clear evidence that the liver-alpha cell axis is more disrupted in patients with NASH and/or significant fibrosis when compared to 'non-NASH' and/or mild fibrosis patients.

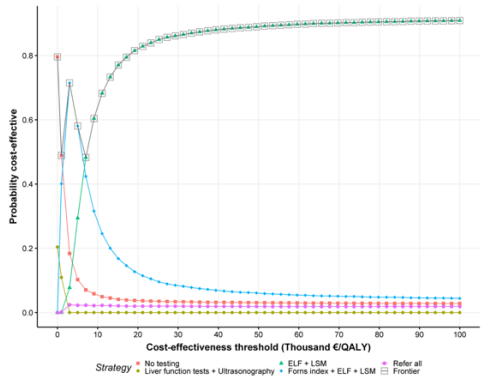
27)

Serial testing with the enhanced liver fibrosis test and liver stiffness is cost-effective for detection of advanced alcoholic liver fibrosis in primary care

Maja Thiele[1,2], Lars Asphaug[3], Aleksander Krag[1,2], Hans Olav Melberg[3]
1: Center for Leverforskning, Afdeling S, Odense Universitetshospital, Odense, Danmark; 2: Klinisk Institut, Syddansk Universitet, Odense, Danmark; 3: Institut for Sundhed og Samfund, Oslo Universitet, Oslo, Norge

Background: Alcoholic liver fibrosis is a preventable disease that is largely asymptomatic until decompensated cirrhosis. Primary care based screening of individuals with excessive alcohol consumption could reveal those with progression to advanced fibrosis earlier. We therefore aimed to evaluate the cost-effectiveness of screening for advanced fibrosis.
Method: We evaluated three strategies: 1) standard-of-care using routine liver function tests applied in parallel with follow-up ultrasonography for test-positives, 2) the enhanced liver fibrosis (ELF) test, with follow-up liver stiffness measurement (LSM) for positives above 10.5, and 3) three-tier strategy using the indirect marker Forns Index to control before strategy two. We compared the screening strategies to no testing, and FibroScan for all. We used a decision model of linked decision trees and Markov state-transition models. The primary outcomes were lifetime quality-adjusted life-years (QALYs) and direct health care costs.
Results: The optimal screening strategy was ELF test and LSM follow-up, which correctly identified the true disease status of 97.9%. At an incremental cost-effectiveness ratio of €5,707 per QALY gained, the strategy had an 80% chance of being cost-effective. This result was robust to probabilistic sensitivity analysis. The Forns-index followed by ELF and LSM had the best positive predictive value and the lowest incremental cost-effectiveness ratio (€1,005 per QALY gained), but a lower negative predictive value and resulted in worse patient outcomes over the lifetime according to our model. The strategy of referring all to LSM had the best negative predicted value, but lower effectiveness and higher costs. Standard-of-care had lower effectiveness and higher incremental cost-effectiveness ratio.
Conclusion: Primary care based screening for advanced alcoholic fibrosis is likely a cost-effective intervention. The optimal strategy was serial testing with the ELF test, followed by liver stiffness measurement if positives, while the cheapest strategy included adding Forns test first in the sequence.

Figure:



28)

The macrophage activation marker soluble CD163 is elevated and associated with liver disease phenotype in patients with Wilson's disease

E. Glavind[1]; D.N. Gotthardt[2], J. Pfeiffenberger[2], T.D. Sandahl[1], T. Bashlekova[2], G.L. Willemoe[3], J.P. Hasselby[3] K-H. Weiss[2], H.J. Møller[4], H. Vilstrup[1], W.M. Lee[5], M. Schilsky[6], P. Ott[1], H. Grønbæk[1]

[1] Department of Hepatology and Gastroenterology, Aarhus University Hospital, Aarhus, Denmark. [2] Department of Internal Medicine IV, University Hospital Heidelberg, Heidelberg, Germany.; [3] Department of Pathology, Rigshospitalet, Copenhagen, Denmark.; [4] Department of Clinical Biochemistry, Aarhus University Hospital, Aarhus, Denmark. [5]Division of Digestive and Liver Diseases, UT Southwestern Medical Center at Dallas, Dallas, TX, United States. [6] Yale University Medical Center, New Haven CT 06520, USA.

Background: Macrophages play a significant role in liver disease development and progression. The macrophage activation marker soluble (s)CD163 is associated with disease severity and prognosis in patients with acute and chronic liver diseases. We investigated sCD163 levels in patients with acute and chronic Wilson's disease (WD) and hypothesized associations with liver disease phenotype and biochemical markers of liver injury.

Methods: We investigated sCD163 in two independent cohorts of WD patients: 28 patients with fulminant presentations from the US Acute Liver Failure (ALF) Study Group registry and 147 patients with chronic disease from a German WD registry. We included a control group of 19 healthy individuals. Serum sCD163 levels were measured by ELISA.

Results: In the ALF cohort, median sCD163 was 10-fold higher than in healthy controls (14.6(2.5-30.9) vs. 1.5(1.0-2.7) mg/L, $p<0.001$). In the chronic cohort, median sCD163 was 2.6(0.9-24.9) mg/L and higher in patients with cirrhosis than in those without cirrhosis (3.0(1.2-24.9) vs. 2.3(0.9-8.0) mg/L, $p<0.001$), both cohorts significantly lower than the ALF patients. Further, sCD163 correlated positively with ALT, AST, GGT and INR (rho=0.27-0.53); and negatively with albumin (rho=-0.37), ($p\leq0.001$, all). We observed immunohistochemical CD163 expression in liver tissue from ALF patients.

Conclusion: sCD163 was elevated in WD patients, especially in those with ALF. Further, sCD163 was higher in patients with cirrhosis compared to patients without cirrhosis and associated with biochemical markers of liver injury and hepatocellular function. Thus, macrophage activation is evident in WD and associates with liver disease phenotype and biochemical parameters of liver disease severity.

29)

Seven weeks high-dose vitamin D treatment in Crohn's disease reduces the need for intensified infliximab treatment during 52 weeks follow up.

Mia Bendix1*, Anders Dige1, Søren Peter Jørgensen1, Jens Frederik Dahlerup1, Bo Martin Bibby3, Bent Deleuran2,4 and Jørgen Agnholt1.

1Department of Hepatology and Gastroenterology, Aarhus University Hospital, Aarhus, Denmark.; 2Department of Rheumatology, Aarhus University Hospital, Aarhus, Denmark. 3Department of Public Health - Department of Biostatistics, Aarhus University, Aarhus, Denmark.; 4Department of Biomedicine, Aarhus University, Denmark.

Introduction: Seven weeks of high-dose vitamin D treatment to Crohn's disease (CD) patients with active disease reduces calprotectin and CRP levels at 15 and 23 weeks follow up.

Aims & methods: To investigate if seven weeks of vitamin D treatment affect the disease activity at 52 weeks follow up.

Forty CD patients were randomised into four arms: 1) infliximab+vitamin D; 2) infliximab+placebo vitamin D; 3) placebo infliximab+vitamin D; and 4) placebo infliximab+placebo vitamin D. Infliximab or placebo-infliximab was administered at weeks 0, 2 and 6. Vitamin-D or placebo-vitamin-D was administered as a 5mg bolus week 0 followed by 0.5mg/day for 7 weeks. Afterwards patients received infliximab every 8 weeks. Infliximab intervals where shortened to every 6 or 4 weeks in patients with disease activity. CRP and calprotectin were measured at weeks 15, 23, 31 and 52. Results are reported for Group D+ (1+3) and Group D- (2+4).

Results: Post-vitamin D (weeks 15-52) median calprotectin levels decreased in weeks 15 and 23 in group D+ compared to group D- (p <0.02) but at weeks 31 and 52 group D- had reduced calprotectin levels comparable to group D+. However, 46% of D- patients needed intensified infliximab treatment, initiated within weeks 23 to 31, compared to 23 % of D+ patients (p = 0.05). During follow up, group D+ had 2.2 times lower median CRP levels compared with D- (p = 0.02).

Conclusion: High-dose vitamin D combined with infliximab was associated with improved long-term anti-inflammatory effects and reduced the need for infliximab intensification.

30)

QT interval is not associated with mortality in patients with cirrhosis and ascites

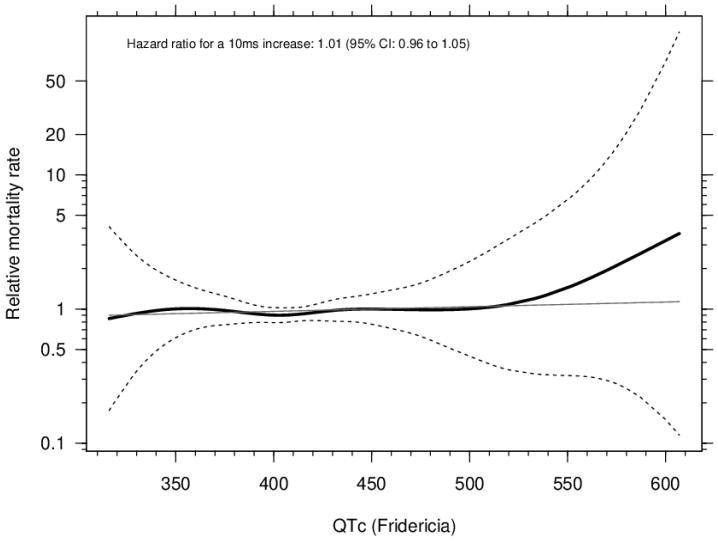
Konstantin Kazankov[1], Henrik Kjærulf Jensen[2,3], Hugh Watson[4,5], Hendrik Vilstrup[1], Mauro Bernardi[6], Peter Jepsen[1,7]

1) Department of Hepatology and Gastroenterology, Aarhus University Hospital, Aarhus, Denmark;
2) Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark
3) Department of Clinical Medicine, Health, Aarhus University, Denmark
4) Evotec ID, Lyon, France
5) Department of Clinical Pharmacology, Aarhus University Hospital, Aarhus, Denmark
6) Alma Mater Studiorum, University of Bologna, Bologna, Italy
7) Department of Clinical Epidemiology, Aarhus, Denmark

Background and Aims: Prolonged QT interval is frequent in cirrhosis. An association between QT and clinical outcomes has been reported, but the results of the published studies are conflicting, and the significance of QT interval in cirrhosis remains unclear.

Method: We examined the association between QT interval and mortality in a large cohort of well-classified patients with cirrhosis and ascites included in three randomized 1-year trials of satavaptan. All patients in the trials had their QT interval measured at the time of inclusion and regularly during the follow-up, corrected for heart rate (QTc) using the Fridericia formula. According to the design of the original study, patients with prolonged QTc (>480 ms) were excluded. We also excluded patients who were using nonselective beta-blockers or quinolone antibiotics. We used Cox regression to examine the association between QTc and mortality hazard rate, controlling for gender, age, sodium, albumin, bilirubin, creatinine, INR, refractory ascites (yes/no), hospitalization (yes/no), history of variceal bleeding, history of spontaneous bacterial peritonitis, history of HCC, and cirrhosis etiology. We used splines to illustrate the nature of the association between QTc and mortality hazard rate.
Results: In the present study, 915 patients were included, and 220 died during the follow-up. We found no association between QTc interval and mortality (mortality hazard ratio for a 10 ms increase in QTc = 1.01 [95% CI: 0.96 – 1.05]).
Conclusion: In this study, which excluded patients with a QTc interval > 480ms, QTc interval was not associated with mortality among patients with cirrhosis and ascites.

Figure 1. Association between QTc and mortality hazard rate relative to patients with a QTc of 450ms. The flexible spline (black line) shows the association between QTc and mortality rate across the range of observed QTc values, with a 95% confidence interval (dashed lines). The spline does not depart very far from the straight line representing the 1.01-fold increase per 10ms increase in QTc (grey line). The increase in relative mortality rate at high QTc values is based on very few observations of patients who developed high QTc values during the follow-up.



31)

Macrophage activation marker soluble CD163 is associated with improvement in liver injury and hepatic insulin sensitivity in obese patients following bariatric surgery

Konstantin Kazankov[1], Kirstine Nyvold Bojsen-Møller [2,3], Holger Jon Møller[4], Sten Madsbad[2,3], Henning Grønbæk[1]

1) Department of Hepatology and Gastroenterology, Aarhus University Hospital, Aarhus, Denmark
2) Department of Endocrinology, Copenhagen University Hospital Hvidovre, Hvidovre, Denmark
3) Novo Nordisk Foundation Center for Basic Metabolic Research, University of Copenhagen, Copenhagen, Denmark
4) Department of Clinical Biochemistry, Aarhus University Hospital, Aarhus, Denmark

Background and Aims: Macrophages are important in obesity, insulin resistance and non-alcoholic fatty liver disease (NAFLD). Bariatric surgery induces major weight loss and drastically improves insulin resistance and the metabolic profile. We aimed to investigate macrophage activation using the macrophage activation marker soluble (s)CD163 in terms of the effects of bariatric surgery.
Methods: In a previously published study, ten glucose-tolerant and ten type 2 diabetic obese patients undergoing Roux-en-Y gastric bypass (RYGB) were included. A comprehensive metabolic workup was performed, including estimation of hepatic insulin sensitivity, as well as liver function tests. We now measured sCD163 using an in-house ELISA assay in these patients.
Results: Patients with diabetes had numerically higher baseline sCD163 compared with glucose-tolerant subjects (2.7±1.2 vs. 2.2±0.5 mg/L, p=0.2). Baseline sCD163 correlated with ALT (r=0.58, p=0.007) and tended to an inverse association with hepatic insulin sensitivity (r= -0.38, p=0.1). Following RYGB, sCD163 decreased in both groups, but more consistently in diabetics (p=0.04). The decrease in sCD163 after 3 months post-RYGB was associated with the corresponding decrease in ALT (r=0.46, p=0.03) and improvement in hepatic insulin sensitivity (r= -0.65, p=0.01). Whereas the further decrease in sCD163 from 3 to 12 months post-RYGB was associated with the change in ALAT (r= 0.41, p=0.09), it was not associated with the change in hepatic insulin sensitivity (p=0.36).
Conclusion: Macrophage activation assessed by sCD163 is associated with liver damage and with hepatic insulin resistance in obese patients, and improvement in these measures especially during the first three months following bariatric surgery.

32)

Postprandial changes in the hepatic bile acid transport in healthy human subjects measured by ^{11}C-CSar PET/CT

Nikolaj Worm Ørntoft[1], Peter Ott[1], Ole Lajord Munk[2], Susanne Keiding[1,2], Lars Christian Gormsen[2], Michael Sørensen[1].
[1]Dept. of Hepatology & Gastroenterology, Aarhus University Hospital; [2]Dept. of Nuclear Medicine & PET Centre

Background and Aims: PET/CT with the bile acid tracer ^{11}C-CSar provides new possibilities for in vivo studies of hepatic handling of conjugated bile acids. The aim of the present study was to quantify the postprandial changes in hepatic ^{11}C-CSar kinetics in healthy human subjects.
Method: Six healthy subjects underwent two subsequent 60-min dynamic liver ^{11}C-CSar PET/CT scans with measurements of arterial and hepatic venous blood concentration of ^{11}C-CSar: one before (fasting) and one 15 minutes after ingestion of a standard liquid meal (4291 kJ; 33% protein, 32% fat, and 35% carbohydrates).
Results: In the postprandial state, mean hepatic blood perfusion increased by 34% (P<0.01). Mean fasting PS_{mem} was 3.72 ml blood/min/ml liver tissue and did not change (P=0.51). Rate constant for backflux from hepatocyte to blood did not change (P=0.55), whereas the rate constant for transport from hepatocytes to bile increased from 0.40 min^{-1} to 0.67 min^{-1} (P<0.05) in agreement with an increase in the flow-independent intrinsic clearance from 1.82 ml blood/min/ml liver tissue to 2.13 ml blood/min/ml liver tissue (P<0.05). Accordingly, mean hepatic residence time for ^{11}C-CSar decreased from 2.8 min to 1.9 min (P<0.05). Rate constant for bile flow increased from 0.07 min^{-1} to 0.10 min^{-1} (P<0.05).
Conclusion: Both the transport capacity from hepatocyte to bile and bile flow increased significantly in all subjects. Accordingly, the mean residence time in hepatocytes decreased despite increased influx of tracer from blood. The increased secretion could be due to recruitment of transporters at the apical membrane.

33)

How Dyspepsia, Gastroesophageal Reflux Symptoms and Overlapping Symptoms Affect Quality of Life and use of Health Care and Medication - A Long-term Population Based Cohort Study

Maria Bomme Høgh, Katrine Mie Klausen, Marc David, Ove B Schaffalitzky de Muckadell, & Jane Møller Hansen.

Afdeling for Medicinske Mavetarmsygdomme S, Odense Universitetshospital

Background and aim: The prevalence of gastroesophageal reflux symptoms (GERS) and dyspepsia is high. Overlapping of GERS and dyspepsia has been described to affect quality of life. However, studies are few. This long-term population based study evaluates how having GERS, dyspepsia and overlapping symptoms, affect quality of life and use of health care and medication.

Methods: This study presents data for the control group of the randomised population study, HEP-FYN. 10,000 individuals, aged 40–65, received questionnaires at baseline and after 1, 5 and 13 years. The questionnaire included questions regarding demographics, use of health care resources, gastrointestinal symptoms (the Gastrointestinal Symptom Rating Scale (GSRS)), and the Short-Form 36-Item Health Survey (SF-36) to assess quality of life.

Results: At the 13-year follow-up, complete symptom data was available for 4,403 individuals. Half of these reported symptoms during follow-up and were categorized in groups according to symptoms. The group reporting overlapping symptoms used more drugs, and more of them visited their general practitioner and had sick leave days during the last year due to upper abdominal symptoms compared to the groups reporting no symptoms or solely GERS or dyspepsia. They also reported clinically relevant lower quality of life scores in all eight dimensions compared to individuals with no symptoms or solely GERS or dyspepsia.

Conclusions: Overlapping symptoms was associated with lower quality of life scores and substantial use of health-care resources. Having solely GERS or dyspepsia also impaired the same aspects compared to those having no symptoms, however, less severe.

34)

Gene co-expression network analysis of precursor lesions in familial pancreatic cancer

Ming Tan[1,2], Ove B. Schaffalitzky de Muckadell[1,2] , Maiken Thyregod Jørgensen[1,2]

1) Medical Gastroenterology, University of Southern Denmark (SDU); 2) Department of Medical Gastroenterology, Odense University Hospital (OUH)

Introduction: High-grade Pancreatic Intraepithelial Neoplasia (PanIN) are aggressive pre-malignant lesions, associated with risk of progression to pancreatic ductal adenocarcinoma (PDAC). A depiction of dysregulated gene activity in high-grade PanIN lesions in patients with Familial Pancreatic Cancer (FPC) can characterize the molecular events during the progression of familial PanIN lesions to PDAC.

Materials and Methods: We performed weighted gene co-expression network analysis (WGCNA) to identify genes associated with FPC related PanIN lesions using microarray gene expression profiles from 13 pancreatectomy specimens with PanIN-2/3 lesions from FPC patients, 6 pancreatectomy specimens with PDAC from sporadic pancreatic cancer (SPC) patients, and 4 specimens of normal pancreata.

Results: WGCNA detected co-expressed genes as modules and summarized each module by a representative gene: the module eigengene. Correlation analysis identified 1 up-regulated gene module ($p<1e-04$) and 3 down-regulated modules ($p<1e-03$) in FPC compared to SPC. The

upregulated gene module includes 14 significant genes (p<1e-06) including: MYOC, ZBTB47, TTTY15, NAPRT, PTK2. The down-regulated gene modules include 170 significant genes (p<1e-06), among them 13 highly significant genes (p<1e-10) consisting of: COL10A1, SAMD9, PLPP4, COMP, POSTN, IGHV4-31, THBS2, MMP9, FNDC1, HOPX, TMEM200A, INHBA, SULF1. The down-regulated modules are significantly enriched for Gene Ontology (GO) terms functionally related to: extracellular structure organization, substrate adherens junction, focal adhesion, mitochondrion structure and function, ATP metabolic-process, etc.
Conclusions: The differential molecular pathology of FPC and SPC involves multiple co-expressed gene clusters significantly enriched for GO terms including functions in extracellular activities and mitochondrion function. These findings provide reference for genomic characterization of the progression of PanIN lesions to PDAC in FPC.

35)

TERT mutation is detectable in plasma in nearly half of Danish patients with hepatocellular carcinoma and predicts poor prognosis

Stine Karlsen* [1], Michelle S. Clement[2], Britta Weber[3], Niel Kristian Aagaard[1], Gerda E. Villadsen[1], Henning Grønbæk[1], Stephen J. H. Dutoit [4], Boe S. Sorensen[2], Jens Kelsen[1]

[1]Department of Hepatology and Gastroenterology, [2]Clinical Biochemistry, [3]Clinical Oncology, [4]Clinical Pathology, Aarhus University Hospital, Denmark

Background: No biochemical marker has been able to definitively diagnose hepatocellular carcinoma (HCC) or provide clinically useful prognostic guidance. Tumor-specific mutations in circulating tumor DNA represents an attractive biochemical marker. The C228T *Telemerase Reverse Transcriptase* (TERT) promotor mutation is the most prevalent point mutation in HCC and studies indicate a correlation to mortality.
Material and methods: We analyzed the TERT mutation in ctDNA from plasma of 95 patients with HCC, and matched tissue samples from the primary tumor in 34 patients using droplet digital PCR. Results were correlated to clinical information on survival, disease stage, and treatment response. Furthermore, we analyzed plasma from 47 patients with liver cirrhosis without HCC.
Results: The TERT mutation was detected in 41 of 95 plasma samples (43%) and in 23 of 34 tumor samples (68%). Mutational status correlated in 62% of cases. Absence of TERT mutation in plasma while present in tissue was associated with early BCLC stage. Mortality was significantly increased in patients with TERT mutation in plasma (OR 4.62, P=0.0008). TERT mutation in the tissue sample did not predict increased mortality (OR 2.275, P=0.27). None of the non-HCC patients were positive for the TERT mutation.
Conclusion: TERT mutation was detectable in plasma of nearly half of Danish HCC-patients. TERT mutation in plasma but not in tissue predicted increased mortality. TERT mutation was detected only in patients with HCC. Circulating tumor DNA is a promising, easily accessible biomarker in HCC that could help clinicians improve diagnostic and prognostic information to patients with HCC.

36)

The Role and Modulation of T-lymphocyte 4-1BB in alcoholic hepatitis

Lotte Lindgreen Eriksen[1], Sidsel Støy[1], Morten Aagaard Nielsen[2], Tea Lund Laursen[1], Bent Deleuran[2], Hendrik Vilstrup[1]

[1] Department of Hepatology and Gastroenterology, Aarhus University Hospital, [2] Department of Biomedicine, Aarhus University

Background and aim: Acute alcoholic hepatitis (AAH) has a high mortality due to liver failure and infection. Dysfunctional T-lymphocytes are thought to be involved in the high susceptibility towards infection. To exploit the currently available T-lymphocyte targeting agents, knowledge about the balance between co-stimulatory and inhibitory receptors is needed. We, therefore, characterised the expression of the co-stimulatory receptor 4-1BB on T-lymphocytes and its anti-inflammatory soluble form in relation to expression of the inhibitory receptor PD-1 and the presence of infections.
Methods: Blood from patients with AAH (diagnosis, day 7 and 90) was compared with healthy abstinent controls (HC). T-lymphocyte receptor expression was quantified by flow cytometry and plasma soluble 4-1BB by ELISA.
Results: The frequency of 4-1BB$^+$ CD4 (AH 74%(CI95% 71-78), HC 59%(46-71), $p<0.05$) and CD8 (AH 91%(88-94), HC 83%(74-92), $p<0.05$) T-lymphocytes were higher in AAH compared with HC. In patients with AAH, the frequency of 4-1BB$^+$ relative to PD-1$^+$ T-lymphocytes was decreased ($p<0.05$). Also, the frequency of T-lymphocytes expressing both 4-1BB+ and PD-1 ($P<0.05$) and only PD-1 ($P<0.05$) was increased in AAH. Plasma soluble 4-1BB tended to be elevated in AAH compared with HC ($p=0.07$). Patients who developed infection at day 7 had a decrease in T-lymphocyte expression of 4-1BB and an increase in soluble 4-1BB within the first week compared to those uninfected. The same was found comparing those who had died by day 90 to those still alive.
Conclusion: In patients with AAH, T-lymphocytes are skewed towards an inhibitory phenotype associated with infection and mortality.

37)

Non-invasive markers Accurately Predict Liver-Related Outcomes in Compensated Alcoholic Liver Disease

Ditlev Nytoft Rasmussen, Maja Thiele, Bjørn Stær Madsen, Steen Antonsen; Sönke Detlelefsen og Aleksander Krag
Afdeling S OUH ; (På nær Steen Antonsen, der er fra kliniskbiokemisk afdeling, Svendborg og Sönke Detlefsen, der er fra patologisk afdeling, OUH)

Background: The traditional liver biopsy has been largely replaced by novel non-invasive methods for the diagnosis of fibrosis in alcoholic liver disease. However, the ability of the novel methods to predict the prognosis has not been assessed. We aimed to provide head-to-head comparisons between four non-invasive methods and liver biopsy for their ability to predict a first decompensation in alcoholic liver disease.
Methods: Inclusion was prospective with biopsy and the four non-invasive tests (TE, 2D-SWE, ELF and FT) performed on the same day. Follow-up was from retrospective review of the patients' medical charts. The outcome variable that denoted a first decompensation of liver disease was a composite of several detrimental clinical outcomes such as variceal bleeding, ascites, hepatic encephalopathy and hepatorenal syndrome. The predictive ability of the individual tests were compared using Harrell's C computed from univariate Cox regression.
Results: 250 alcoholised patients were included between April 2013 and December 2015 with a mean follow-up of 52 months (IQR 43-58). TE and ELF predicted the first decompensation to the same degree as a liver biopsy. Among the non-invasive markers, TE, ELF and 2D-SWE outperformed Fibrotest. The Harrell's Cs were 0.86; 0.84; 0.84 and 0.80, respectively.
Conclusions: Non-invasive tests accurately predicts the first liver related outcome in patients with compensated, biopsy-controlled alcohol-related liver disease. Four this purpose, the invasive liver

biopsy should be replaced by one of the non-invasive tests. Our data suggests that ELF and TE are the best replacements of liver biopsy, while FT is the poorest replacement.

38)

Development of advanced alcoholic liver fibrosis involves intensive remodelling of a wide range of extracellular matrix proteins and is characterised by imbalance between collagen formation and -degradation

Stine Johansen[1], Natasja S. Gudmann[2], Bjørn S. Madsen[1], Maria Kjærgaard[1], Mette Juul Nielsen[2], Diana J. Leeming[2], Suganya Jacobsen[1], Sönke Detlefsen[4], Aleksander Krag[1,3], Morten Karsdal[2], Maja Thiele[1,3] on behalf of the H2020-funded GALAXY consortium

[1]Department of Gastroenterology and Hepatology, Odense University Hospital; [2]Nordic Bioscience A/S, Herlev, Denmark; [3]Institute of Clinical Research, University of Southern Denmark; [4]Department of Pathology, Odense University Hospital.

Background and aims: Liver fibrosis drives liver-related mortality in alcoholic liver disease (ALD). In search of key mechanisms for progression, we aimed to investigate remodelling of extracellular matrix (ECM) proteins as a function of the histological severity of asymptomatic ALD.

Method: We measured 15 markers of fibrosis and ECM remodelling in a biopsy-controlled study of 305 ALD patients and 50 gender-, age- and BMI-matched healthy controls. We excluded decompensated cirrhosis or alcoholic hepatitis patients. We evaluated total fibrosis by elastography (FibroScan) and serum hyaluronic acid (HA). Specific ELISAs quantified collagen type III, V and VI formation (PRO-C3, PIIINP, PRO-C5, PRO-C6), tissue inhibitor of MMP1 (TIMP1), collagen type IV and V degradation (C4M, C5M), collagen cross-linking (LOXL2, PRO-C3X) and vascular and elastin remodelling (PRO-C18, ELM, ELM7, EL-NE). We correlated all markers with central histological scoring of fibrosis, inflammation, ballooning and steatosis, as well as with alcohol consumption, age and gender (figure).

Results: Mean age was 55±10 years, 75% male, BMI 27±7 kg/m^2. Compared to healthy controls, ALD patients had elevated levels of total fibrosis, collagen formation and degradation, and vascular and elastin remodelling, as a sign of ongoing ECM remodelling. Patients with fibrosis stage F3-4 showed an imbalance favouring collagen formation over degradation (34% higher PRO-C5 in F3-4 vs F0-2, compared to 6% higher C5M). A similar observation was seen in patients with severe ballooning and lobular inflammation (18% higher PRO-C5 vs 7% higher C5M).

Conclusion: ALD is characterised by extensive ECM remodelling. This study indicates that development of advanced fibrosis involves more collagen formation than degradation.

		Histological characteristics								
		Fibrosis stage (0-4)	Lobular inflammation (0-3)	Portal inflammation (0-1)	Ballooning (0-2)	Steatosis (0-3)	Healthy controls	Abstinent at inclusion (yes-no)	Age*	Gender
Total fibrosis	TE	0,759	0,540	0,455	0,565	0,279	-0,399	0,082	0,140	-0,058
	HA	0,662	0,509	0,378	0,558	0,209	-	-0,058	0,408	-0,069
Collagen formation	PRO-C3	0,670	0,511	0,451	0,519	0,201	-0,422	-0,016	0,087	-0,078
	PIIINP	0,587	0,409	0,381	0,451	0,081	-	0,050	0,187	-0,027
	PRO-C5	0,311	0,226	0,077	0,221	0,150	-0,117	0,069	0,109	0,015
	PRO-C6	0,434	0,230	0,282	0,302	-0,036	-0,347	0,191	0,117	0,047
	TIMP1	0,640	0,552	0,340	0,503	0,344	-	-0,169	0,201	-0,110
Collagen degradation	C4M	0,344	0,242	0,148	0,279	0,159	-0,150	0,071	0,104	0,044
	C5M	0,123	0,070	-0,031	0,080	0,009	-0,058	0,034	0,148	0,004
Cross-linking	LOXL2	-0,110	0,058	-0,101	-0,014	0,096	-0,065	0,047	0,050	-0,081
	PRO-C3X	0,560	0,381	0,280	0,483	0,119	-0,116	-0,041	0,087	0,077
Vascular remodeling and elastin	PRO-C18	-0,071	-0,022	-0,071	-0,092	-0,011	-0,197	0,037	0,023	-0,042
	ELM	0,089	0,009	0,111	0,018	0,023	0,167	-0,114	0,080	-0,057
	ELM7	0,120	0,157	0,082	0,122	0,115	0,083	-0,070	0,078	-0,068
	EL-NE	0,033	0,046	0,044	0,048	0,008	-0,309	0,170	0,032	-0,038

Spearman's rho for pairwise correlations between the 15 markers and semiquantitative histological scores for fibrosis, inflammation and ballooning, together with drinking status at inclusion, age and gender. *Age in decades (<30, 30-39, 40-49, 50-59, 60-69 and ≥70)

39)

Remote ischaemic conditioning in active ulcerative colitis: An explorative randomised clinical trial.

Line Godskesen[1,4], Thomas Ravn Lassen[2], Nichlas Riise Jespersen[2], Michael Melik Nielsen[1], Gunvor Madsen[3], Hans Erik Bøtker[2], Michael Rahbek Schmidt[2], Aleksander Krag[1], Jens Kjeldsen[1].

[1] Department of Medical Gastroenterology, Odense University Hospital and University of Southern Denmark, Odense, Denmark. [2] Department of Cardiology, Aarhus University Hospital Skejby, Denmark. [3] Department of Pathology, Odense University Hospital, Odense, Denmark. [4] OPEN - Odense Patient data Explorative Network, Department of Clinical Research, University of Southern Denmark.

Background and Aims: Remote ischaemic conditioning is a method whereby brief periods of ischaemia in an extremity render organs more resistant to prolonged ischaemic injury. The protection is partly through down-regulation of the inflammatory response. We investigated the effects of remote ischaemic conditioning in patients with active ulcerative colitis.

Method: In an explorative, randomised, sham-controlled clinical trial we included 22 patients with active ulcerative colitis. The patients were randomly assigned in a 1:1 remote ischaemic conditioning (induced in the arm through four cycles of 5-min inflation (200mmHg) and 5-min deflation of a blood-pressure cuff) and sham (incomplete inflation of the blood-pressure cuff (20mmHg)). Eleven patients were assigned to each group. The primary outcome was changes in faecal calprotectin from day 1 to day 11. Secondary outcomes were changes in clinical, endoscopic, mucosal and circulating markers of disease activity. The Langendorff heart model was used to assess activation of the organ protective mechanism. (ClinicalTrials.gov, number NCT02445365)

Results: There was no treatment effect of the remote ischaemic conditioning on faecal calprotectin at day 11 (treatment effect: -147, 95% CI [-1244, 950], p=0.80). There were no changes in any of the secondary outcomes. The Langendorff heart model did not confirm activation of the organ protective mechanism in the ulcerative colitis patients.

Conclusion: This is the first study to evaluate the effects of remote ischaemic conditioning in patients with ulcerative colitis. Remote ischaemic conditioning does not attenuate faecal, clinical, endoscopic, mucosal and circulating markers of inflammation in patients with moderate activity ulcerative colitis.

40)

Effects of direct-acting antiviral therapy on markers of type III and IV collagen formation and degradation in the course of chronic hepatitis C viral eradication and follow-up

Tea Lund Laursen[1], Ida Falk Villesen[2], Diana Julie Leeming[2], Morten Asser Karsdal[2], Christina Sølund[3], Britta Tarp[4], Lena Hagelskjær Kristensen[5], Charlotte Henneberg Holmboe[6], Peter Leuthcher[7], Alex Lund Laursen[8], Natasja Stæhr Gudmann[2*], Henning Grønbæk[1*].

1. Department of Hepatology & Gastroenterology, Aarhus University Hospital, Aarhus, Denmark. 2. Nordic Bioscience, Herlev, Denmark. 3. Department of Infectious Diseases, Hvidovre Hospital, Hvidovre, Denmark. 4. Diagnostic Centre, Silkeborg Regional Hospital, Silkeborg, Denmark. 5. Department of Medicine, Viborg Regional Hospital, Viborg, Denmark. 6. Department of Gastroenterology and Hepatology, Aalborg University Hospital, Aalborg, Denmark. 7. Centre for Clinical Research, North Denmark Regional Hospital & Department of Clinical Medicine, Aalborg University, Aalborg, Denmark. 8. Department of Infectious Diseases, Aarhus University Hospital, Aarhus, Denmark.

Background and aims: In chronic hepatitis C (CHC), imbalanced hepatic extracellular matrix (ECM) turnover is prominent, however the effect of direct-acting antiviral (DAA) therapy and viral clearance is unknown. ECM turnover generates protein fragments, where PRO-C3 and PRO-C4 reflect type III and IV collagen formation, and C3M and C4M reflect degradation. We aimed to assess the dynamics of these markers with DAA-therapy in CHC patients.

Methods: Plasma PRO-C3, PRO-C4, C3M, and C4M were assessed before, during, and one year after 12-24 weeks of DAA-therapy in 77 CHC patients with advanced fibrosis (n=14) or cirrhosis (n=63). Liver stiffness was evaluated using transient elastography.

Results: During the study period, PRO-C3, C3M and C4M levels decreased significantly ($p<0.00001$); the PRO-C4 level did not change ($p=0.20$). There was a steep decrease in the PRO-C3/C3M ratio during DAA-therapy and further during follow-up ($p<0.02$). There was no change in the PRO-C4/C4M ratio ($p>0.27$). The dynamics of the collagen markers behaved similarly between patients with advanced fibrosis and cirrhosis. The cirrhosis patients had more than 20% higher levels of C3M, PRO-C4, and C4M at all time points ($p<0.05$). The collagen markers correlated with liver stiffness at baseline and follow-up.

Conclusion: Markers of type III and IV collagen formation and degradation, decrease during and after successful DAA-therapy in CHC patients with advanced liver disease and are associated with liver stiffness at baseline and during follow-up. These results indicate an altered balance between collagen formation and degradation after viral clearance suggesting a favorable effect on liver fibrosis.

Sponsorer


ALEXION
CALPRO
the Calprotectin company
Pharmanovia
SYNMED
Takeda
Pfizer
OLYMPUS
Janssen Immunology
PHARMACEUTICAL COMPANIES OF Johnson&Johnson
MSD
INVENTING FOR LIFE
ZERIA GROUP
TILLOTTS PHARMA
GI-health is our passion™
VINGMED VICARE
PHARMACOSMOS
PO MEDICA
NORGINE
FERRING
PHARMACEUTICALS
KEM
EN
TEC
Nordic
Navamedic
KEBOMED
Mylan
Better Health
for a Better World