Joint EGIR-MASLD Study Group Meeting

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Abstract Book

02-The impact of hormone replacement therapy on major adverse liver outcomes in peri-menopausal patients with metabolic dysfunction-associated steatotic liver disease: real-world evidence

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Background and Aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common liver disease globally. Menopause is linked to greater hepatic fat deposition and metabolic dysfunction, contributing to progressive liver disease and heightened cardiovascular risk. These associations make hormone replacement therapy (HRT) an appealing intervention, supported by pre-clinical data, though clinical evidence remains limited.

Materials and Methods: We performed a retrospective cohort study using the TriNetX global federated research network. Eligible participants were peri-menopausal women (ICD-10 codes N95 & Z78.0), AND age 40–65 years, with pre-existing MASLD (ICD-10 codes K76.0, K75.81) OR positive modified hepatic steatosis index, PLUS ≥1 metabolic trait. Patients initiating HRT (oestrogen ± progesterone) were compared with untreated controls using 1:1 propensity score matching for demographics, comorbidities, biochemistry and medications. The primary outcome was major adverse liver outcomes (MALO: portal hypertension, varices, ascites, spontaneous bacterial peritonitis, encephalopathy, hepatorenal/pulmonary syndromes, cirrhosis, decompensated liver disease, hepatocellular carcinoma, liver transplant). Secondary outcomes were the individual MALO endpoints, type 2 diabetes (T2D), and major adverse cardiovascular events (MACE). Cox regression generated hazard ratios (HRs) with 95% CIs over 5 years. Sensitivity analyses adjusted for geography, hormone type, and degree of obesity.

Results: After matching, 21,639 patients were included in each treatment arm. HRT was associated with a significantly reduced risk of MALO (HR 0.80; 0.71, 0.9), largely driven by reductions in ascites and SBP (0.78; 0.64, 0.95), and liver cirrhosis (0.75; 0.63, 0.90), as well as in the cardiometabolic outcomes: T2D (0.90; 0.84, 0.96), and MACE (0.90; 0.83, 0.98)

Conclusion: Oestrogen was linked to greater benefits compared to progesterone, and patients with lower levels of obesity experienced more significant improvements. Treatment of peri-menopausal symptoms with HRT, in patients with pre-existing MASLD, is associated with lower risk of major liver and cardiometabolic disease. These findings support early basic science research and should prompt a closer examination through clinical trials.

Eligible for award

03-PNPLA3 p.I148M variant affects lipid droplets number and composition in patient-derived liver organoids

Presenter: Elia Casirati [1,] Laura Cerami [1], Fabrizia Carli [2,] Francesco Malvestiti [1,] Daniele Prati, Daniele Dondossola [3], Amalia Gastaldelli [2], Alessandro Cherubini [1], Luca Valenti [1, 4]

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Background and Aims: PNPLA3 rs738409 C>G p.I148M variant is the main genetic determinant of metabolic associated steatotic liver disease (MASLD). Due to the lack of comprehensive human models, the molecular mechanism linking the genetic variation with progressive intracellular fat accumulation and progressive liver disease are still largely unknown. To overcome this gap in knowledge, we generated patient-derived human liver organoids (HLOs. studied morphological features of lipid droplets (LDs. and lipid accumulation across different PNPLA3 genotypes.

Materials and Methods: To model MASH, HLO (3 per genotype. were exposed to 300 (M Palmitic:Oleic acids, LDs average size and number (normalized for nuclei. were stained with NileRed and quanti'ed by ImageJ. Results were validated in histological slides from MASLD patients. Lipidomics and transcriptomics were conducted to dissect PNPLA3-driven alterations in lipid composition and transcriptional response. Genotype-phenotype associations were tested by generalized linear models assuming an allelic genetic effect. To examine the mechanism of association and translational relevance, we developed PNPLA3-targetting siRNAs and compared their effect to that of resmetirom in HLOs.

Results: We found that PNPLA3 risk alleles correlated with LDs total area (β Estimate(139.68, SE(18.00, p(0.0001(and number (β Estimate(23.55, SE(4.71, p(0.0001., whereas LDs average size was only increased in homozygous HLOs (β Estimate(0.227, SE(0.075, p(0.0047., independently of fatty acids and other confounders. Results were con'rmed in 29 liver biopsies (p(0.0009(. Lipidomics highlighted an enrichment of long-chain unsaturated fatty acids and a milieu reminiscent of MASH, with increased ceramides and sphingomyelins correlating with the number of risk alleles. In keeping, bulk RNA-Seq indicated increased proneness to in'ammation, (brosis, uncontrolled proliferation and, importantly, compromised metabolic control. At the single cell level, scRNA-Seq allowed to pinpoint a subset of cells enriched in HLOs homozygous for the risk variant. At gene ontology analysis, this subset showed increased oxidative phosphorylation, ROS production, adipogenesis, and activation of cancer-related pathways. Finally, PNPLA3-driven lipid accumulation and LD number could be rescued by PNPLA3 silencing via siRNA (correlating with the reduction of PNPLA3 protein. and by resmetirom.

Conclusion: We found a strong direct correlation of PNPLA3 risk alleles with lipid accumulation in HLOs, which was accounted by the number rather than average size of LDs and associated with qualitative alterations of lipid composition and activation of MASH-related pathways. These morphological alterations were replicated in clinical samples, which could be partially reversed by PNPLA3 silencing or resmetirom, suggesting they are related to PNPLA3 accumulation and involved in liver disease development.

Eligible for award

04-Parallel Exploration of Serum and Interstitial Fluid Lipoproteins and In‌ammatory Signatures of Atherosclerosis in Type 2 Diabetes

Presenter: Jennifer H‌rdfeldt [1,2,,]

Collaborators: Emelie Barreby [1,,] P‌r Bj‌rklund [1,2,,] Giulia Fiscon [3,,] Paola Paci [3,1,,] Sara Straniero [1,], Lauri ‌ik‌s [4,5,] , Katariina ‌rni [4,5,,] Mats Rudling [1,,] Bo Angelin [1,2,,] Cecilia Morgantini [1,6,]

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Background and Aims: Patients with Type 2 Diabetes ‌T2D. are disproportionately affected by atherosclerosis compared with non-diabetics. Central to this process are both vascular retention of atherogenic lipoproteins and chronic in‌ammation. While serum biomarkers have been extensively studied, interstitial ‌uid ‌IF. – a dynamic medium adjacent to vessel wall cells –remains largely unexplored despite its unique proximity to atherogenesis. By conducting a parallel exploration of lipoprotein properties and in‌ammatory biomarkers in serum and IF, we aim to bridge systemic and local microenvironments to elucidate mechanisms governing lipoprotein turnover and vascular health in T2D.

Materials and Methods: Serum and IF from abdominal skin blisters were collected after an overnight fast from 29 T2D patients and matched controls. Lipoprotein pro‌les were evaluated through FPLC. Transvascular interstitial ‌uid to serum ratios ‌IF:S‌ for cholesterol and ApoB were determined, and serum LDL functionality was assessed by ex vivo binding to human aortic proteoglycans ‌LPBS‌ and their aggregation susceptibility. Parallel proteomics analyses in serum and IF were conducted with the Olink‌ Target In‌ammation panel. Data analysis employed a network-based topological approach integrating lipoprotein, in‌ammatory, and physiological characteristics.

Results: In controls, the IF:S was approximately 0.2 for total cholesterol, and the relative abundance of IF lipoproteins was inversely related to particle size. In T2D, atherogenic lipoproteins were signi‌cantly sparser in IF, and IF:S for ApoB was reduced by more than half. LPBS was increased in T2D and inversely associated with IF:S for ApoB in both controls and T2D patients. These alterations in lipoprotein distribution and function coincided with elevated in‌ammatory biomarkers linked to cardiovascular disease and human atherosclerotic lesions in T2D. Network analysis revealed positive correlations between expression of pro-in‌ammatory biomarkers in IF and metabolic parameters related to T2D, including fasting blood glucose and HbA1c. In contrast, inverse correlations were found between less aggregation-prone LDL and several in‌ammatory biomarkers in IF in T2D, which were not present in controls.

Conclusion: Analyzing data from both serum and the rarely studied IF reveals distinct pathways involved in lipoprotein retention and in‌ammation. This unique approach provides valuable insights into potential targets for future diagnostic and therapeutic strategies, underscoring the importance of IF in understanding atherosclerosis in T2D

Eligible for award

05-Targeting epigenetic readers rewires the metabolic and inflammatory shift of the vascular-perivascular adipose tissue interface in cardiometabolic disease

Presenter: Alessandro Mengozzi [1,2,3]
Collaborators: Sarah Costantino [2,4], Alessia Mongelli [2], Emiliano Duranti [1], Shafeeq A Mohammed [2], Era Gorica [2], Marialucia Telesca [2], Silvia Armenia [1], Rosario Bellini [4], Federica Cappelli [1], Omer Dzemaili [2,4], Stefano Taddei 1, Stefano Masi [1], Frank Ruschitzka [2,5], Agostino Virdis [1], Francesco Paneni [2,5]

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Background and Aims: BET proteins, which read histone modifications, are emerging as key epigenetic regulators of gene transcription and have been increasingly linked to cardiometabolic disease. In particular, BRD4 plays a central role in orchestrating inflammatory transcriptional programs. In this study, we investigated its involvement in cardiometabolic disease, focusing on the vascular and perivascular adipose tissue (PVAT), pivotal players in cardiometabolic disease initiation.

Materials and Methods: To mirror cardiometabolic disease, we adopted two models characterized by the combination of metabolic and hemodynamic stress: i. patients with obesity and hypertension and ii. mice administered high-fat diet and L-name supplementation. In the human model, we assessed the impact of ex-vivo BRD4 inhibition on vascular function by using RVX-208 (an FDA-approved BET inhibitor) in small vessels (100-300 μM) dissected from omental fat biopsies. In mice, we evaluated chronic BRD4 inhibition by a 14-days oral administration of RVX-208. Vascular function was evaluated in the presence and in the absence of PVAT. The effect of BRD4 inhibition was compared to anti-inflammatory drugs. We corroborated our functional data with molecular characterisation of the metabolic and inflammatory pathways involved, leveraging transcriptional screening, proteomics, metabolomics and lipidomics analyses. An in vitro crosstalk model employing human perivascular adipocytes and endothelial cells and ex vivo functional experiments with gain and loss-of-function approaches were employed to recapitulate the findings.

Results: In vessels from mice and patients with cardiometabolic disease, we show that pharmacological editing of BET proteins by RVX-208 prevents a maladaptive crosstalk between PVAT and blood vessels. This epi-drug exerted a potent anti-inflammatory action and a marked effect on endothelial function as compared to well-established anti-inflammatory drugs, namely IL-1β, IL-6 or TNF-α inhibitors. The effects of BET inhibition on endothelial function were more pronounced in the presence of PVAT, suggesting a pivotal role of this organ. In mouse and human PVAT, RVX-208 rescued maladaptive transcriptional programs, with a marked downregulation of hexokinase-2 (HK-2), involved in glycolysis and insulin resistance, predominantly expressed in adipocytes. HK-2 overexpression in human PVAT adipocytes led to glycolytic overload, lipid accumulation and secretome changes eventually promoting endothelial damage. Of clinical relevance, pharmacological inhibition of HK-2 in vessels from cardiometabolic patients restored endothelial dysfunction.

Conclusion: Inhibition of BRD4 downregulates HK2 and reverses pro-glycolytic changes and triglyceride accumulation in PVAT. This leads to vascular dysfunction rescuing. The unveiling of a BET-

dependent crosstalk between PVAT and blood vessels supports therapeutic strategies cardiometabolic damage.

Eligible for award

06-Impact of overweight and obesity on fasting insulin secretion in men and women without diabetes: effect sizes and mechanisms

Presenter: Martina Chiriac[1,2,] Domenico Tric[1], John R. Petrie[3], Rafael Gabriel[4], Amalia Gastaldelli [2,5], John Nolan[6], Nebojsa Lalic[7], Geltrude Mingrone[8,9,10], Andrea Mari[11], Andrea Natali[1]

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Background and Aims: Fasting hyperinsulinemia is a key feature of obesity and is implicated in diabetes progression. However, it is still unclear: ¦i¦ which index of obesity is most important; ¦ii¦ what is the shape of the dose-response curve between obesity and insulin secretion; ¦iii¦ what physiological mechanisms sustain insulin hypersecretion; ¦iv¦ what are the underlying causes; and ¦v¦ whether sex-related differences exist

Materials and Methods: We analyzed data from 1,250 healthy participants ¦547 men, 703 women¦ of the EGIR-RISC cohort followed up for 3.5 years, with age 30-60 years and BMI 18.5-40.0 kg¦m². Assessments included body composition, insulin secretion, beta cell function modelling from an OGTT and clamp-derived insulin sensitivity, including endogenous glucose production ¦EGP¦ in a subset of 368 participants. Multivariable regression models and strati¦cations for BMI, body fat percent, waist-to-hip ratio ¦WHR¦ and fat mass were applied to evaluate the effect of obesity on insulin secretion and β-cell function.

Results: The impact of obesity on fasting insulin secretion ¦FIS¦ was continuous across the full spectrum of BMI and WHR values. Among adiposity indices, fat mass ¦Stβ 0.27, p 0.0001¦ and waist circumference ¦Stβ 0.21, p 0.0001¦ were the strongest predictors of FIS. Insulin secretion increased 2.4-fold across BMI deciles, and adiposity-associated insulin hypersecretion appears to be driven by the combination of hyperglycemia and an increase in a speci¦c beta cell function ¦ISR¦5¦. At follow-up, weight gain ¦weight 5.1 3.8 kg. was associated with an increase in FIS and fasting glucose 0.20 0.63 mM, p 0.03., whereas weight loss ¦weight -4.7 2.8 kg. led to a reduction in FIS and fasting glucose 0.06 0.55 mM, p 0.006¦. ISR¦5 declined in both weight losers and those with stable weight -0.17 1.9 and -0.16 1.0 U¦h, respectively; p 0.002 for both¦, but not in weight gainers ¦-0.06 1.1 U¦h¦. Peripheral insulin resistance, plasma NEFA, and leptin accounted for only part of obesity¦s effect on insulin secretion. Subset analysis of fasting and clamp EGP data suggested a rightward shift in the dose-response curve across fat mass quintiles, indicating progressive hepatic glucose overproduction despite a preserved hepatic insulin response.

Conclusion: The effect of body mass on insulin secretion is continuous, more pronounced in men, driven by fat mass and waist, sustained by elevated plasma glucose and ISR¦5 and is only partially explained by typical hormonal and metabolic consequences of obesity. We suggest that hepatic glucose overproduction contributes to the fasting hyperinsulinemia observed in individuals with obesity.

Eligible for award

07-G6PD as a novel therapeutic target for MASLD-induced HCC

Presenter: Andrea Caddeo[1]

Collaborators: Jessica Nurcis[2], Beatrice Foglia[2], Marina Maggiora[2], Alessandro Gambella[3], Ugo Chianese[4], Claudia Bocca[2], Gian Paolo Caviglia[5,6], Rosaria Benedetti[4], Francesca Boss[i2], Patrizia Carucci[6], Silvia Gaia[6], Francesca Sedda[1], Renato Romagnoli [7,] Elisabetta Bugianesi[5,6,] Lucia Altucci[4], Maurizio Parola[2], Simona Rapposelli[8] , Andrea Perra[1], Stefania Cannito[2] and Marta Anna Kowalik[1]

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Background and Aims: MASLD-related hepatocellular carcinoma HCC incidence, driven by the increasing prevalence of obesity, type 2 diabetes, and metabolic syndrome, continues to rise worldwide. To maintain the redox homeostasis and to support their increased bioenergetic and biosynthetic needs, neoplastic cells undergo a metabolic reprogramming characterized by impaired oxidative phosphorylation OXPHOS, increased glycolysis and pentose phosphate pathway PPP. activity. In this regard, sustained activation of glucose-6-phosphate dehydrogenase G6PD, the rate-limiting enzyme of the PPP, has been associated with tumor growth, redox balance, and therapy resistance.

Materials and Methods: To further investigate the role of G6PD in the progression of MASLD-related HCC, we analysed G6PD levels in vivo in a MASLD- associated hepatocarcinogenesis rat model and in a human MASH-associated HCC cohort, and in vitro by studying the main molecular pathways involved in the cell cancer proliferation following the exposure to a newly synthesized G6PD inhibitor.

Results: In a MASLD-associated hepatocarcinogenesis rat model, preneoplastic lesions that progress towards HCC were characterized by impaired OXPHOS, increased expression of G6PD and, therefore, by enhanced glucose utilization to fuel the PPP. Analysis of paraf n-embedded liver samples from MASH patients with varying brosis stages F0–F4 and from MASH-associated HCC cases revealed an increase in G6PD levels. Noteworthily, G6PD expression was higher in the MASH-related HCC group compared to the HCC mixed aetiology group, composed of alcoholic and viral HCC cases. Moreover, higher G6PD expression correlated with more advanced BCLC stage and reduced overall survival in HCC patients. In vitro, hepatocyte-derived carcinoma cell line stably overexpressing G6PD exhibited a profound metabolic reprogramming characterized by the up-regulation of genes involved in glucose and lipid metabolism. G6PD-overexpressing cells generated signi cantly larger 3D spheroids compared to controls, con rming the importance of G6PD in tumor cell proliferation. A pharmacological inhibition of G6PD by a novel non-steroidal small molecule G6PD inhibitor, that effectively inhibit the enzymatic activity of G6PD, impaired cell proliferation and the expression of genes involved in the metabolic rewiring of tumorigenic cells.

Conclusion: These ndings pointed out the relevance of G6PD in the metabolic reprogramming and tumor progression in vitro, in a MASLD-associated hepatocarcinogenesis rat model and in human MASH-associated HCC, suggesting its potential role as a prognostic marker. Moreover, the use of a novel G6PD inhibitor showed promising results in limiting the onset of the metabolic rewiring in tumorigenic hepatocytes, thus proposing G6PD as a potential therapeutic target in metabolic-related HCC.

08-Comparative outcomes of glp-1 receptor agonists versus bariatric surgery in obese patients with type 2 diabetes mellitus

Presenter: Asmita Saner[1]
Collaborator: Banshi Saboo[1]

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Background and Aims: The optimal management strategy for obese patients with type 2 diabetes mellitus remains a subject of clinical interest. Both glucagon-like peptide-1 receptor agonists (GLP-1Ras) and bariatric surgery have shown significant impacts on glycemic control and weight reduction. his study compares glycaemic outcomes and weight reduction at 4 months.

Materials and Methods: A retrospective, two tertiary care center study was conducted involving 40 adults with T2DM (baseline Hb1c 9.0). and BMI (30 kg/m²). Patients were stratified into two groups (n=20 each): Group A received GLP-1RA therapy (weekly Tirazepatide, Semaglutide) along with standard lifestyle management; Group B underwent bariatric surgery (Roux-en-Y gastric bypass or sleeve gastrectomy). Baseline demographics, metabolic parameters, and comorbidities were recorded. Outcomes measured at 4 months included body weight reduction, glycemic control (HbA1c). Descriptive analysis was undertaken.

Results: Baseline demographic characteristics: Group A (n=20) and Group B (n=20) Mean age - 45 years in both groups. Mean weight - 90.2kg in both groups. Number of males and females: Group A - Males 12 females 8. Group B- males 14 females 6. Median HbA1c: Group A - 9.1 Group B - 9.9. At the end of 4 months, mean weight loss in the GLP-1RA group was significantly lower than in the surgery group (Group A 10.7 vs Group B 25.4 3.2 kg 2.3 kg. HbA1c at the end of 4 months in Group A was median 7.5, Group B median HbA1c 6.8 (Baseline median HbA1c 9.

Conclusion: Both GLP-1RA therapy and bariatric surgery significantly improved metabolic outcomes in obese T2DM patients. Bariatric surgery achieved superior weight reduction and improved glycaemic outcome, while GLP-1RAs offered favorable safety. Long- term follow-up is warranted to assess durability and cost-effectiveness of both interventions.

09-Sex-specific development of MASH and glucose intolerance in a murine MASH Model

Presenter: Kristiaan Wouters[1],
Collaborators. Tuneille Adelaar[1], Margee Teunissen[1], Casper Schalkwijk[1], Sabine Daemen[1]
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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD. is the leading cause of liver disease and is closely linked to obesity and type 2 diabetes. In fact, an estimate of 65% of people with type 2 diabetes have MASLD. MASLD is characterized by liver steatosis, and 20–30% of individuals progress to metabolic dysfunction-associated steatohepatitis (MASH), marked by immune cell infiltration and activation. MASH can progress to liver fibrosis, strongly increasing the risk of intra- and extrahepatic complications. MASH and related complications show clear sex differences, yet the underlying immunometabolic drivers remain poorly understood. This study aimed to characterize hepatic and systemic immunometabolic alterations during MASH progression in both sexes.

Materials & Methods: Male and female mice received the Gubra-Amylin NASH diet (40% kcal fat (including 15% palm oil, 2% cholesterol, 20% fructose. or matched control diet for 10, 15, 20 or 25 weeks. MASH development and systemic metabolic and inflammatory changes were assessed using histology, spectral flow cytometry, biochemical lipid assays and glucose tolerance tests.

Results: Both sexes exhibited limited weight gain and no significant increase in adiposity. Infiltration of monocyte-derived macrophages (MdMs), a key hallmark of MASH inflammation, occurred earlier in females (onset at 15 weeks, control 7913±2749 vs. MASH 75462±54670 MdM count/gr liver, p=0.004. than males (15 weeks control 5637±1622 vs. MASH 43170±57507 MdM count/gr liver, p=0.139). Female mice demonstrated overall higher liver steatosis (steatosis score MASH females 1.68±0.65 vs. males 1.05±0.49, p=0.001), whereas fibrosis occurred almost exclusively in males (fibrosis score MASH females 0.32±0.48 vs. males 1.00±0.98, p=0.011). Female mice had earlier onset of glucose intolerance (10 weeks AUC control 1506±257 vs. MASH 2001±261, p=0.003) than males (10 weeks AUC control 1720±342 vs. MASH 1893±343, p=0.401). Inflammation was not observed in visceral or subcutaneous adipose tissue and blood immune cells remained largely unchanged.

Conclusion: Sex differences were evident in liver steatosis, inflammation and fibrosis, and glucose intolerance, independent of peripheral inflammatory changes.

Eligible for award

11-A target trial emulation for the reduction in major adverse cardiovascular events in patients with metabolic dysfunction-associated steatotic liver disease following treatment with resmetirom: a retrospective cohort study

Presenter: Alex E Henney [1,2,3], Uazman Alam [1,2,3,4,] Daniel J Cuthbertson [1,2,3]

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4.Centre for Musculoskeletal Research, Faculty of Biology Medicine and Health, The University of Manchester, Manchester, UK.

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic liver disease globally, ranging from simple steatosis to steatohepatitis (MASH), fibrosis, and cirrhosis. Cardiovascular disease is the leading cause of death in patients with MASLD. The FDA recently approved resmetirom, an oral thyroid hormone receptor beta-selective agonist, for patients with MASH fibrosis. Resmetirom has demonstrated improvements in liver fibrosis and cardiovascular risk factors, such as lowering triglycerides. This study aims to compare the effectiveness of resmetirom, glucagon-like peptide-1 (GLP-1. receptor agonists (Ras), and other anti-obesity medications (AOMs) in reducing the risk of major adverse cardiovascular events (MACE) in patients with MASLD/MASH.

Methods: We conducted a target trial emulation using the TriNetX global health network. Eligible patients were adults with MASLD/MASH (ICD-10 codes K76.1 or K75.81, or modified hepatic steatosis index) prescribed resmetirom, GLP-1 RAs (tirzepatide, semaglutide, liraglutide, dulaglutide), or other AOMs. Three cohorts were created: i. resmetirom vs. other AOMs, ii. resmetirom vs. GLP-1/GIP RAs, and iii. GLP-1/GIP RAs vs. other AOMs. Propensity score matching was used to balance demographics, comorbidities, and medications. The primary outcome was a composite of MACE: sudden cardiac death, acute coronary syndrome, stroke, and decompensated heart failure. Cox regression analysis was conducted.

Results: After matching, cohort 1 included 978 patients per arm, cohort 2 had 985 per arm, and cohort 3 included 75,976 per arm. Resmetirom was associated with significantly lower MACE risk vs. other AOMs (HR 0.50; 0.26-0.94), but not vs. GLP-1/GIP RAs (HR 0.61; 0.32-1.17). GLP-1/GIP RAs also reduced MACE risk vs. other AOMs (HR 0.87; 0.82-0.92).

Conclusion: Resmetirom and GLP-1/GIP RAs are associated with lower MACE risk than other AOMs, supporting their use in MASLD patients at high cardiovascular risk.

12-Clustering approach from early pregnancy data for predicting gestational diabetes and adverse delivery outcomes

Presenter: Agnese Piersanti [1],
Collaborators: Evelyn Huhn [2, 3], Grammata Kotzaeridi [4], Florian Heinzl [4], Irene Hösli [2] Gernot Desoye [5], Mireille van Poppel [6], Micaela Morettini [1], Christian Göbl [4], Andrea Tura [7], DALI Core Investigator Group, GESTDIA Core Investigator Group

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Background and Aims: Gestational diabetes mellitus (GDM) is a frequent pregnancy complication associated with adverse outcomes. A possible explanation is that pregnant women often experience relative insulin resistance, even in the absence of dysglycemia. However, insulin resistance alone appears insufficient to identify those women at higher risk of adverse outcomes. Also, current diagnostic GDM thresholds, derived from glycemia testing in second/third trimester, may not accurately reflect adverse outcomes risk. This study applies a data-driven clustering approach integrating glycemia and clinical factors in early pregnancy (before 24 weeks., which may already convey prognostic information. The aim is to identify high-risk women, to improve precision in risk stratification and guide timely intervention strategies.

Materials and Methods: Data from two cohorts (DALI, Graz and GESTDIA, Vienna) were combined (1,560 women). Input features included age, body mass index (BMI), glycemic response at fasting and following diagnostic oral glucose tolerance test (OGTT: 1- and 2-hours), and triglycerides. K-means clustering with Euclidean distance was applied using 50–50 training-testing split. Relevant adverse outcomes included GDM onset, maternal delivery complications, pregnancy-induced hypertension (PIH), cesarean section, hyperbilirubinemia, large for gestational age (LGA) infants.

Results: Two clusters were identified (CL1 and CL2). CL1 included 46.4% of women, whereas the remaining 53.6% were in CL2. Performance metrics demonstrated adequate clustering discrimination (average silhouette width 0.15) and stability (Jaccard index 0.90). In CL1, all input features were higher ($p<0.0001$). Importantly, CL1 women had higher rates of the indicated adverse outcomes ($p<0.05$; Figure, top), and deteriorated insulin sensitivity and beta-cell function ($p<0.0001$; Figure, bottom).

Conclusion: Our clustering approach based on clinical features at early pregnancy typically available in clinical routine successfully identified women at increased risk for GDM and adverse maternal/neonatal outcomes (CL1). This may support early stratification and prevention.

13-Sugar rationing in the first 1000 days after conception and long-term risk of metabolic dysfunction associated steatotic liver disease and major adverse liver outcomes: a natural experiment study

Presenter: Daniel J Cuthbertson[12,13,14†,]
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Background: Excessive early-life sugar intake may predispose individuals to metabolic liver disease, yet robust population-level evidence remains limited.

Methods: Leveraging the UK's sugar rationing policy (1942–1953) as a natural experiment, we investigated whether early-life sugar restriction influenced long-term liver health. Our analysis leveraged the termination of sugar rationing in September 1953 as a natural experiment to assess the long-term effects of restricted sugar intake during the critical first 1,000 days after conception, on risk of incident chronic liver disease. This policy change led to a marked increase in sugar consumption, without affecting the intake of other food categories, enabling a comparison between individuals exposed to low versus high sugar intake during early development. We were able to classify individuals into exposure groups according to their birth dates, pre- or post 1953.

Results: In this quasi-randomized cohort of 63,698 UK Biobank participants, exposure to sugar rationing in utero plus 1–2 years postnatally was associated with significantly lower risks of severe metabolic dysfunction-associated steatotic liver disease (MASLD; hazard ratio (HR), 0.70; 95% CI, 0.58–0.85), major adverse liver outcomes (MALO; HR, 0.65; 95% CI, 0.49–0.84), and cirrhosis (HR, 0.68; 95% CI, 0.48–0.97). Using MRI data (fat, PDFF and brain inflammation, cT1), sugar restriction corresponded to reductions in liver fat content (mean difference in proton density fat fraction, −0.50; 95% CI, −0.86 to −0.20. and fibro-inflammation (mean difference in corrected T1, −52.2 ms; 95% CI, −73.8 to −20.2). Mediation analysis revealed that metabolic syndrome traits accounted for 68.8% of the protective association with MASLD, with type 2 diabetes mediating 36.6%. Protective effects were consistent across PNPLA3 and TM6SF2 genetic risk groups and independent of secular trends, supported by placebo and contemporaneous control analyses.

Conclusion: These findings suggest that early-life sugar restriction confers durable benefits on liver health, potentially via mitigation of metabolic dysfunction.

Eligible for award

14-A functional genomic framework to elucidate novel causal metabolic dysfunction-associated fatty liver disease genes

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Background and Aims: Metabolic dysfunction-associated fatty liver disease (MASLD) is the most prevalent chronic liver pathology in western countries, with serious public health consequences. Efforts to identify causal genes for MASLD have been hampered by the relative paucity of human data from gold standard magnetic resonance quantification of hepatic fat. To overcome insufficient sample size, genome-wide association studies using MASLD surrogate phenotypes have been used, but only a small number of loci have been identified to date. In this study, we combined genome-wide association studies of MASLD composite surrogate phenotypes with genetic colocalization studies followed by functional in vitro screens to identify bona fide causal genes for MASLD.

Materials and Methods: We used the UK Biobank to explore the associations of our novel MASLD score, and genetic colocalization to prioritize putative causal genes for in vitro validation. We created a functional genomic framework to study MASLD genes in vitro using CRISPRi.

Results: We have developed a powerful functional genomic framework to study MASLD-genes in vitro at scale. Our data identify VKORC1 , TNKS , LYPLAL1 , and GPAM as regulators of lipid accumulation in hepatocytes and suggest the involvement of VKORC1 in the lipid storage related to the development of MASLD.

Conclusions: Complementary genetic and genomic approaches are useful for the identification of MASLD genes. Our data supports VKORC1 as a bona fide MASLD gene. We have established a functional genomic framework to study at scale putative novel MASLD genes from human genetic association studies.

15-Early enhancement of oral glucose absorption characterizes metabolic dysfunction–associated steatotic liver disease

Presenter: Domenico Tric[1],
Collaborators: Tongzhi Wu[2], Noemi Cimbalo[1], Martina Chiriac[1,3], Cong Xie[2], Luca Sacchetta[1,3], Lorenzo Nesti[1], Simone Gallo[1], Lorenza Santoni[1], Maria Chiara Masoni[1], Giovanni Petralli[1], Teresa Vanessa Fiorentino[4], Roberto Bizzotto[5], Maria Tiziana Scozzaro[1], Silvia Frascerra[1], Simona Baldi[1], Maurizia Rossana Brunetto[1], Andrea Mari[5], Christopher K Rayner[2], Andrea Natali[1]

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Background and Aims: Hepatic glucose ux plays a crucial role in the progression of metabolic dysfunction-associated steatotic liver disease MASLD, promoting de novo lipogenesis, in ammation, and brosis. This study evaluated the kinetics of oral glucose absorption and one of its key modulators, gastric emptying, in individuals with early-stage MASLD versus matched controls.

Materials and Methods: We quanti ed glucose metabolic uxes during a 75g oral glucose tolerance test OGTT. using stable isotopes in individuals with MASLD without brosis and healthy controls n42. In a separate cohort n91, gastric emptying rate was measured by the 13C-acetate breath test during OGTT, while hepatic steatosis was estimated by the hepatic steatosis index HIS.

Results: At 1h post-OGTT, the rate of appearance of oral glucose normalized to body weight RaO was 34 higher in the MASLD group 318142 molkg, p0.031, resulting in a 52 increase in total glucose absorption 6.41.8 g, p0.001. MASLD participants exhibited reduced glucose clearance relative to plasma insulin levels, but preserved postload suppression of endogenous glucose production, indicating peripheral rather than hepatic insulin resistance. Among glucose uxes, RaO emerged as the strongest determinant of MASLD, with each 1-SD increase in 1h RaO being associated with a 5-fold higher risk of MASLD OR 4.99 1.44, 31.57, p0.036, independent of potential confounders. Gastric emptying rate was not associated with hepatic steatosis risk.

Conclusion: Oral glucose absorption is augmented in individuals with MASLD without brosis, apparently unrelated to accelerated gastric emptying. This metabolic alteration may represent a critical early driver of MASLD pathogenesis, preceding hepatic insulin resistance. Therapeutic strategies that modulate intestinal glucose absorption may complement existing treatments targeting MASLD.

Eligible for award
16-Early-life gut microbiota transplantation in mice has long-lasting effects on liver development

Presenter: Federica La Rosa[1],
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Background and Aims: The global prevalence of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) has reached alarming levels, increasingly linked with obesity and type 2 diabetes mellitus (T2DM). MASLD, obesity and T2DM represent closely interconnected components of metabolic dysfunction, with accumulating evidence emphasizing the pivotal role of gut microbiome interactions in their development and progression. The increasing incidence of obesity and T2DM, particularly among children, further highlights the need to elucidate the long-term effects of early-life interventions. We performed this study to investigate how early-life FMT from children to young mice influences liver metabolism and inflammation in adult life.

Materials and Methods: Germ-free mice were colonized with fecal microbiota from children with or without obesity. An additional group of sham mice received gavage with the vehicle only (no microbiota) to assess the effects of microbiota depletion. We monitored fecal microbiota trajectories for 5 months after FMT. We assessed liver-specific glucose metabolism by PET-CT imaging and liver histological analyses were performed to assess steatosis, portal inflammation grade and glycogen droplets size in hepatocytes. Microbial communities were characterized by standard sequencing approaches.

Results: Mice receiving FMT from children with obesity showed enlarged and heavier livers compared to recipients of lean children (1.40±0.04 vs 1.25±0.04 g, p=0.02), with a tendency towards greater microsteatosis (p=0.07 and p=0.09 vs lean and sham groups, respectively). Moreover, FMT from children with obesity resulted in a marked increase in glycogen droplet size within hepatocytes (1.88±0.20 vs 1.32±0.17 a.u., p=0.03. and higher liver glucose uptake (7.67±0.56 vs 6.29±0.47 ID/mmol/L, p=0.03) compared to the lean group. Sham mice exhibited hepatic alterations characterized by a significant increase in portal inflammation (0.75±0.13 vs 0.32±0.09 a.u., p=0.01 vs lean group and 0.40±0.1, p=0.05 vs obese group. and liver glucose uptake compared to FMT mice (9.99±0.58 ID/mmol/L, p=0.0001 vs lean group and p=0.02 vs obese group).

At all time points, fecal microbiota alpha diversity in sham mice was significantly lower than in FMT recipients (p=0.05), which primarily harbored Verrucomicrobiota (24.6). and Bacteroidota (21.5).

Conclusion: Early-life FMT induced long-lasting donor-dependent effects on hepatic glucose metabolism, as seen in adulthood in mice. Gut microbiota depletion was associated with increased portal inflammation, enhancing glucose uptake. These findings underscore the influence of donor characteristics in shaping the gut microbiota ecosystem leading to long-term regulation of liver development.

18-Non-invasive assessment of meal U-13C glucose conversion to hepatic cytosolic acetyl-CoA in T2D MASLD patients using p-amino benzoic acid

Presenter: Jo Jo G. Silva [1,2,]
Collaborators: Cristina Barosa [1], Dulce do [3,] Jo Filipe Raposo [3], Rita Andrade [3], Rog rio Ribeiro [3], Ana Gil[4,] Ludgero Tavares[5] and John G. Jones[1]

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Background and Aims: In the liver, p-Aminobenzoic acid PABA is metabolized via several pathways including conjugation with cytosolic acetyl-CoA with the resulting N-acetyl conjugate cleared into the urine. Enrichment of cytosolic acetyl-CoA from a meal enriched with U-13C glucose can thus be noninvasively measured by analysis of the urinary N-acetyl PABA conjugate, thereby informing the contribution of meal glucose to the hepatic cytosolic acetyl-CoA pool – the immediate precursor for de novo lipogenesis and a key ux of interest in MASLD pathogenesis. We applied this approach to study hepatic glucose metabolism in cohorts of healthy controls and T2D patients who were also assessed for MASLD.

Materials and Methods: After providing informed consent, 21 T2D patients and 7 healthy controls subjects started the study after overnight fasting and collection of blood for baseline biochemical and other parameters of liver and glycemic status. Subjects then ingested a 350-400 ml liquid meal consisting of 47.5g of glucose up to 8g labelled with U-13C Glucose plus 2.5g fructose and 24g of vegan protein shake powder containing 20g of protein. This was accompanied by ingestion of a 500mg PABA capsule. Each subject also underwent a Fibroscan exam. After meal ingestion, capillary blood was collected at regular intervals, together with cumulative urine collections from 0-2 and 2-4 hr post meal. Urinary PABA conjugates were puri ed by preparatory HPLC and 13C-isotopomer enrichments of the N-acetyl moiety was quanti ed by 13C NMR.

Results: Both Fibroscan exams and liver indices showed more MASLD prevalence in the T2D cohort compared to healthy subjects as expected. 13C-NMR of the PABA conjugates demonstrated the presence of UDP-glucose, cytosolic acetyl-CoA and glycine 13C-isotopmers in all subjects con rming the hepatic metabolism labelling of U-13C glucose via all three intermediates. Preliminary analyses indicate that N- U-13C acetyl-PABA enrichment showed signi cant positive correlations with steatosis grade, consistent with a more ef cient conversion of dietary glucose to cytosolic acetyl-CoA in the setting of T2D-MASLD.

Conclusions: This study demonstrates a simple and effective non-invasive method for tracking macronutrient carbons - in this case glucose, into the hepatic cytosolic acetyl-CoA pool – the precursor for de novo fatty acid synthesis and elongation. Our preliminary results suggest that dietary glucose conversion to hepatic cytosolic acetyl-CoA is somehow more ef cient in the setting of T2D-MASLD.

Eligible for award

19-The expression of PLIN2 in monocytes is a metabolic marker of obesity and metabolic dysfunction-associated steatohepatitis (MASH., independent of type 2 diabetes, reflecting an altered metabolomic profile

Presenter: Patrizia Infelise[1],
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Background and Aims: Metabolic dysfunction-associated steatohepatitis (MASH), obesity and type 2 diabetes (T2D. are characterized by metabolic dysfunction and inflammation. Perilipin 2 (PLIN2. has a key role in lipid metabolism and its expression in monocytes has been associated with the severity of MASLD(MASH. The hypothesis is that circulating PLIN2 could reflect metabolic inflammation status of the liver. The aim was to elucidate whether PLIN2 expression in monocytes is associated with a metabolic signature of metabolic syndrome.

Materials and Methods: We included 190 individuals (114 with and 76 without MASH) and divided according the presence of obesity and/or T2D. We calculated index of insulin resistance (HOMA-IR and Adipo-IR) and evaluated the expression of PLIN2 in monocytes extracted from PBMCs. Mass spectrometry-derived metabolomic and lipidomic data were assessed in all participants.

Results: PLIN2 expression in monocytes increased in obese subjects without T2D or MASH compared to those non-obese (p = 0.031). It was also significantly higher in individuals with MASH compared to those without, independently of T2D status. PLIN2 showed strong positive correlation with age, BMI, glycemia, HbA1c, insulin, free fatty acids (FFA), HOMA-IR and Adipo-IR (rho = 0.35, p = 0.001). Furthermore, PLIN2 expression was associated with histological features of liver damage including lobular inflammation, hepatocytes ballooning, steatosis severity and presence of fibrosis. Metabolomic and lipidomic profiling revealed significant positive correlation between PLIN2 and specific metabolites such as lactate, branched-chain amino acids (BCAAs), lysine, leucine, Cer(d18:1/22:0), glutamic acid, PC 42:1,PC42:2, Cer(d18:0/22:0) and DAG 34:1, which remained significant after adjustment for HOMA-IR, BMI, sex, age and NAS. In contrast, some metabolites and lipids indexes showed significant and negative correlations with PLIN2, but these associations lost significance after adjustment.

Conclusions: Elevated PLIN2 expression in circulating monocytes characterizes individuals with obesity and MASH, independent of type 2 diabetes, and reflects underlying hepatic injury. Its association with insulin resistance and specific metabolomic and lipidomic profiles further supports a functional link between adipose tissue metabolism and liver pathology. These findings position monocyte PLIN2 as a promising noninvasive biomarker for assessing hepatic damage and metabolic risk, and as a potential tool for liquid biopsy–based monitoring of MASH progression.

20-Sex-dependent hepatic transcriptomic remodeling in a weight cycling mouse model of MASLD

Presenter: Vanessa Dubois[1],
Collaborators: Sandra Calvo Blanco1, Maya Mukasa[1], Jietse Verweirder[1], Eva Viho[2], Vera Sommers[3], Sander Lefere[4], Julie Dubois-Chevalier[5], Joel Haas[5], Louise Deldicque[6], Greetje Vande Velde[7], Frank Claessens[3], Lindsey Devisscher[8], J[illegible]me Eeckhoute[5]

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD). exhibits marked sexual dimorphism, with men showing higher disease prevalence and severity. Despite increasing recognition of sex as a biological variable, the molecular mechanisms underlying sex differences in MASLD are not fully understood. Here, we established a preclinical model of MASLD integrating weight cycling, a clinically relevant feature that often accompanies lifestyle-based disease management, to investigate sex-dependent mechanisms driving disease progression.

Materials and methods: Adult C57BL/6J mice of both sexes were subjected to repeated cycles of Western diet (WD) feeding and chow diet (CD) recovery, mimicking the metabolic 'yo-yo effect', while control groups were maintained on CD or exposed to a single WD challenge. Metabolic pro[illegible]ling, liver histology, micro-computed tomography, and transcriptomic analyses were performed at multiple time points. Differential gene expression, pathway enrichment, and cell-type–speci[illegible]c analyses were conducted to identify sex-dependent molecular signatures.

Results: A repeated WD challenge induced more pronounced hepatic steatosis and higher serum ALT levels in males compared to females, accompanied by a more severe upregulation of steatotic, in[illegible]ammatory and [illegible]brotic genes. Systemic glucose intolerance was similar between sexes. Transcriptomic pro[illegible]ling revealed a collapse of liver-speci[illegible]c regulatory networks in males, accompanied by downregulation of the transcriptional repressor Bcl6 and a marked feminization of the hepatic transcriptome. This feminization was associated with increased expression of genes involved in lipid catabolism, suggesting an adaptive response aimed at mitigating metabolic stress, but also severely altered pharmacogene expression. Preliminary analyses in human liver transcriptomes indicate that a similar feminization of gene expression occurs in men with increasing MASLD severity.

Conclusion: Using a weight-cycling mouse model of MASLD, we demonstrate that repeated metabolic insults trigger a loss of liver transcriptional identity with a pronounced feminization of the male hepatic transcriptome, driven by Bcl6 repression. This transcriptional reprogramming might represent a coping mechanism to enhance lipid catabolism but also rewires pharmacogene expression, potentially altering drug metabolism. These [illegible]ndings highlight hepatic feminization as a key adaptive process with functional consequences and underscore the importance of sex-speci[illegible]c molecular responses in MASLD pathogenesis and treatment.

Eligible for award

21-The association between adipose tissue dysfunction and MASH severity is mediated by insulin resistance, regardless of BMI

Presenter: Silvia Sabatini[1]

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Background and aims: In metabolic dysfunction–associated steatohepatitis (MASH), lipotoxicity and insulin resistance are key drivers of disease pathogenesis. Adipose tissue dysfunction contributes primarily through excessive free fatty acid (FFA) release and dysregulated adipokine signaling. However, the relationship between adipose tissue insulin resistance (AT-IR), AT dysfunction, and the histological severity of hepatic inflammation and fibrosis remains unclear, partly due to limited biopsy-based data on inflammation.

Materials and methods: Markers of AT dysfunction (MCP-1, TNF-α, leptin, adiponectin), insulin resistance (AT-IR, FFA, insulin and HOMA-IR), hepatic lipid oxidation (β-hydroxybutyrate, BHB), circulating lipids and apolipoproteins were measured in individuals with biopsy-proven metabolic dysfunction-associated steatotic liver disease from the European SLD Registry. Stable isotope lipidomics was used to investigate AT-lipolysis in a subgroup of patients. MASH severity was evaluated in terms of fibrosis stage and activity score. Multivariable regression and mediation analysis were used to elucidate direct and indirect associations.

Results: The cohort included 463 individuals (235 females) with and without type 2 diabetes (T2D, 41 vs 59, respectively) and with a wide range of BMI (20-60 kg/m2), ranging across the full spectrum of MASLD. MASH severity was found associated with increased AT-IR and altered cytokine profiles, independently of BMI and T2D. In particular, we found an association with fibrosis (increased TNF-α and MCP-1. and activity score (2 (increased MCP1 and decreased adiponectin). On the contrary, FFA and BHB, as well as triglycerides and apoliproteins, were not associated with MASLD severity or BMI, but instead they were increased with T2D. Given the strong correlation between AT-IR and the cytokines' levels (TNF-α, MCP-1 and Leptin), we used mediation analysis to untangle the observed net of associations. We found that the association between TNF-α and MASH severity is mediated by AT-IR, while MCP-1 showed also a direct effect on both hepatic inflammation and fibrosis, independently of BMI and T2D.

Conclusion: MASH severity is not strictly linked to BMI or T2D alone, but rather to dysfunctional adipose tissue and insulin resistance. Moving toward a holistic phenotyping of individuals with MASLD is essential to improve risk strati cation and targeted interventions.

22-Exploring the role of circadian rhythms in CDKL5 deficiency disorder

Presenter: M.G. Giuliano[1]
Collaborators: A. Tognozzi[2,4], A. Miniati[1], K.C. Ashtiani[3], G. Vecchieschi[2], F. Damiani[4], S. Cornuti[4], E. Putignano[5], P. Baldi[3], T. Pizzorusso[4], R. Mazziotti[6], P. Tognini[1]

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Background and Aims: CDKL5 deficiency disorder CDD is a rare neurodevelopmental disorder characterized by intellectual disability, seizures, and comorbidities such as stereotyped hand movements and sleep disturbances. Although sleep issues severely affect the quality of life of patients and caregivers, the underlying mechanisms remain poorly understood. In particular, the potential contribution of circadian rhythm disruption and abnormal arousal states to CDD pathogenesis has not been fully investigated. Here, we conducted an in-depth analysis of circadian rhythms in a widely used CDD mouse model.

Materials and Methods: To assess circadian rhythms, we performed long-term thermographic monitoring of locomotor activity and body temperature in CDKL5 KO and wild-type WT mice. Metabolic cages were used to monitor 24-hour patterns in respiratory exchange ratio, feeding, and drinking behaviors. Transcriptomic profiling was conducted on brain samples collected at six Zeitgeber times, to explore the circadian gene expression profile in WT and KO animals.

Results: CDKL5 KO mice exhibited increased locomotor activity and elevated body temperature, especially during light-phase transitions. Automated sleep detection showed reduced total sleep time and shorter sleep bouts during the dark phase. Transcriptomic analysis showed an increased number of oscillating genes in KO mice, with altered phase distributions. In the SCN, gene ontology enrichment highlighted immune- and inflammation-related processes suggesting broader immune involvement in the brain potentially driven by disrupted circadian regulation in the absence of a functional CDKL5 protein. Metabolic cage data further revealed altered rhythms in feeding, drinking, and respiratory exchange in KO mice.

Conclusions: Overall, these findings indicate that CDKL5 loss may affect circadian regulation, with consequences not only on the sleep-wake cycle but also on broader metabolism and immune system activity. By uncovering circadian and immune dysregulation in a CDD model, our study provides novel insights into the multifaceted impact of CDKL5 deficiency and suggests new avenues for therapeutic intervention. Accordingly, ongoing work aims to evaluate the role of orexin signaling in modulating arousal disturbances observed in CDKL5 KO mice.

23-Succinate Modulation as a Biochemical Correlate of Metabolic and Neurobehavioral Changes Associated with Intermittent Fasting in Obesity

Presenter: Andrea Tognozzi[1,2,]
Collaborators: Fabrizia Carli[3], Sherif Abdelkarim[4], Sara Cornuti[2], Francesca Damiani[2], Maria Grazia Giuliano[5], Alice Miniati[5], Martina Nasisi[3,] Lia De Benedictis[3], Kousha Changizi Ashtiani[4], Gaia Scabia[3], Margherita Maffei[3], Pierre Baldi[4], Amalia Gastaldelli[3] Paola Tognini[5]

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Background and Aims: Obesity profoundly affects the central nervous system (CNS), contributing to neuroinflammation, cognitive impairment, and increased risk of neuropsychiatric disorders. Intermittent fasting (IF) has emerged as a promising intervention improving metabolic health and potentially support brain function. However, the mechanisms linking IF to CNS metabolism and behavior remain poorly understood. This study investigates how IF influences metabolic, neuroinflammatory, and behavioral outcomes in a mouse model of diet-induced obesity.

Materials and Methods: Male mice were initially fed a high-fat diet for 10 weeks, then assigned to one of four groups depending on the dietary regimen for the following 4 weeks: HFD, HFD with IF (HFD-IF), a control chow diet (CC), and chow with IF (CC-IF). Body weight, fat mass, and glucose tolerance were assessed. Behavioral tests evaluated exploration and anxiety-like responses. To elucidate underlying mechanisms, integrated transcriptomic and metabolomic analyses of hippocampus and liver identified succinate as a key metabolite potentially mediating the effects of IF. To explore the potential role of succinate in CC-IF, it was administered for 4 weeks in drinking water, specifically to the HFD and CC groups.

Results: The dietary switch reduced body weight, fat mass, and improved glucose tolerance. CC-IF uniquely enhanced exploratory behavior and reduced anxiety-like responses. Hippocampal transcriptomics revealed that HFD upregulated immune and neuroinflammatory pathways, while CC-IF attenuated these effects, potentially via decreased plasma and increased hepatic and BAT succinate levels. Succinate supplementation replicated several metabolic, behavioral, and anti-inflammatory benefits observed in CC-IF mice.

Conclusion: Our findings suggest that targeted modulation of succinate metabolism may represent a novel biochemical correlate underlying the metabolic, neuroinflammatory, and behavioral improvements induced by IF.

24-A new small-molecule M21 targets TRPA1 to engage GLP-1 biology, induce food intake-independent weight loss, and reduce fatty–brotic liver injury in dbdb mice

Presenter: Giuseppe Daniele[1],
Collaborators: Valentina Citi[2], Lucrezia Comparini[2], Giorgia Bray[2], Giulia Galgani[2], Alma Martelli[2], Vincenzo Calderone[2], Mauro Pineschi[2]

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Background and Aims: Transient Receptor Potential Ankyrin 1 TRPA1. is a polymodal Ca^{2+}-permeable channel expressed in sensory and non-neuronal cells. Beyond nociception and in ammation, TRPA1 regulates body weight, gut hormone secretion, and thermogenesis. We developed M21, a patented small-molecule TRPA1 agonist, to test TRPA1-dependent GLP-1 release and thermogenic signaling in vitro and to assess metabolic ef cacy in dbdb mice.

Materials and Methods: A 30-compound library was screened for TRPA1 activation in STC-1 enteroendocrine cells by Ca^{2+} in ux Fluo-4 withwithout the selective TRPA1 blocker A967079. Active chemotypes were pro led for GLP-1 secretion. Lead compound M21 was tested in 3T3-L1 adipocytes for UCP-1 expression and citrate synthase activity thermogenesismetabolic ux. Male dbdb mice and C57BL6 controls were acclimatized 6 weeks. and randomized to: C57BL6, dbdb vehicle, dbdbmetformin 200 mgkgday, or dbdbM21 20 mgkgday. Treatments were delivered continuously in drinking water under standard housing with ad libitum chowwater until 18 weeks. Outcomes: weekly body weight; serial non-fasted glucose; HbA1c; terminal plasma triglycerides, total cholesterol, insulin; liver histology steatosis and perivascular collagen. Food and water intake were recorded.

Results: Multiple compounds increased intracellular Ca^{2+} in STC-1 cells; responses were abolished by TRPA1 blockade, con rming on-target activity. GLP-1 secretion correlated with TRPA1 activation, nominating M21 as lead. In 3T3-L1 cells, M21 increased UCP-1 and citrate synthase, consistent with browningthermogenesis. In dbdb mice, M21 induced progressive 27 weight loss vs dbdb vehicle despite unchanged foodwater intake; metformin produced a small, non-signi cant weight change. Glycemia improved in both active arms, with HbA1c reductions of 25M21. vs 17metformin. M21 normalized triglycerides to C57BL6 levels; metformin caused a modest, non-signi cant decrease. Total cholesterol was unchanged across dbdb groups. Plasma insulin was elevated in dbdb and increased further with M21 metformin tended to lower insulin. Liver histology aligned with systemic effects: M21 markedly reduced neutral lipid droplets numbersize., attenuated perivascular collagen on Sirius RedFast Green, and decreased red-orange birefringence under polarization, consistent with less mature type-I collagen and reduced tissue stiffness. Metformin showed partial, generally inferior improvement.

Conclusion: Oral TRPA1 agonism with M21 yields intake-independent weight loss, HbA1c improvement, full triglyceride normalization, and amelioration of hepatic steatosis and perivascular brosis in dbdb mice. These actions, compatible with enhanced thermogenesisenergy expenditure and gut incretin engagement, support M21 as a liver-bene cial strategy for metabolic disease and MASLD.

25-Mass spectrometry-based untargeted metabolomics in lean patients with MAFLD

Presenter: Gokcen Basaranoglu MD[1]
Affiliations: 1. Bezmialem Vakif University Hospital

Background and Aims: MAFLD is a disease characterized by the accumulation of fat in the liver with or without fibrosis which requires non-invasive diagnostic biomarkers. While typically observed in overweight individuals. Comparative studies on lean MAFLD patients is rare. This study aimed to conduct a using liquid chromatography-high resolution mass spectrometry (LC-MS/MS.-based metabolic profiling of lean MAFLD patients and healthy controls.

Materials and Methods: The patient group consisted of 27 individuals with MAFLD, while the healthy control group included 39 individuals. Both groups were between 18 and 40 years old, had a BMI of less than 25 and had alcohol consumption less than 20 g/week for men and 10 g/week for women. Serum samples were collected and analyzed using LC-MS/MS. The data were analyzed using the TidyMass and MetaboAnalyst.

Results: The LC-MS/MS analyses detected significant changes in D-amino acid metabolism, vitamin B6 metabolism, apoptosis, mTOR signaling pathway, lysine degradation, and phenylalanine metabolism pathways in lean MAFLD patients. Overall, the study provides valuable insights into the metabolic changes associated with lean MAFLD patients and can contribute to the development of non-invasive diagnostic biomarkers for MAFLD.

Conclusions: This study sheds light on the metabolic changes in lean MAFLD patients. Further research is needed to better understand the metabolic changes associated with MAFLD and to develop effective treatment options.

Eligible for award

26-Improving Cardiovascular Risk Stratification Through the Derivation and Validation of an Elevated Triglyceride-Glucose Index

Presenter: Stavros Athanasopoulos
Collaborators: Georgios Mavraganisa, , Georgios Georgiopoulosa,b, , Stavros Athanasopoulosa, , Dimitrios Terentes-Printziosc, , Georgios Zervasa, Christina Konstantakia, Maria Eleni Koilakouc, Sofia-Panagiota Giannakopouloud, Maria-Angeliki Dimopouloua, Christina Chrysochoouc, Konstantinos Tsioufisc, Christos Pitsavosc, Evangelos Liberopoulose, Konstantinos Stellosf,g,h,i, Charalambos Vlachopoulosc, , Demosthenes Panagiotakosd, , Kimon Stamatelopoulosa,j,
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Background and Aims: Triglyceride-glucose (TyG. index, is an emerging prognostic biomarker in atherosclerotic cardiovascular disease (ASCVD). Validation of its clinical value and of clinically relevant prognostic cut-off, remains an unmet need to integrate TyG into primary prevention protocols.

Materials and Methods: To assess the clinical applicability of TyG, a composite of cardiovascular mortality, myocardial infarction, coronary revascularization or stroke was used as the primary endpoint in a general population cohort (ATTICA cohort, n=1,677, derivation cohort). Next, we derived an optimal prognostic TyG cut-off and externally validated it in a primary prevention cohort (n=1,237). To assess the clinical value of TyG, we analyzed 1,170 consecutively recruited patients from an ongoing registry aiming to stratify ASCVD risk (Athens Cardiometabolic Cohort. and assessed indices of subclinical arterial injury and progression of atherosclerosis. TyG index was calculated by the formula: ln(fasting triglycerides (mg/dL. x fasting glucose (mg/dL.)/2).

Results: TyG index was independently associated with increased CVD events in the derivation cohort (HR=1.33, p=0.020). The incremental value of a derived optimal cut-off of 8.46 over SCORE2 was confirmed in both derivation and validation cohorts (net reclassification index (NRI.=0.668 and 0.469 respectively, Delta Harrell's C index=0.054 and 0.044 respectively, p<0.05 for all). Elevated TyG index was associated with more diseased vascular beds (OR=2.00, 95% CI 1.24-3.24., progression of subclinical carotid atherosclerosis (OR=2.99, 95% CI 1.10-8.17. at follow-up and established ASCVD (p<0.05 for all).

Conclusions: TyG is associated with increased prevalence and progression of subclinical and clinically overt ASCVD. In individuals assessed for primary prevention a TyG>8.46 may serve as a risk enhancer.

27-A Nutritional Challenge Reprograms Microglial Transcriptome and Function via Gut Microbiota–Brain Crosstalk

Presenter: Alice Miniati[1], Sara Cornuti[2], Kousha Changizi Ashtiani[3], Andrea Tognozzi1,[4], Sherif Abdelkarim[3], Valentino Totaro[2], Maria Grazia Giuliano[1], Pierre Baldi[3], Paola Tognini[1]

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Background and Aims: High-fat diet (HFD. consumption and obesity are associated with cognitive deficits, depression, and anxiety, affecting emotional and social behaviours. The metabolic dysregulation induced by HFD disrupts systemic homeostasis, engaging immune and inflammatory pathways and promoting chronic low-grade inflammation that can extend to the brain, increasing neuroinflammatory risk. Microglial cells, as key mediators of neuroimmune communication, are highly responsive to peripheral metabolic and inflammatory cues. However, how HFD-driven metabolic alterations reshape microglial function and influence brain physiology and behaviour remains incompletely understood.

Materials and Methods: Adult CX3CR1-GFP male mice were fed an HFD for six weeks to induce metabolic imbalance. Behavioural assessments included the Y-maze (exploratory activity. and the three-chamber test (social behaviour). Microglial involvement was tested through pharmacological ablation using clopidogrel injections.

To identify molecular mechanisms, RNA sequencing was performed on isolated microglia to define their transcriptomic profile. Immune responsiveness was examined after lipopolysaccharide (LPS. administration. Gut microbiota composition was analysed by 16S rRNA sequencing, and fecal microbiota transplantation from HFD-fed donors to control recipients was conducted via oral gavage. Body composition and microglial gene expression were subsequently evaluated.

Results: Behavioral analyses revealed that exploratory behavior remained unchanged, while social behavior was significantly altered following HFD exposure. Microglial ablation confirmed that these behavioral changes were microglia dependent. To elucidate the underlying molecular mechanisms, transcriptomic profiling of microglia was performed, revealing extensive HFD-induced transcriptional remodeling, characterized by downregulation of immune-related transcripts and upregulation of mitochondrial metabolism-associated annotations. To further explore these pathways, mice were challenged with LPS, which uncovered a reduction in microglial proliferation across multiple brain regions in HFD-fed mice compared to chow-fed controls, suggesting impaired neuroimmune responsiveness under metabolic stress. The 16S rRNA sequencing revealed marked shifts in gut microbial communities in HFD-fed mice. Following fecal microbiota transplantation, recipient mice exhibited increased fat depot weight and microglial transcriptional profiles overlapping with those of HFD donors, indicating that the alterations observed in HFD-fed mice could be partially transferred through the gut microbiota. To further explore the HFD microbiota-driven phenotype transfer, LPS-mediated effects were also assessed.

Conclusion: These results demonstrate that HFD profoundly reprograms microglial activity and immune function, leading to altered brain immune responses and behavioral outcomes. Part of these effects are mediated through nutrition-driven remodeling of the gut microbiota, emphasizing the gut–brain–

immune axis as a critical mechanistic link between metabolic dysfunction and neuropsychiatric manifestations associated with obesity, and highlighting its role as a potential therapeutic target.

29-Differential Associations Between Liver Fat and Postprandial Glucose Levels Across Sex and Menopausal Status; The Maastricht Study

Presenter: Esther J. Kemper[1], Michiel Adriaans[2], Carla J.H. van der Kallen [3,4], Annemarie Koster [5,6], Martijn C.G.J. Brouwers [3,7], Bastiaan E. de Galan [3,7], Marleen van Greevenbroek [3], Ellen E. Blaak [1], Ruth C.R. Meex [1]

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Background and Aims: Metabolic dysfunction-associated steatotic liver disease (MASLD. is the most common liver disorder and is characterized by hepatic steatosis. Interestingly, women develop steatosis more slowly and experience less associated metabolic complications than men, but this protection diminishes after menopause. However, some research suggests that once steatosis occurs in women, MASLD progression is associated with worse metabolic outcomes. Importantly, research is limited and often lacks age strati+cation and details on steatosis severity, limiting insights into how liver fat is related to metabolic health across sex and menopausal status.

Materials and Methods: We analyzed data from 1,835 participants of the Maastricht study, a large population-based cohort, to investigate sex and menopause-speci+c associations between liver fat and metabolic health. Strati+ed linear mixed-effect models were applied in premenopausal (n=242. and postmenopausal women (n=664. and age-matched men (n=201 and n=728 respectively., adjusting for age, BMI, alcohol consumption, smoking status and physical activity.

Results: Liver fat was lower in premenopausal women compared to postmenopausal women and older men (2.88%, 3.86%, 4.02% and 4.47% in pre- and postmenopausal women and age-matched men, respectively; p<0.05). Linear regression analyses showed that liver fat was positively associated with HOMA-IR and with fasting and 2h-OGTT insulin levels in all groups (β= 0.16, p<0.05 for all associations). The association between liver fat and 2h-glucose levels was signi+cant in all groups (p<0.01., except in pre-menopausal women (β= 0.06, p=0.24).

Conclusion: The relationship between liver fat and metabolic health differs between pre- and postmenopausal women and men. Notably, liver fat was not associated with 2h-glucose concentrations in premenopausal women. Analyses in the near future will incorporate interaction effects to further clarify the nature and extent of sex- and menopause-related differences.

30-Long-term real-life experience of semaglutide in a monocentric cohort with type 2 diabetes and metabolic dysfuction-associated steatotic liver disease (MASLD).

Presenter: Petralli Giovanni [1-2],

Collaborators: Salvati Antonio [1], Cappelli Simone [3], Surace Lidia [1], De Rosa Laura [4], Damone Francesco [3], Tricò Domenico [3], Solini Anna [2], Brunetto Maurizia Rossana [1-3]

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Background and Aims: MASLD is the liver manifestation of a multifaceted metabolic disorder, strongly associated with type 2 diabetes (T2D). Subcutaneous semaglutide, highly effective in T2D treatment, has recently been shown to induce resolution of steatohepatitis, albeit at the higher 2.4 mg weekly dose. We longitudinally evaluated a T2D-MASLD cohort following the introduction of semaglutide 1 mg weekly for diabetes optimization, aiming to assess its long-term effects on liver disease activity.

Materials and Methods: Ninety patients (age 60.7±9.9years; 38%female; T2D-duration 5 (1–8) years. were evaluated non-invasively through anthropometry, biochemical profiling, and transient elastography (FibroScan®. at baseline (t0., 6 months (t1, range 5-8 months., and 24 months (t2, range 21-31 months, n=67) Variations (Δ. in alanine aminotransferase (ALT., controlled attenuation parameter (CAP., and liver stiffness measurement (LSM. were used as proxies of liver disease burden. The PNPLA3 I148M polymorphism was also assessed. Ultrasound evidence of irregular liver margins, left-lobe hypertrophy, and a nodular echo-pattern defined compensated cirrhosis.

Results: After treatment, significant reductions (p<0.01. were observed in BMI (t0 32.6±5.7 kg/m²; Δt1–t0 −6±1, Δt2–t0 −6±1., glycated hemoglobin (HbA1c; t0 53±13 mmol/mol; Δt1–t0 −17±2, Δt2–t0 −13±2., ALT (t0 35 (22–54). U/L; Δt1–t0 −22±5, Δt2–t0 −20±5, CAP t0 339 (288–372). dB/m; Δt1–t0 −33, Δt2–t0 −6±4, and LSM (t0 8.2 (5.5–11.0). kPa; Δt1–t0 −25±4, Δt2–t0 −11±5. No significant differences were detected between t1 and t2, except for a mild HbA1c increase (+2.4±0.8 mmol/mol; p=0.006). At t1, a −17 U/L ALT reduction occurred in 36% of patients, while ≥30% reductions in CAP and LSM were observed in 14% and 39% of patients, respectively, comparable to t2–t0 changes. Variations in ALT, CAP, and LSM were not influenced by PNPLA3 polymorphisms, baseline BMI, or HbA1c. Compared with the patients without cirrhosis (n=77., those with cirrhosis (n=13. exhibited a significant increase in CAP over time (Δt1–t0 −5±4 vs −8±9, respectively, p=0.169; Δt2–t0 −9±4 vs −21±12; p=0.02. Numerical subgroup differences were also observed regarding ALT (Δt1–t0 −18±5 vs −42±12; Δt2–t0 −19±6 vs −32±15., and LSM (Δt1–t0 −24±5 vs −32±12; Δt2–t0 −10±5 vs −22±14.

Conclusion: Semaglutide at a 1 mg weekly dose effectively reduces steatotic and fibro-inflammatory liver involvement in diabetic MASLD, with early improvements at 6 months that persist over time without further enhancement. Baseline anthropometric parameters, glycemic control, and PNPLA3 genotype do not modify the hepatic response to semaglutide. Notably, steatohepatitis improvement was maintained even in cirrhotic patients, though the observed CAP increase warrants further investigation.

Eligible for award

31-Adipose tissue insulin resistance, not muscle insulin resistance, is associated with impaired metabolic health in humans

Presenter: Kiana Meshkat[1], Anouk Gijbels[2], Lydia A. Afman[2], Gijs H. Goossens[1], Ellen E. Blaak[1], Ruth C.R. Meex[1]
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Background and Aims: Obesity is a major contributor to insulin resistance IR. and increases the risk of cardiometabolic diseases. While insulin resistance is traditionally considered a multi-organ condition, emerging evidence suggests that it can manifest in a tissue-specific manner, leading to discordant IR phenotypes. In fact, IR may be present in one metabolic tissue, whilst other tissues remain relatively insulin sensitive IS. This study aims to characterize metabolic and clinical differences among individuals with discordant IR patterns in adipose tissue and skeletal muscle.

Materials and Methods: Baseline data from the PERSON study were analyzed, including 229 adults age 40–75 years, BMI 25–40 kg m². Participants were categorized into four groups based on medians of muscle and adipose tissue IS indices: muscle-IS adipose-IS, muscle-IR adipose-IS, muscle-IS adipose-IR, and muscle-IR adipose-IR. Muscle IR was assessed using a 7-point oral glucose tolerance test, while adipose tissue insulin resistance was determined from fasting plasma insulin and non-esterified fatty acid concentrations. Detailed phenotyping was conducted in controlled laboratory settings and daily life. Associations between adipose tissue and muscle IR phenotypes and cardiometabolic markers were analyzed through group-based and continuous analyses.

Results: Based on the median of tissue-specific IR, 42 of participants showed discordant patterns of IR between skeletal muscle and adipose tissue. Independent of skeletal muscle IR, individuals with adipose IR had an unfavorable cardiometabolic profile, characterized by abdominal fat accumulation, higher fasting insulin std β 0.74, p 0.001. and HOMA-IR std β 0.53, p 0.001., higher triglycerides std β 0.24, p 0.001., higher glycemic variability, more liver fat std β 0.29, p 0.006., and hepatic IR HIRI. std β 0.47, p 0.001., compared to those with adipose insulin sensitivity. In contrast, individuals with muscle IR but adipose tissue IS maintained a relatively healthy cardiometabolic profile, with no major disruptions in glucose regulation or lipid metabolism. Notably, regardless of adipose IR, muscle IR was linked to higher HOMA-IR std β -0.29, p 0.005., muscle fat infiltration std β -0.33, p 0.020., and HIRI std β -0.19, p 0.047. in women, but not in men, suggesting a sex-specific effect in muscle IR as well as a liver-muscle cross-talk.

Conclusion: Individuals with adipose tissue IR are characterized by a more unfavorable cardiometabolic risk profile compared to those with isolated skeletal muscle IR. These findings highlight the need for tailored lifestyle. interventions targeting specific IR phenotypes to optimize cardiometabolic health.

Eligible for award

32-Glucagon and Nutrient Composition Shape Postprandial Metabolic Responses After Gastric Bypass Surgery

Presenter: Samantha Pezzica [1],
Collaborators: Azam Alamdari [2], Marzieh Salehi [2], Amalia Gastaldelli [1,2]

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Background and Aims: The metabolic benefits of gastric bypass (GB) are well established, but the role of GB-induced hyperglucagonemia in postprandial metabolism remains unclear. This study examined how nutrient composition and increased plasma glucagon concentration by 1.5-fold by exogenous glucagon administration influence postprandial glucose and metabolomic responses after GB.

Materials and Methods: Five non-diabetic GB subjects (9.0±1.7 years post-surgery) and seven matched non-surgical controls (CT) underwent 3 tests: oral glucose (50g. (OGT), oral glucose (50g.)+protein (50g. (OGPT), oral glucose (50g.)+protein (50g.) with iv glucagon infusion (2ng/kg/min. (OGPT+GCG).
Measurements included prandial (0-180min.) plasma concentrations of glucose and hormones, glucose kinetics (endogenous production (EGP), oral rate of appearance (OralRa), clearance (GluClear), and Insulin Secretion Rate (ISR) and metabolomic profile (evaluated by GC-MS).

Results: Compared to CT, GB had higher prandial GLP-1, ISR, EGP and GluClear regardless of nutrient composition. During OGT, GB vs CT had higher GluClear, ISR, GLP-1 and glucagon concentrations but similar mean glucose and insulin concentrations, EGP and OralRa, although in GB most of glucose appeared in the first 60min. Adding protein to glucose (OGPT) vs OGT increased insulin and glucagon and reduced GIP in both groups; reduction of glucose concentrations in CT and increase in EGP in GB only were observed, while the other variables were similar. The amino acid profile was increased during the OGPT vs OGT, but higher in GB vs CT. GB also had higher concentrations of glucogenic and branched-chain amino acids (BCAAs). Glucagon and alanine were positively correlated during OGPT in all subjects and only in GB during OGT.Raising glucagon concentration within the physiological range during OGPT+GCG did not alter insulin or glucose kinetics, but slightly reduced OralRa and postprandial amino acids (AA) compared with OGPT in both groups, although the BCAA were reduced only in GB. Finally, free fatty acids (FFA) and beta-hydroxybutyrate (BHB) prandial concentrations were unchanged, but correlated across all 3 studies in both GB and CT.

Conclusion: Protein ingestion modulates glycemia, AA, and hormonal responses differently in GB versus CT, indicating altered nutrient sensing after surgery. Enhanced AA responses and glucagon–alanine coupling in GB suggest rerouted gut metabolism alters AA kinetics. Physiological glucagon elevations lower plasma AAs, particularly in GB, while preserved FFA–BHB correlations indicate intact lipolysis–ketogenesis linkage regardless of nutrient composition or glucagon levels.

Eligible for award

33-Genetic markers for prediction of clinical outcomes in metabolic dysfunction associated steatotic liver disease

Presenter: Elias Badal Rashu[1,3], Silvia Sabatini[5], Mikkel Parsberg Werge[1], Liv Eline Hetland[1], Mira Thing[1], Puria Nabilou[1], Nina Kimer[1], Anders Ellekaer Junker[1] Anne-Sofie Houlberg Jensen[1,4,] Amalia Gastadelli[5], Stefan Stender[2,3],[] Lise Lotte Gluud[1,2]

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Background and Aims: The use of genetic variants associated with metabolic dysfunction associated steatotic liver disease (MASLD) in clinical practice remains a significant area of interest. Understanding of the interplay between genetic and metabolic risk factors in the development and progression of MASLD may facilitate a more precise risk stratification and referral.

Materials and methods: Patients with MASLD were evaluated yearly in a prospective cohort study. 688 individuals with MASLD that underwent liver biopsy and/or liver elastography were considered. Genetic variants were identified using an Illumina GWAS chip. The prevalence of significant fibrosis, cardiovascular disease, all-cause mortality, and major liver related outcomes (MALO) in association with genetic and cardiometabolic risk.

Results: Of 688 patients included, at baseline 50.1% had fibrosis, 5.5% had cardiovascular disease, 6.1% (N=42) had experienced MALO. During follow-up 3.6% (of N=25) died of which 2.5% were cirrhosis related death, and 4.1% (N=28) developed MALO. The individual genetic variants and the GRS were associated with fibrosis but not cardiovascular disease. A high vs low GRS was associated with increased all-cause mortality (odds ratio (OR) 1.38, 95% confidence interval (CI) 1.01–1.90; P=0.04). The risk of MALO was approximately 9.2-fold and 11.7-fold higher in patients with type 2 diabetes and PNPLA3 risk variants (CG or GG) or a high GRS, respectively, as compared to those without diabetes and either PNPLA3 CC or a low GRS (P=0.004 and P=0.0001). Similar findings were seen in patients with obesity and a high GRS (OR 6.69 (3.01–16.99)).

Conclusions: The study found a link between clinical outcomes in MASLD and genetic risk, with stronger associations in patients with type 2 diabetes and obesity suggesting that genetic risks could help tailor patient management in MASLD with metabolic comorbidities.

34-Circulating microRNA signatures as potential biomarkers in diabetic kidney disease phenotypes strati cation

Presenter: A. Sgalippa [1], M. Cabiati [2], L. Guiducci [2], D. Lucchesi[3], M. Garofolo[3], G. Penno[3], S. Del Ry[1,2]

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Background and aims: Diabetes mellitus DM. is a major global health challenge, with type 2 diabetes T2DM. representing 85–90 of all cases. Up to 40 of T2DM patients develop diabetic kidney disease DKD., a heterogeneous condition characterized by glomerular and tubular injury leading to a decline in eGFR, which may occur with or without microalbuminuria. Epigenetic mechanisms, particularly non-coding RNAs such as microRNAs miRNAs., are emerging as key regulators of DKD pathogenesis. However, current ndings remain inconsistent, highlighting the need for further research before clinical translation. This study aimed to investigate the expression patterns of selected circulating miRNAs involved in DKD-related pathways in T2DM patients with different DKD phenotypes, in order to identify those predictive of disease progression.

Materials and Methods: T2DM patients n40. were enrolled and strati ed into 4 groups according to DKD phenotype: T2DM without DKD group 1, n10.; T2DM with DKD stages 1-2 group 2, n10.; T2DM with non-albuminuric Alb-. DKD stages 3 group 3, n10.; T2DM with albuminuric Alb. DKD stages 3 group 4, n10. All patients were characterized by clinical and biohumoral parameters. The transcriptional pro le of selected circulating miRNAs miR21-5p, miR192-5p, miR214-3p and miR29a-3p. was analysed through Real-Time PCR.

Results: miR21-5p was signi cantly overexpressed in groups 3 and 4 compared to group 2 p0.002 and p0.0005, respectively., consistent with its role in promoting brosis typical of DKD progression. miR192-5p expression decreased progressively with disease severity p0.03 and p0.002, group 1 vs 3 and 4 respectively. Conversely, miR29a-3p levels were higher in groups 2, 3, and 4 than in group 1 p0.0001, p0.004, p0.004 respectively., indicating upregulation in DKD. miR214-3p expression was signi cantly lower in group 2, 3 and 4 compared to group 1 p0.0005, p0.0001, p0.0001 respectively. Moreover, among DKD groups miR214-3p levels resulted higher in Alb patients compared to Alb- p0.005. A preliminary multiregression analysis including miRNAs expression data and biohumoral clinical parameters, identi ed miR21-5p as an independent determinant of DKD p0.02.

Conclusion: This is a pilot study due to its innovative strati cation of patients based on DKD-phenotypes. Our results on circulating miRNAs, although preliminary and to be validated in the full cohort of 160 currently enrolled subjects, suggest their potential role in disease modulation, with distinct expression patterns among phenotypes. These ndings support the hypothesis that non-coding RNAs contribute to DKD pathophysiology, highlighting miR21-5p as a potential disease-related biomarker.

35-Dynamic Stress Hyperglycemia Ratio during OGTT Uncovers Metabolic Alterations in Subjects with Hepatic Steatosis

Presenter: Annamaria Dagostino

Collaborators: Mariangela Rubino, Annamaria Dagostino, Daniela Calipari, Flora Barreca, Mattia Massimino, Stefania Belviso, Rosaria Isabella, Valeria Casciaro, Diego Mesoraca, Giorgia Natale, Maria Caterina Gioia, Gaia Chiara Mannino, Francesco Andreozzi

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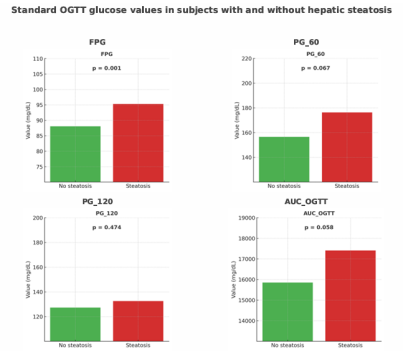
Background and Aims: Stress Hyperglycemia Ratio (SHR), defined as the ratio between current glucose and estimated average glucose, quantifies relative hyperglycemia compared with chronic glycemic exposure. Although traditionally used in acute settings to assess stress-induced hyperglycemia, its dynamic assessment during an oral glucose tolerance test (OGTT) may reveal early metabolic alterations related to current stress. Our study assessed dynamic SHR profile during OGTT to determine its utility as an early marker of metabolic dysfunction in hepatic steatosis.

Materials and Methods: Ninety-nine normotolerant adults (77 with and 22 without hepatic steatosis confirmed by transient elastography). were enrolled. Anthropometric, biochemical and metabolic variables were recorded. SHR was calculated at fasting, 60 and 120 minutes during OGTT (SHR0, SHR60, SHR120). The novel Area Under the SHR Curve (AUC-SHR). was derived using the trapezoidal rule.

Results: Participants with hepatic steatosis exhibited several risk factors: higher systolic (p=0.004). and diastolic blood pressure (p=0.001)., lower HDL-cholesterol (p=0.024)., higher triglycerides (p=0.034). and ALT (p=0.011). BMI, HOMA-IR, total cholesterol, LDL-cholesterol, HbA1c and insulin sensitivity were not significantly different. Metabolic analysis revealed steatosis was associated with significantly higher SHR_0 (0.829 ± 0.092 vs 0.763±0.066, p=0.001)., SHR60 (1.527±0.396 vs 1.347±0.312, p=0.031). and AUC-SHR (150.99±28.10 vs 136.70±23.43, p=0.021). Conversely, among conventional OGTT parameters, only fasting plasma glucose was significantly higher in steatosis (p=0.001)., while post-load glucose values and AUC-OGTT were not significantly different.

Conclusions: Hepatic steatosis in non-diabetic individuals is characterized by a disproportionate glycemic response to glucose load, a perturbation effectively captured by dynamic SHR indices (SHR_0, SHR_{60}). and the novel AUC-SHR, but missed by standard glucose assessment. The AUC-SHR may serve as a novel integrated marker of recurrent post-prandial glycemic stress that drives early cardiometabolic risk in MASLD. This suggests a heightened vulnerability to the "glucose insult" at mealtime, potentially reflecting an amplified oxidative/inflammatory response within the steatotic liver.



Eligible for award

36-Mind the Liver-Heart Axis in Metabolic Dysfunction-Associated Steatotic Liver Disease: MRI-derived extracellular volume fraction mapping reveals subclinical cardiac tissue remodeling

Presenter: Puria Nabilou[1],
Collaborators: Signe Wiese [1,2,4], Liv E. Hetland[1], Mikkel Parsberg Werge[1], Elias Badal Rashu[1], Mira Thing[1], Anders Ellekær Junker[1], Mads Barløse[3,4], Hartwig Roman Siebner[4,5,6], Flemming Bendtsen [1,7], Søren Møller[3,4], Jens D. Hove[4,7], Lise Lotte Gluud[1,4]

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is increasingly recognized as a systemic inflammatory disorder that is linked to elevated cardiovascular risk. This study evaluated whether magnetic resonance imaging (MRI)-derived extracellular volume fraction (ECV) mapping of the heart, liver, and pancreas reflects extracel-lular matrix remodeling in relation to liver disease severity.

Materials and Methods: We prospectively examined 39 adults with biopsy-confirmed MASLD and no clinically evident cardiovascular disease and 10 healthy controls with contrast-enhanced 3.0-Tesla MRI. T1 mapping provided ECV values for the myocardium (n = 49), liver (n = 30), and pancreas (n = 20). In MASLD patients, non-invasive fibrosis markers were assessed, including the Fibrosis-4 index (FIB-4), liver stiffness measurement (LSM) and the Enhanced Liver Fibrosis test (ELF).

Results: Myocardial ECV did not differ between patients and controls but was significantly higher in patients with advanced liver fibrosis identified by FIB-4 (2.67, p = 0.046), LSM (12.5 kPa, p = 0.030), and ELF (9.8, p = 0.036). Myocardial ECV correlated positively with FIB-4 (r = 0.39, p = 0.012). Liver ECV was elevated in histologically advanced fibrosis and correlated positively with portal pressure (r = 0.63, p = 0.039), LSM (r = 0.60, p = 0.001), and histological stage (r = 0.48, p = 0.001). Pancreatic ECV was unrelated to liver fibrosis but correlated with glycated hemoglobin HbA1c (r = 0.40, p = 0.038).

Conclusion: Multi-organ ECV quantification may serve as a non-invasive biomarker of sys-temic inflammatory remodeling in MASLD. This MRI-derived approach holds potential for non-invasive disease monitoring and assessment of therapeutic response.

Eligible for award

37-Longitudinal interactions between insulin clearance and the main glucose homeostasis mechanisms in non-diabetic individuals: An IMI-DIRECT study

Presenter: C. A. Rossi[1,2]; L. Marchetti[2]; M. Lauria[2]; G. Fantoni2; E.R. Pearson[3]; A. Mari1; R. Bizzotto[1]

Affiliations

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3 University of Dundee, Dundee, UK.

Background and aims: Insulin clearance is an important determinant of glycaemic control in non-diabetic subjects, but its relationships with the main glucose homeostasis mechanisms are unclear, especially in longitudinal terms. We investigated the independent associations between OGTT-derived insulin clearance and metabolic parameters over 4 years in individuals at risk of type 2 diabetes (T2D).

Materials and methods: OGTTs were performed at months 0, 18 and 48 in white North European individuals from the IMI-DIRECT study (N=1885). OGTTs were used to derive oral insulin clearance (CLIo., insulin sensitivity (OGIS and Stumvoll indices., insulin secretion (ISR. and β-cell function parameters, i.e. β-cell glucose sensitivity (slope of the ISR-glucose relationship, GS., rate sensitivity (marker of first-phase ISR., potentiation ratio (potentiation of ISR over the 2-h OGTT., and standardized ISR at fixed 6.3 mmol/L glucose.
Other investigated parameters included HbA1c, fasting and incremental glucose, family history of T2D, lifestyle, blood pressure, anthropometrics and MRI-derived ectopic fat measurements (e.g., visceral, subcutaneous, hepatic, and pancreatic fat; N=854). Insulin sensitivity indices were replaced by their first principal component (80% variance explained).
Independent associations between changes (18 vs 0 and 48 vs 18 months. in CLIo and changes and/or baseline values of all other parameters were assessed via linear mixed-effect modelling through stepwise backward selection.

Results: Longitudinal reduction of CLIo was independently associated (p<0.001. with the following longitudinal patterns (R2=0.30.: increasing insulin resistance (standardized β=-0.42. and BMI (β=-0.09.; decreasing GS (β=0.06. and potentiation ratio (β=0.06., suggesting a potential compensatory mechanism; increasing total insulin output (β=-0.12. and fasting ISR (β=-0.12., likely due to insulin utilization saturation. Moreover, both fasting (β=0.12. and incremental glucose (β=0.20. were associated with increasing CLIo, consistent with our previous cross-sectional findings suggesting that increased insulin clearance may be an independent factor contributing to glycaemic deterioration. When including MRI-derived variables in the stepwise selection, baseline pancreatic-to-visceral fat ratio was independently and negatively associated with CLIo temporal changes (β=-0.10).

Conclusion: In individuals at risk of developing T2D, we identified longitudinal, independent associations between oral insulin clearance and distinct glucose homeostasis mechanisms. The analysis extended, at a longitudinal level, the potential existence of two adaptive processes involving oral insulin clearance: the first reduces insulin clearance with insulin resistance, the second reduces insulin clearance with lowering β-cell response to oral glucose and higher pancreatic-to-visceral fat ratio. These processes are partially dysregulated with increasing glycaemic levels.

Eligible for award

38-Adipose tissue insulin resistance is a marker and a major driver of severe MASH

Presenter: Nateneal Beyene[1], Joel Haas[5], Silvia Sabatini[6], Wilhelmus Kwanten[1,2], Ann Driessen[3], Eveline Dirinck[4], Bart Staels[5], Christophe De Block4, Sven Francque[1,2,] Amalia Gastaldelli [6,7] and Luisa Vonghia[1,2]

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7. UT Health Science Center San Antonio, TX, USA.

Background and aims: It has been shown that insulin resistance in the adipose tissue (ADIPO-IR index. and excess free fatty acids (FFA, due to impaired suppression of lipolysis. are associated with a more severe (brosis in MASLD but whether and how ADIPO-IR marks also the severity of MASH and of hepatic in(ammation is still unknown. We aimed to determine whether ADIPO-IR is an independent predictor of MASH and (brosis, and to explore its links with hepatic in(ammation and response to intervention.

Materials and Methods: the cohort included 375 individuals without diagnosis diabetes at enrollment with liver biopsy categorized as MASH n(219, No-MASH n(104 (including MASL n(64. and CT n(52 (healthy liver. and liver transcriptomics in a subgroup. Participants were also characterized for ADIPO-IR (FFAxInsulin., waist-to-height ratios (Waist(height., visceral (VAT. and subcutaneous adipose tissue (SAT., by computed tomography, glucose tolerance by OGTT and PNPLA3 variants. A subgroup underwent liver transcriptomic analysis. An intervention subgroup with severe obesity was followed for 12 months after receiving either bariatric surgery (BS, n(34. or lifestyle intervention (LS, n(37., with post-intervention histology to identify MASLD responders and non-responders. Logistic regression conducted to assess ADIPO-IR as a predictor of MASH and (brosis at baseline, adjusted for age, gender and BMI. Multivariate linear regression was used to evaluate predictors of change in ADIPO-IR, adjusted for interventions.

Results: Subjects with MASH, No MASH or CT had comparable BMI (38.2-39.5 kg(m2. and SAT(p(0.05. but MASH and No-MASH had higher waist(height and VAT compared to CT (p(0.05(. ADIPO-IR increased with the severity of steatosis, in(ammation, and (brosis. After adjusting for age, sex, and BMI, ADIPO-IR independently predicted the presence of MASH (OR(1.72, p(0.003. and signi(cant (brosis (OR(1.92, p(0.004(. PNPLA3 variant carriers had similar ADIPO-IR. Liver transcriptomic analysis revealed that ADIPO-IR was positively correlated with the enrichment of gene sets related to in(ammatory and immune responses, including neutrophil degranulation and interferon-gamma signalling. Post-intervention, ADIPO-IR was signi(cantly reduced (p(0.0001. and reduction below the overall median (FU(baseline(0.4877. was more prevalent in the BS group (67.6(vs. 32.4(for LS. and in MASLD responders (60.5(vs. 32.1(for non-responders(. Regardless of the intervention type, the change in waist(height was a signi(cant predictor of the change in ADIPO-IR.

Conclusions: ADIPO-IR is an independent predictor of both MASH and signi(cant (brosis in MASLD. Its correlation with hepatic in(ammatory gene expression combined with its signi(cant reduction following histologic improvement, highlights ADIPO-IR as a key marker and driver of MASH.

Eligible for award

39- Non-invasive liver fibrosis tests as independent predictors of cardiac remodeling

Presenter: Kaya Esingul[1], Eliana Maraglino[1], Antonio Salvati[2], Federico Pagani[1], Licia Rugani[3], Amalia Gastaldelli[4], Maurizia Brunetto[1], Alessandro Antonelli[3], Stefania Camastra[1]

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4. Institute of Clinical Physiology, CNR, Pisa.

Background and Aims: We investigated the association between non-invasive tests of inflammation fibrosis and cardiac remodelling in patients pts. with a wide range of age and BMI.

Materials and Methods: We obtained echocardiography measures left ventricular ejection fraction EF, left atrial area LAA, septum thickness SIV, ventricular wall thickness VWT, aortic root AR. and fibro-inflammatory indices FIB-4, FNI. in 130pts 74F56M; age18-75; BMI20-58 kgm2. without cirrhosis and cardiopathy. In 64 pts 31F33M. we also obtained elastography Liver stiffness LSM and CAP. measurements Fibroscan. and calculated AGILE3 and FAST

Results: Pts with FIB4 1.3 n36., showed significant increase in LAA 18.6vs21.5 cm2., SIV 1.03vs1.13 mm., VWT 0.95vs1.03 cm., AR 3.3vs3.7., all 0.001, no difference in EF. Pts belonging to the groups identified by the FNI cutoff 0.1, 0.1–0.33, 0.33, with 69, 41, and 18 pts, respectively. showed a significant increase in LAA, SIV, VWT, AR with FNI all p 0.001. Pts with High Moderate LSM 8 kPa; n21. vs Low LSM 8 kPa, n43. had a significant increase in SIV 1.16vs1.03 . and VWT 1.03vs0.95. LAA, SIV and VWT were associated with higher scores for MASH with significant fibrosis AGILE3 and FAST p 0.01. In simple regression analysis, FIB4, AGILE3, FAST, LSM were directly associated with LAA, SIV, VWT all p 0.001. AGILE3 inversely related to EF p 0.03. In multiple regression model the relationships of LSM with SIV and VWT p 0.004. and of AGILE3 with SIV, VWT, AR p 0.003. were maintained after adjustment for blood pressure, sex, FIB4

Conclusion: In a population with a wide range of ages and BMIs, free of cirrhosis and overt cardiac disease, liver stiffness measurements and surrogate fibro-inflammatory indices were found positively associated with worsening of cardiac remodelling. These findings highlight the interplay between cardiac and hepatic pathophysiology and suggest the importance of cardiovascular assessment in patients with MASLD

Eligible for award

40-Diet-induced induction of hepatic serine threonine kinase STK38 triggers proin ammation and hepatic lipid accumulation

Presenter: Kajal Jaswal[1], Priya Rawat[1], Shilpa Thakur[1] , Surbhi Dogra[1], Budheswar Dehury[2] , and Prosenjit Mondal[1]

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Background and aims: Metabolic dysfunction–associated fatty liver disease MAFLD. is one of the most common liver diseases worldwide. Several studies have reported that chronic overnutrition, such as excessive consumption of fats high-fat diet, HFD., can cause insulin resistance and in ammation in the development of MAFLD. However, the mechanisms by which HFD exerts in ammation and thereby promotes insulin resistance and intrahepatic fat accumulation remain poorly understood. In search of an unconventional target that may be the putative node between obesity and in ammation, we found serine threonine kinase 38 STK38. Our study reveals that STK38 is a critical node in the lipogenic immune axis, providing a potential therapeutic target to alleviate in ammation and insulin resistance in both lean and non-lean MAFLD.

Materials and methods: To determine the role of STK38 in hepatic insulin signalling and intrahepatic fat accumulation, STK38 was overexpressed using adenovirus via tail vein injection. in C57BL6 mice fed on an RCD, and its downstream effects were analyzed. Phosphorylation of AKT S473. and T308. was measured as a surrogate for insulin resistance. Next, we analyzed the impact of STK38 knockdown using shRNA lentivirus on HFD-induced hepatic insulin resistance and MAFLD. Glucose and insulin tolerance tests were performed to assess systemic insulin sensitivity. Immunoblotting, histopathological analysis, immunohistochemistry, co-immunoprecipitation, etc. were performed to explore the molecular mechanisms.

Results: HFD induces the expression of hepatic STK38, which, in turn, causes systemic in ammation and leads to insulin resistance, accompanied by enhanced chromatin accessibility at its promoter region and upregulation by complement C3a. Ectopic expression of STK38 in the mouse liver results in a lean MAFLD phenotype characterized by hepatic in ammation, insulin resistance, intrahepatic lipid accumulation, and hypertriglyceridemia in mice fed RCD. Moreover, hepatic STK38-depleted mice are protected against HFD-induced insulin resistance, hepatic in ammation, and MAFLD. Mechanistically, STK38 binds to Tank-Binding Kinase 1 TBK1., promoting its phosphorylation and subsequent NF-κB nuclear translocation and the release of proin ammatory cytokines, which ultimately leads to insulin resistance. Additionally, STK38 also reduces AMPK–ACC signaling, thereby enhancing de novo lipogenesis.

Conclusion; This study highlighted STK38 as a novel nutrient-responsive kinase that can act as a potential target to explore the missing link between diet-induced molecular alterations that induce hepatic in ammation and insulin resistance. Our study suggests that STK38 is a critical node in the lipogenic immune axis, providing a potential therapeutic target to ameliorate in ammation and insulin resistance in both lean and non-lean NAFLD.

41-Mitochondrial respiration and morphology are altered in fatty acid induced insulin resistant liver cells

Presenter: Nina Krako Jakovljevic [1], Kasja Pavlovic [1], Tijana Ivanovic [2], Darko Ciric [3], Tamara Martinovic [3], Tamara Kravic-Stevovic [3], Ivanka Markovic [4], Aleksandra Jotic[1,2], Nebojsa Lalic [2,5]

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Background and Aims: In the insulin resistant liver, insulin fails to suppress endogenous glucose production, and instead of storing, keeps releasing glucose into the circulation. Thus, hepatic insulin resistance leads to progression of whole body insulin resistance (IR. and consequently to type 2 diabetes (T2D). An elevation of hepatocellular lipids is the main hallmark of metabolic dysfunction–associated steatotic liver disease (MASLD. that has increased prevalence among people with T2D. Mitochondria with central role in the cellular energy metabolism have been affected in these metabolic conditions. It has also been shown that phosphorylation of Akt, a key molecule responsible for the metabolic effects of insulin, may occur in the mitochondria-endoplasmic reticulum (ER. contact sites, known as MAM (Mitochondria Associated ER Membranes). The aim of this study is to further explore our previously characterized IR cell model, investigating the effects of fatty acids (palmitate and oleate. on human hepatocellular carcinoma (Huh7. cells in terms of mitochondrial function and morphology and MAM subcellular compartment.

Materials and Methods: Human hepatocellular carcinoma (Huh7. cells were treated with 0.4 mM palmitate or 0.3 mM oleate for 24 h to induce IR. Cell viability was estimated by acid phosphatase assay; protein levels were measured by immunoblot; mitochondrial respiration was assessed by high resolution respirometry (HRR., morphological examinations were done by electron and confocal microscopy. Finally, for MAM detection, nucleofection with two specific GFP split plasmids (courtesy of Prof. Tito Cali, University of Padua. was optimized and used together with MitoTracker Red staining.

Results: Palmitate treated Huh7 cells require higher digitonin concentration for plasma membrane permeabilization respect to control cells in order to effectively perform HRR protocols in permebilized cells. Mitochondrial function was altered in fatty acid treated cells, which was observed by lower fatty acid oxidation (FAO. in addition to decrease in OXPHOS and coupling efficiency (previously shown). By confocal image analysis, both, aspect ratio and relative fluorescence intensity of mitochondria staining were lower in palmitate treated cells. Preliminary results showed reduced level of Grp75 (one of the key MAM molecules. together with lower Akt phosphorylation and fewer mitochondria-ER contacts in palmitate treated cells.

Conclusion: Our results implicate the important role of mitochondria and MAM in pathophysiology of liver IR warrant further investigation in this and more complex in vitro models. This might help determining relevant intracellular targets for T2D and MASLD translational research.

42- In uence of the MBOAT7 rs641738 polymorphism on the prognosis of patients with metabolic dysfunction-associated steatotic liver disease and hepatocellular carcinoma

Presenter: Guariglia Marta[1], Caviglia Gian Paolo[1], Rosso Chiara[1], Gaia Silvia[2], Rolle Emanuela[2], Abate Maria Lorena[1], Armandi Angelo[1], Carucci Patrizia[1], Bugianesi Elisabetta[1,2]

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Background and Aims: Several genetic factors have been associated to liver disease onset and progression in patients with metabolic dysfunction-associated steatotic liver disease MASLD. In particular, genetic variants predisposing to liver fat accumulation i.e. PNPLA3, TM6SF2, MBOAT7, GCKR, and HSD17B13. were associated with increased risk of hepatocellular carcino-ma HCC. development. We aimed to investigate the association between genetic variants and prognosis of patients with MASLD-HCC.

Materials and Methods: A total of 258 MASLD patients median age: 73, IQR 49–97 years; males: 224, 86.8. with a diagnosis of HCC were retrospectively enrolled. Most patients had an early stage HCC BCLC: 0A, n162, 62.8.; patients with BCLC stage D were excluded from the analysis. Geno-typing for PNPLA3 rs738409 CG, MBOAT7 rs641738 CT, TM6SF2 rs58542926 CT, GCKR rs780094 CT, HSD17B13 rs72613567: TA was performed by real-time allelic discrimination as-say TaqMan SNP Genotyping Assay, Applied Biosystems. Primary end-point was overall survi-val OS.

Results: Overall, median OS was 28.5 95CI 21.4–32.2. months. Among the ve genetic va-riants analysed, only MBOAT7 rs641738 showed signi cant results at survival analysis. Speci cal-ly, patients who carried the TT risk genotype n65. showed reduced OS compared to those with CCCT genotype n193. OS19.8, 95CI 16.4–27.0 months vs. 32.2, 95CI 29.1–53.9 months, respectively; p0.003. At multivariate logistic regression analysis, MBOAT7 rs641738 TT geno-type resulted associated to reduced OS OR1.72, 95CI 1.11–2.65. independently from BCLC stage OR2.24, 95CI 1.77–2.82.

Conclusion: MBOAT7 rs641738 CT. variant was associated to poor prognosis in patients with MASLD-HCC. In such patients, MBOAT7 rs641738 genotyping may be useful to improve clinical management and to support decision-making.

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43-Comparison of FibroScan and iLivTouch for liver stiffness and steatosis assessment in patients with MASLD

Presenter: Kamela Gjini,

Collaborators: Gian Paolo Caviglia, Marta Guariglia, Eleonora Dileo, Elisabetta Bugianesi

Department s. and institution s. of all contributors 1Division of Gastroenterology and Hepatology, Department of Medical Sciences, University of Turin, Italy

Background and Aims: noninvasive assessment of liver stiffness and steatosis is critical for managing MASLD, given its rising prevalence and risk of progression to brosis and cirrhosis. Vibration-controlled transient elastography VCTE. with FibroScan has been a clinical benchmark. Recently, the iLivTouch device emerged as an alternative. This study evaluates the concordance of FibroScan and iLivTouch in assessing liver stiffness and steatosis in Caucasian patients with MASLD.

Method: this study included 97 adult patients with MASLD, recruited consecutively. Clinical, biochemical and anthropometric data, including weight, height, and BMI, were recorded. Liver stiffness and hepatic steatosis were assessed using FibroScan Echosens, France. and iLivTouch Wuxi Hisky Medical Technologies Co., Ltd., China. on the same day. FibroScan measurements included liver stiffness in kPa and steatosis using CAP dBm. iLivTouch measurements included liver stiffness kPa. categorised into brosis stages F0–F4. based on the device-speci c cut-offs for MASLD F0--F1: 8 kPa, F1–F2: 9–11 kPa, F2–F3: 12–14 kPa, F3: 15–17 kPa, F4: 17 kPa. and ultrasound attenuation parameter UAP. for steatosis severity absent: 244 dBm, mild: 244–269 dBm, moderate: 269–296 dBm, severe: 296 dBm. The diagnostic agreement between the two devices was analysed by Spearman correlation and inter-rater agreement k.

Results: A total of 97 adult patients with MASLD were included in the study. The median age was 60 range: 21–77. years; 57.1 were male. The median BMI was 29.7 kgm² range: 22.5–45.5., and the median ALT level was 24.5 UL range: 9–140.

The correlation between liver stiffness measurements from FibroScan and iLivTouch showed a good concordance rs 0.717, 95 CI 0.78-0.81, p 0.001. Similarly, steatosis measurements based on CAP FibroScan. and UAP iLivTouch. also demonstrated a good correlation rs 0.726, 95 CI 0.64-0.81 p 0.001. When evaluating agreement across brosis stages F01, F2, F3, F4. the weighted kappa showed a substantial agreement κ 0.77, 95 CI 0.64-0.90 p 0.001. For steatosis grades S0, S1, S2, S3., the weighted kappa showed good agreement κ 0.60, 95 CI 0.43-0.75 p 0.001. Patients were further grouped into two clinically relevant brosis categories: F0-F2 mild to moderate brosis. and F3-F4 advanced brosis and cirrhosis. The diagnostic agreement between FibroScan and iLivTouch for identifying advanced brosis F3–F4. showed a moderate concordance κ 0.58, 95 CI, 0.35-0.81 p 0.001.

Conclusion: iLivTouch showed a good agreement with FibroScan for liver stiffness and steatosis assessment in patients with MASLD. These preliminary results suggest that iLivTouch may be a viable alternative for non-invasive evaluation, with further studies needed to con rm its broader applicability.

44-Targeting endothelial dysfunction with zibotentan dapagli ozin, effect on markers of kidney and liver health

Presenter: Phil Ambery

Contributors: Greasley PJ, Fiorino K, Kashioulis P, Sinsakul M, Oscarsson J

Af liation: Late CVRM Clinical Development, AstraZeneca

Background and Aims: Zibotentan dapagli ozin zibodapa. combination treatment has been studied in one phase 2b CKD study, ZENITH., and two phase 2 studies for cirrhosis with portal hypertension ZEAL and ZEAL-UNLOCK. In this data presentation we explore effects on markers of liver and kidney function across the phase 2 development program.

Method: ZEAL Part A explored the effects of zibodapa in 26 patients with cirrhosis and ZEAL Part B explored the effects of zibodapa in 173 patients with cirrhosis, each over 6 and 16 weeks, respectively. ZEAL UNLOCK examined the effects of zibotentan on uid retention in 72 patients with cirrhosis over 6 weeks. ZENITH explored the effects of zibodapa in 447 patients with chronic kidney disease and albuminuria.

Results: No signi cant effect on hepatic venous pressure gradient was seen in the ZEAL phase 2 studies. In the ZENITH phase 2 CKD study a reduction in urine albumin creatinine ratio UACR. of approximately 50 vs baseline was seen over the 12-week study for zibodapa patients. Across the phase 2 trial programs, reductions in blood pressure were seen without signi cantly increased risk of hypotension. Improvements in insulin resistance, HbA1c, in ammatory markers and LDL cholesterol were also seen. In ZEAL Part B a modest reduction in UACR was also seen.

Conclusion: Agents targeting endothelial dysfunction may have broad positive effects beyond their target indication. These will be explored for zibodapa on completion of the ZENITH high proteinuria phase 3 trial.