TIME FOR THE LIVER – CHRONOBIOLOGY, AGING AND CURRENT MATTERS IN HEPATOLOGY

January 26-27, 2023

Symposium

BOCHUM, GERMANY

APPLICATION FOR CME CREDITS SUBMITTED

An application has been made to the UEMS EACCME® for CME accreditation of this event.

PREFACE

Dear colleagues and friends,

Hereby I would like to invite you cordially to the Symposium **„Time for the liver – chronobiology, aging and current matters in hepatology“**, organized by the Falk Foundation e.V. that will take place from January 26th until January 27th, 2023 in Bochum, Germany.

This year we would like to discuss current and novel questions in the field of hepatology that did not receive much scientific attention up to now. These under-explored topics include effects of aging on the liver and liver disease, chronobiology of the liver, specifics of hepatocellular carcinoma in non-alcoholic fatty liver disease, and the influence of the gut microbiome on the liver and liver disease. We hope you share our interest in these special fields of hepatologic research and the host of unanswered questions within their scope.

Complementary to the oral presentations, there will be accompanying poster sessions on both days. As is tradition the symposium precedes the 39th Annual Meeting of the German Association for the Study of the Liver (GASL) to which I also invite you with great pleasure.

I would like to thank all the speakers and participants of this symposium for providing their findings, views, and opinions and for joining us in Bochum. I hope we can create an inspiring symposium on open questions of hepatology and stimulate many new projects and collaborations. I am particularly thankful to the Falk Foundation for the generous support and the professional organization of this event. I wish you a most enjoyable and insightful meeting and very much look forward to welcoming you to our event at the Ruhr University Bochum.

Best wishes and hoping to see you soon in Bochum,

Ali Canbay
GASL President 2022/2023

TIME FOR THE LIVER – CHRONOBIOLOGY, AGING AND CURRENT MATTERS IN HEPATOLOGY

January 26-27, 2023

Scientific Organization:
Prof. Dr. Ali Canbay
Medizinische Klinik
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Scientific Co-Organization:
Jan-Peter Sowa, Bochum

Congress Venue:
Veranstaltungszentrum der
RUB Bochum
Universitätsstraße 150
44801 Bochum
Germany

For admission to scientific events your name badge should be clearly visible. Accompanying persons are not permitted during the conference at any time.

Start of Registration:
Thursday, January 26, 2023
14:00 - 18:00 h
at the congress office

Poster Session Set-up:
Thursday, January 26, 2023
14:00 - 15:00 h

Thursday, January 26, 2023

15:00 Welcome and opening remarks
Ali Canbay, Bochum

SESSION I

Aging of the liver

Chairs: *Claus Hellerbrand, Erlangen; Peter Tessarz, Cologne*

15:05 General and morphological changes of the liver during aging
Peter Tessarz, Cologne

15:20 Liver aging: Epigenetic signatures and biomarkers in transplant setting
Miriam Capri, Bologna

15:35 Intervening on anti-aging genes to hamper liver disease progression
Manlio Vinciguerra, Liverpool

15:50 Effect of age on liver transplantation
Aristotelis Perrakis, Magdeburg

16:05 Summary & End of the Session

16:20 **Coffee break with poster session**

Thursday, January 26, 2023

SESSION II

Chronobiology of the liver

Chairs: *Shadab A. Rahman, Boston; Wolfgang E. Schmidt, Bochum*

16:45	Introduction to Chronobiology *Mustafa Özçürümez, Bochum*
17:00	Liver specific, zonal rhythms *Madlen Matz-Soja, Leipzig*
17:15	The liver-clock coordinates rhythmicity of peripheral tissues in response to feeding *Gad Asher, Rehovot*
17:30	Synchronization and desynchronization of liver rhythms *Shadab A. Rahman, Boston*
17:45	Summary & End of the Session
17:50	Closing remarks *Ali Canbay, Bochum*
18:00	**Networking and light refreshments**

Friday, January 27, 2023

9:25	**Coffee break with poster session**
9:45	Welcome *Ali Canbay, Bochum*

SESSION III

HCC in NAFLD

Chairs: *Ramazan Idilman, Ankara; Andrea Tannapfel, Bochum*

9:50	Epidemiologic trends and risk factors for NAFLD-associated HCC *Hashem B. El-Serag, Houston*
10:05	Clinical course and outcomes of NAFLD-associated HCC *Jan Best, Bochum*
10:20	Screening and diagnosing of HCC in NAFLD – challenges and developments *Rohit Loomba, La Jolla*
10:35	Specific management of NAFLD-associated HCC *Helen Reeves, Newcastle upon Tyne*
10:50	Summary & End of the Session
10:55	**Coffee break with poster session**

Friday, January 27, 2023

SESSION IV

Gut microbiome and liver

Chairs: *Stefan Schreiber, Kiel; Richard Viebahn, Bochum*

11:15	Introduction to gut microbiome-liver-interaction *Konrad Aden, Kiel*
11:30	Gut-liver axis in obesity, NAFLD and metabolic syndrome *Stan van de Graaf, Amsterdam*
11:45	Role of macrophages in the microbiota – gut – liver communication in liver disease *Frank Tacke, Berlin*
12:00	Microbiome transplantation as treatment for metabolic diseases *Vanessa Stadlbauer-Köllner, Graz*
12:15	Summary & End of the Session
12:20	**Lunch with poster session**
13:15	Opening of the annual meeting of the GASL

LIST OF SPEAKERS, MODERATORS AND SCIENTIFIC ORGANIZERS

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REGISTRATION

You can register for the event via our homepage:
www.falkfoundation.org
Registration is only possible online.

CONGRESS FEES

Scientific Program of Symposium	EUR 150
Students (copy of student ID required)	EUR 75

The congress fees include:

- Refreshments during coffee breaks
- Lunch on Friday, January, 27, 2023
- Snacks during scientific discussion on Thursday, January 26, 2023
- A copy of the final program

CONGRESS OFFICE AND REGISTRATION

Opening Hours:

Thursday, January 26, 2023	14:00 - 18:00 h
Friday, January 27, 2023	9:00 – 12:30 h

ARRIVAL

Veranstaltungszentrum der RUB Bochum
Universitätsstraße 150
44801 Bochum
Germany

By car

Motorists can reach the Ruhr-Universität easily via Germany's – and especially North Rhine-Westphalia's – dense motorway network. The fastest route is that via the motorway junction Bochum/Witten, where the motorways A43 and A44 meet. Simply take the exit for Bochum-Querenburg, follow the signs for "Ruhr-Universität" and, once there, look for the (electronic) information boards.
Parking: P9

By plane

The travelling distance between the airports in Dortmund, Münster/Osnabrück, Cologne/Bonn and Düsseldorf and the Ruhr-Universität is two hours at the most. Düsseldorf airport is the most easily accessible one, with up to eight direct trains per hour running between the airport and Bochum's main train station; the journey takes about half an hour.

By tram

At Bochum's main train station, ICE, IC, EC, regional trains and city trains arrive and depart in quick succession. You can reach the Ruhr-University, which has its own station, easily by catching the underground (U-Bahn) train U35 (CampusLinie). On workdays, the U35 (going to Bochum Hustadt) departs in five-minute intervals, and it takes less than 10 minutes to go from the main train station to the university station.

CONFLICT OF INTEREST

Members of the scientific committee declare the following potential conflicts of interest:

Ali Canbay: Abbvie, Academy 2, Alexion Pharma Germany, Allergosan, Ärztekammer Nordrhein, Ärztekammer Westfalen-Lippe, BDI Bundesverband Deutscher Internisten, Böhringer-Ingelheim, CSL-Behring, DeProm Deutsche Gesellschaft für probiotische Medizin, Dr. Falk Pharma, Eisai, Falk Foundation, Gastro Orga, Georg Thieme Verlag, Gesundheitsamt Düsseldorf, Gilead Sciences, Humedics, Intercept Pharma Deutschland, Intercept Pharma Europe, Malteser Waldkrankenhaus St. Marien Erlangen, med publico, Merz Pharmaceuticals, Merz Russland, MSD Sharp & Dohme, Norgine, Novartis Pharma, onkowissen.de, Portola FRG, Sanofi Aventis Deutschland, Schöchl medical education, Shionogi, Shire Deutschland, Sino High-Tech Park Holding, Springer Medizin Verlag, Swedish Orphan Biovitrum, Synlab Holding Deutschland, Takeda Pharma, Universitätsklinikum Düsseldorf, Abt. Gastro, Hep, Inf., Universitätsklinikum Hamburg-Eppendorf

POSTER ABSTRACTS

1. Hepatic hemosiderosis during environmental tobacco smoke (ETS) conditions in mice
   M. Abbasi, N. Sheikh, A. Majid, N. Kawish, A. Riaz, A. Fatima, A. Zafar, M. Khawar (Okara, Lahore, Narowal, PK)
2. Screening of hepatic steatosis and fibrosis among patients with psoriasis using methotrexate: A transient elastography study
   A. Aksoy, B. Hanci, E. Umutlu, E. Kumas, S. Emanet, M. Baskent, M. Yalcin, Z. Duzyol, A. Teker, Y. Yilmaz (Maltepe/Istanbul, Istanbul, Rize, TR)
3. Assessment of liver fibrosis patients with hemosiderosis and hepatitis C virus coinfection
   M. Alsenbesy, A. Shimaa, A. Irian, A. Nafady (Manama, BH, Qena, EG)
4. Effects of Bifidobacterium breve CNCM I-4035 supernatant in a hepatic model of inflammation
   A. Alvarez Mercado, F. Luis, S. Maria Jose (Granada, ES)
5. Anti-fibrotic effect of quercetin in comparison to silymarin on thioacetamide-induced hepatic fibrosis through modulation of oxidative stress and inflammatory cytokines
   A. Aslam, N. Sheikh, T. Akhtar (Lahore, PK)
6. A case with increased urine Cu and hepatic F3 fibrosis recovered by only Cu-restrictive diet
   M. Basaranoglu (Istanbul, TR)
7. Prevalance of Hep B and C infection and Hep B vaccination rates in patients with IBD
   M. Basaranoglu, D. Sertel, E. Ercan, A. Uslu (Istanbul, TR)
8. Plasticity of hepatic spliceosome in response to 4:10 cycles of very low-calorie intake
   A. Diaz-Ruiz, J. Lopez-Canovas, R. Martin-Hernandez, M. Bernier, M. Gahete-Ortiz, R. De Cabo (Madrid, Córdoba, ES; Baltimore, US)
9. Role of bone morphogenetic protein 6 in hepatocellular carcinoma
   H. Ehnis, J. Sommer, C. Hellerbrand (Erlangen, DE)
10. Assessment of serum neuropilin 1 as a single serum marker for HCC in cirrhotics
    M. Elkady (Benha, EG)
11. Assessment of serum vitamin D in patients with non-alcoholic fatty liver disease
    M. Elkady, H. Ragheb, H. Alegaily, A. Qayed (Benha, EG)
12. Predictive factors of rebleeding and mortality in cirrhotic patients with acute variceal bleeding
    S. Harrathi, M. Yakoubi, A. Ben Mohamed, M. Medhioub, M. Mahmoudi, A. Khsiba, M. Hamzaoui, M. Azouz (Nabeul, TN)
13. Prognostic value of hypochloremia in cirrhotic patients
    S. Harrathi, M. Yakoubi, A. Ben Mohamed, M. Medhioub, M. Mahmoudi, A. Khsiba, M. Hamzaoui, M. Azouz (Nabeul, TN)
14. A new mouse model to study the pathogenesis of PSC
    S. Kaminski, H. Dorner, J. Mattner, A.E. Kremer, P. Dietrich, M.F. Neurath, C. Günther (Erlangen, DE; Zurich, CH)
15.* MicroRNA-ITGA6/Has2 signaling regulates liver fibrosis
    R. Khanal, J. Markovic, R. Li, H. Buening, A. Balakrishnan, M. Ott, A. Sharma (Hannover, DE)
16. Relevance of microRNAs in SARS-CoV-2 infection of primary human hepatocytes
    R. Khanal, N. Heinen, A. Bogomolova, T. Meister, D. Todt, F. Vondran, R. Brown, E. Steinmann, G. Zimmer, M. Ott, S. Pfaender, A. Sharma (Hannover, Bochum, Langen, DE; Bern, CH)

17. A case of colon cancer complicated with synchronous HCC
E. Koc, C. Aygun, A. Yazar, N. Tozun (Beykoz, Istanbul, TR)

18. Predictive value of red cell distribution width to platelet ratio for liver fibrosis
E. Koc, C. Aygun, E. Kutsal, N. Tozun (Beykoz, Sarıyer, TR)

19.* Comparing survival in liver transplant recipients with hepatocellular carcinoma
E. Koc, A. Ozer, F. Onder (Istanbul, Sarıyer, TR)

20.* Tick-tock – Circadian regulation of liver metabolism represented in a kinetic model
C. Koerner, M. Matz-Soja, F. Ott, E. Marbach-Breitrueck, R. Gebhardt, T. Berg, N. Berndt (Leipzig, Berlin, DE)

21.* Cell plasticity of liver cancer cells is blunted by fasting in combination with the cocktail metformin-sorafenib
J. Lopez-Canovas, M. Castejon-Mariscal de Gante, B. Naranjo, P. Navarro Amador, A. Diaz-Ruiz (Madrid, ES)

22. Low-density granulocytes expressing myeloperoxidase as novel markers of autoimmune hepatitis
A. Michalak, W. Domerecka, A. Rycyk, B. Kasztelan-Szczerbinska, T. Malecka-Massalska, H. Cichoz-Lach (Lublin, PL)

23. Metabolic-associated fatty liver disease, microRNAs and hematological indices – A novel diagnostic pathway in hepatology?
A. Michalak, A. Rycyk, B. Kasztelan-Szczerbinska, H. Cichoz-Lach (Lublin, PL)

24.* Expression and transcriptional regulation of fibroblast growth factor receptors in hepatocellular carcinoma
T. Seitz, K. Freese, L. Vorhauer, J. Sommer, W. Thasler, C. Hellerbrand (Erlangen, Planegg/Martinsried, DE)

25. Platelet-rich plasma (PRP)-driven changes in the gene expression of hepatic glucose metabolism of diabetic mice
N. Sheikh, A. Arif, M. Abbasi, M. Khawar, A. Farooq (Lahore, Okara, Narowal, PK)

26.* Four-and-a-half LIM-domain protein 2 (FHL2) in hepatocellular carcinoma
J. Sommer, C. Hellerbrand (Erlangen, DE)

27. Gut-Liver axis dilemma: Genetically determined linkage of NAFLD and intestinal dysbiosis via impaired mesenteric circulation
A. Sydorchuk, V. Stepan, R. Sydorchuk, R. Knut, L. Sydorchuk, N. Stepan, I. Sydorchuk, I. Hryhorchuk, I. Sydorchuk, P. Kyfiak, N. Kyfiak (Neu-Ulm, Siegen, DE; Chernivtsi, UA)

28. Xenobiotic-dependent changes of liver circadian biorhythms and oxidative stress
L. Sydorchuk, I. Hryhorchuk, A. Sydorchuk, I. Semeniuk, I. Sydorchuk, I. Plehutsa, I. Sydorchuk, V. Stepan, R. Sydorchuk, N. Stepan (Chernivtsi, Storozhynets, UA; Neu-Ulm, Siegen, DE)

29.* Circadian pattern of pro- and antioxidants in liver
R. Sydorchuk, V. Stepan, L. Sydorchuk, A. Sydorchuk, N. Stepan, I. Sydorchuk, P. Kyfiak, I. Plehutsa, N. Kyfiak, I. Hryhorchuk (Chernivtsi, Storozhynets, UA; Neu-Ulm, DE)

30. Extrahepatic cancer risk in patients with cirrhosis
N. Trad, G. Mohamed, S. Bizid, K. Boughoula, B. Ben Slimen, H. Ben Abdallah, R. Bouali, M. Abdelli (Ariana, Tunis, TN)

31. Prognostic performance of Toronto HCC risk index in patients with hepatocellular carcinoma
    N. Trad, G. Mohamed, S. Bizid, K. Boughoula, B. Ben Slimen, H. Ben Abdallah, R. Bouali, M. Abdelli (Tunis, TN)
32. Gallstones associated with non-alcoholic steatohepatitis (NASH) and metabolic syndrome
    O. Yener (Istanbul, TR)
33. Hepatitis B serology in non-alcoholic steatohepatitis-induced liver cirrhosis and hepatocellular carcinoma
    E. Yorulmaz (Bagcilar, TR)

FULL CONTENT OF POSTER ABSTRACTS

Poster Numbers 1 – 33
(* = Posters of Distinction)

1. Hepatic hemosiderosis during environmental tobacco smoke (ETS) conditions in mice

Muddasir Hassan Abbasi (Okara, PK), Nadeem Sheikh (Lahore, PK), Ayesha Majid (Okara, PK), Naseer Kawish (Lahore, PK), Amna Riaz (Okara, PK), Arooj Fatima (Okara, PK), Azka Zafar (Okara, PK), Muhammad Babar Khawar (Narowal, PK)

Introduction: Environmental tobacco smoke (ETS) is one of the largest environmental issues in the world. Many people die due to the deleterious constituents of ETS. Smoking affects almost every organ of the body. Even the organs that are not in direct contact with the smoke are negatively affected by smoking, for instance, the liver. The present study was conceded to highlight any effects of acute exposure to ETS on the hepatic iron metabolism in Mus musculus.

Methods: To mimic ETS conditions, normal male mice (n = 10) were exposed to cigarette smoke (CS) for 7 consecutive days in a purpose-built smoking chamber (Fig. 1). Mice were exposed to a total of 16 cigarettes/day with an interval of 30 minutes while the control group (n = 10) was kept in a well-ventilated chamber of similar dimensions. On the day after CS exposure mice were dissected, and liver tissues were excised and processed further for histological sectioning and iron staining.

Results: Results revealed iron accumulation in hepatic sections. Ferritin (clear blue soluble iron storage proteins) was much more visible within hepatocytes and Kupffer cells. Moreover, dilated sinusoidal spaces (DS) with changes in the nucleus in the hepatocytes directed attention toward the damage of cells.

Discussion/Conclusion: To conclude, even short-term ETS exposure can be dangerous for overall health and destructive to many indirectly exposed vital organs.

2. Screening of hepatic steatosis and fibrosis among patients with psoriasis using methotrexate: A transient elastography study

Ahsen Nihal Aksoy (Maltepe/Istanbul, TR), Burak Hanci (Istanbul, TR), Emine Gul Umutlu (Istanbul, TR), Eda Nur Kumas (Istanbul, TR), Suleyman Umit Emanet (Istanbul, TR), Mehmet Furkan Baskent (Istanbul, TR), Mehmet Oguz Yalcin (Istanbul, TR), Zeynep Duzyol (Istanbul, TR), Ayse Gulsen Teker (Istanbul, TR), Yusuf Yilmaz (Rize, TR)

Introduction: Methotrexate is a steatogenic medication which is used in treatment of psoriasis. However, presence of hepatic steatosis and fibrosis in psoriasis patients using methotrexate has not been fully investigated. In our study, we aimed to investigate prevalence and of hepatic steatosis and advanced fibrosis for patients with psoriasis using methotrexate for their treatment.

Methods: We retrospectively reviewed the medical records of the patients with psoriasis who referred to our center for transient elastography examination between 2013 and 2021. The cut-off for hepatic steatosis was defined as a controlled attenuation parameter (CAP) value of > 238 dB/m and advanced fibrosis as a liver stiffness measurement (LSM) value of > 10 kPa.

Results: The study consisted of 328 patients with psoriasis (mean age: 49.5 3 12.7 years, 163 male [49.7%], 63 obese [57.8%]). From those 326 patients (99.4%) had hepatic steatosis and 56 patients (33.1%) advanced fibrosis. A total of 286 patients (87.2%) were on methotrexate. Methotrexate use was significantly higher among patients with advanced fibrosis (n = 44 [78.6%], p = 0.046).

Discussion/Conclusion: In our study, we showed that almost all of the patients with psoriasis showed evidence of hepatic steatosis. Moreover, methotrexate was associated with a worse hepatic outcome. Our results indicate that screening of the psoriasis patients in terms of hepatic steatosis and fibrosis is crucial. Methotrexate use is a risk factor for advanced fibrosis and requires strict hepatic follow-up.

3. Assessment of liver fibrosis patients with hemosiderosis and hepatitis C virus coinfection

Mohamed Alsenbesy (Manama, BH), Abdallah Shimaa (Qena, EG), Abdelhakim Irian (Qena, EG), Asmaa Nafady (Qena, EG)

Introduction: The frequent blood transfusion in patients with Beta Thalassemia major (BTM) leads to iron precipitation in various organs particularly the liver (hemosiderosis). These patients are prone to hepatitis C virus (HCV) infection and the resultant Iron overload is a risk factors for development and progression of liver fibrosis. Transient elastography (TE) is a non-invasive and reproducible bedside method to indirectly assess liver fibrosis by quantitively measuring liver stiffness. Although liver biopsy is still considered the standard to evaluate fibrosis, TE has intensively taken part in clinical evaluation of hepatic fibrosis due to different etiologies.

Methods: The aim of this study is to evaluate the role of TE in detection of liver fibrosis in BTM patients co-infected with HCV and detect associated risk factors of liver fibrosis. This cross-sectional study included Fifty BTM patients aged ≥ 12 years at the internal medicine department in Qena University hospital, Egypt. Patients with hereditary haemochromatosis, Wilson disease, positive HBsAg, cardiac cirrhosis, fatty liver and other causes of fibrosis were excluded. Liver function tests, anti HCV antibodies, HCV RNA and TE were performed, then we analysed the data using Statistical Package for Social Sciences (SPSS) software program (version 21).

Results: 22 Patients (44%) with beta thalassemia showed positive HCV viremia and splenectomy was more frequent among these patients ($p < 0.0001$). The TE values increased with platelet count ($R2 = 0.312$, p-value 0.028), alanine transaminase (ALT) level ($R2 = 0.533$, $p < 0.001$), aspartate transaminase (AST) level ($R2 = 0.577$, $p < 0.001$), total bilirubin level ($R2 = 0.565$, $p < 0.001$) and ferritin ($R2 = 0.716$, $p < 0.001$). On the other hand, TE values showed negative correlation to serum albumin level ($R2 = 0.605$, $p < 0.001$).

Discussion/Conclusion: Maximum TE values & higher ferritin levels were detected in HCV positive BTM augmenting the evidence of association between iron overload and HCV. TE, as a validated indirect test, can easily and non-invasively assess the response to chelation therapy in BTM patients. Monitoring blood transfusion and controlling HCV infection in these patients is mandated to reduce the progression of liver fibrosis.

4. Effects of Bifidobacterium breve CNCM I-4035 supernatant in a hepatic model of inflammation

Ana Isabel Alvarez Mercado (Granada, ES), Fontana Gallego Luis (Granada, ES), Saez Lara Maria Jose (Granada, ES)

Introduction: Non-alcoholic fatty liver disease (NAFLD) causes more than 2 million deaths per year worldwide. This pathology comprises a group of diseases ranging from steatosis to hepatocellular carcinoma.

The intestine and liver communicate through the portal vein, the biliary tract, and systemic circulation. Unbalanced gut microbiota increases intestinal permeability, which facilitates the influx of microbial metabolites into the liver, leading to impaired bile acid metabolism and the development of systemic inflammation. The alterations in gut microbiota that may be involved in the pathophysiology of liver disease have not been fully characterized.

Probiotics regulate gut microbiota and have been shown to have potential as a therapeutic strategy for several diseases mainly because of their role in modulating the immune system and anti-inflammatory properties. Evidence suggests that toll-like receptors (TLRs) play an essential role in the pathogenesis of liver diseases because their deregulation can lead to dysbiosis.

This work aimed to evaluate the effect of B. breve CNCM I-4035 in an in vitro hepatic model.

Methods: We used the hepatic cell line WRL-68 and induced an inflammatory state with the addition of lipopolysaccharide and interleukin-1β. Cell viability was assessed after probiotic addition for 8 and 24 hours. We measure lactate concentration as an indicator of cell damage, protein levels of VEGF-a (activator of hepatocyte proliferation), PPAR-γ (regulator of hepatic lipid metabolism), activation of AKT (cell survival signal), NFκB (inflammation signal) and TLR 4 and TLR 9 gene expression.

Results: B. breve CNCM I-4035 decreased lactate concentration, increased VEGF-a and PPAR-γ levels, induced NFκB activation, and induced changes in TLR 4, and 9 gene expression as well as the activation of the AMPK signaling pathway.

Discussion/Conclusion: B. breve CNCM I-4035 exerts an immunomodulatory and protective effect on the WRL-68 cell line that may be of interest for application in inflammatory liver diseases.

5. Anti-fibrotic effect of quercetin in comparison to silymarin on thioacetamide induced hepatic fibrosis through modula-tion of oxidative stress and inflammatory cytokines

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Introduction: Hepatic fibrosis is a matter of serious concern worldwide. Hepatic fibrosis progresses to cirrhosis and can eventually lead to hepatocellular carcinoma. It is widely accepted that inflammatory cytokines and oxidative stress play vital roles in the process of hepatic fibrosis. Quercetin, one of the main flavonoids in vegetables, has shown hepatoprotective potential, but its effect on hepatic fibrosis is still under investigation. The purpose of this experimental work is to probe the potential of quercetin for ameliorating hepatic fibrosis by regulating oxidative stress and inflammatory cytokines.

Methods: Progressive hepatic fibrosis was induced by administration of an intraperitoneal injection of thioacetamide (200 mg/kg) twice a week for 6 weeks. After induction of hepatic fibrosis, rats were treatment with daily oral intake of quercetin (50 mg/kg) and silymarin (50 mg/kg) for 28 days. Superoxide dismutase, glutathione activity, expression of inflammatory cytokines and histopathological findings were used to assess the effect of quercetin on hepatic fibrosis.

Results: The results indicate that quercetin and silymarin significantly improved SOD activity. mRNA expression of TNF-α and NFκ-β was significantly upregulated after the induction of

hepatic fibrosis, while treatment with quercetin and silymarin significantly reduced the expression of TNF-α and NFκ-β in comparison to the group with fibrosis and also minimized the thioacetamide induced histopathological changes, as confirmed by a lower degree of hepatic lobule degeneration, the intralobular occurrence of inflammatory cells, and a lower degree of hepatocytic fibrosis.

Discussion/Conclusion: From the current study, it can be inferred that quercetin has the potential to ameliorate hepatic fibrosis by regulating oxidative stress and inflammatory cytokines and its effects are comparable to those of silymarin, which is a well-known hepatoprotective agent.

6. A case with increased urine Cu and hepatic F3 fibrosis recovered by only Cu-restrictive diet

Metin Basaranoglu (Istanbul, TR)

Introduction: Wilson's disease is a rare autosomal recessive inherited disease of copper metabolism. It's caused by mutations in the ATP7B gene. As a result, an excessive amount of copper accumulates in the body. We present a case who admitted to our hospital with elevated liver enzymes and low platelet count and reached to normal levels with only copper-restricted diet treatment in 14 months.

Methods: In 2017, a 67-year-old male admitted to our hospital with liver enzyme abnormality and low platelet count of 111.000 Ql. The patient's physical examination was unremarkable. The patient, who does not use alcohol and smoke. The patient's BMI was 24 kg/m2. Fibroscan elastography (Echosense) result was F3 (10.4 kPa).

Results: In May 2017; the patient's laboratory findings were as follows: ALT 90 U/l, AST 44 U/l, ALP 54 U/l, GGT 32 U/l, total bilirubin 1.1 mg/dl. Abdominal ultrasound was normal. The results of 24-hour urine copper excretion are shown in Table 1. Kayser-Fleischer ring wasn't seen in the eye examination. Neurological examination and brain MRI results were normal. Liver biopsy showed portal and lobular inflammation with stage 3 fibrosis. There is no fatty infiltration and without copper staining positivity. In October 2017, the patient was started on a copper-restricted diet. 3 months later, 24-hour urine copper excretion was measured as 100 Qg. The patient's 24-hour urine copper excretion result after 14 months with only copper-restricted diet was 4.4 Qg and it was the first normal test result of urine copper excretion. As of December 2018, the patient returned to normal except the low platelet levels of 111.000 Ql.

Discussion/Conclusion: Our patient was presented with elevated liver enzymes and low platelet count. Further examination showed that portal and lobular inflammation with stage 3 fibrosis with liver biopsy. 24-hour urine copper level was checked several times and they're found above the level of 100 Qg. As there wasn't any major organ involvement, the patient was started a copper-restricted diet without any chelation and after 14 months, the urine copper levels came to the normal range and the patient didn't have any complaints anymore. Levels of liver enzymes was normal range. In conclusion, without major organ involvement, Cu restrictive diet may work in some cases.

7. Prevalance of Hep B and C infection and Hep B vaccination rates in patients with IBD

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Introduction: HBV and HCV infections can reactivate in case of immunosuppression. Biological agents and immune modulators that suppress the immune system are usually using in treatment of IBD. Therefore, IBD treatment is a risk factor for HCV and HBV reactivation. In this study, we aimed to investigate the prevalence of HBV and HCV infection in patients with IBD, and the effectiveness of the vaccination during immune suppressive therapy.

Methods: 255 patients with IBD were chosen randomly from Bezmialem University' database. Laboratory findings as follows HbsAg, anti-Hbs, anti-Hbc IgG and anti-HCV were evaluated. Patients' demographic informations were considered, too. Patients who anti-Hbs (+) are immune to hepatitis B; if anti-Hbc IgG (+) it is by past infection, otherwise by vaccined. It is considered active infection if HbsAg was (+).

Results: Of the 255 patients 98.4% (251 pts) were screened for HBV and 2% (5 pts) had active infection; while 94.9% (242 pts) were screened for HCV and none of them had HCV.

9.1% (20 pts) are immune to HBV by past infection.

HBV vaccination rate is 42.7% (109 pts) but only 29.2% (64 pts) developed immunity. 40% (54 pts) not developed immunity after vaccine were using azathioprine 44.4% (24 pts) and biologic agent 77.8% (42 pts). It was demonstrated that patients using biological agents have not developed immunity after vaccine ($p < 0.01$). No difference for developing immunity by using azathioprine ($p = 0.292$).

Discussion/Conclusion: According to the results, most of the IBD patients have screened for past HBV and HCV infection in daily practice; but only a small group were vaccined for Hep B before immunosuppressive therapy. We should increase Hep B vaccination rate before immunosuppressive therapy to save liver health.

8. Plasticity of hepatic spliceosome in response to 4:10 cycles of very low-calorie intake

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Introduction: Aging and cancer are two interrelated processes, with antiaging interventions receiving increasing attention as effective anti-cancer strategies, and vice versa. Energy restriction (ER) delays the aging process and the severity of age-associated diseases, with remarkable results for protection against cancer. Last year, we demonstrated that, in mice fed to standard diet, implementation of short cycles of very low calorie intake (VLCI), consisting of 4 days of severe ER followed by 10 days of ad libitum feeding, improves metabolic health in middle-aged mice [Nat Comm. 2021 November 9;12(1):6463] and confers strong immune protection against cancer [Nat Comm. 2021 October 27;12(1):6201].

Methods: Built on the salutary benefits of ER, herein we aim to decipher plasticity events that occur in the liver of mice undergoing fasting/refeeding cycles, whose dysregulation could represent pathological drivers of aging and/or liver cancer. The phenomenon of splicing, a biological process that increases the repertoire of mRNAs/specific proteins present in a given cell, is recognized as the 11th hallmark of cancer and has been recently postulated, within the splicing-energy axis, to modulate the aging process.

Results: In line with this, our data demonstrate that the hepatic spliceosome is directly and rapidly influenced by fasting/refeeding paradigms, with up to 7 gene clusters showing distinctive patterns of plasticity in response to 4:10 cycles. Furthermore, we have identified a liver-specific fingerprint consisting in 64 splicing genes that are strongly modulated by fasting. Interestingly, 80% of these genes were found to be downregulated. Remarkably, in silico

analysis of the expression of these genes in several liver cancer databases revealed that 90% of them are oppositely altered in liver cancer when compared with liver tissue from healthy individuals. The expression of several splicing genes strongly correlated with anabolic and energy balance signals in liver and plasma, including insulin, the mTOR pathway, or beta-hydroxybutyrate.

Discussion/Conclusion: When viewed together, our results therefore suggest a potential role for these specific splicing factors in the metabolic regulation of aging and cancer.

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9. Role of bone morphogenetic protein 6 in hepatocellular carcinoma

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Introduction: Bone morphogenetic protein 6 (BMP6) belongs to the transforming growth factor-β (TGF-β) superfamily. The role of BMPs is heterogeneous in different types of cancer. Also, in hepatocellular carcinoma (HCC), BMPs have been shown to act as tumour-suppressors as well as oncogenes. Increased expression of BMP6 has been described in HCC, but its role is largely unknown. The aim of this study was to gain insight into the molecular mechanisms of BMP6 effects on HCC cells.

Methods: Human HCC cell-lines were stimulated with recombinant BMP6 (rBMP6). In order to identify the BMP receptors involved in BMP6 signalling, cells were pre-treated with dorsomorphin 1 (DMH1), a pharmacological inhibitor of the intracellular kinase domains of the activing-like receptor kinases 2 and 3 (Alk2, 3).

Results: Initial in silico analysis revealed that enhanced BMP6 expression in HCC correlates with poor patients' survival. Treatment of human HCC cell-lines with rBMP6 led to a time- and dose-dependent induction of the expression of the transcription factor inhibitor of differentiation 1 (ID1) a known target of BMP-signalling and promoter of HCC progression. In line with this, stimulation with rBMP6 induced the phosphorylation of Smad1/5/8. In contrast, rBMP6 had no effect on ERK and SMAD2 phosphorylation.

The treatment with DMH1 completely inhibited the stimulatory effect of rBMP6 on the phosphorylation of Smad1/5/8 as well as the increased ID1 expression.

Discussion/Conclusion: The enhanced expression of BMP6 in HCC and its inverse correlation with patients' survival indicate BMP6 as promotor of HCC progression. This is supported by in vitro data that indicate that the protumorigenic effects are mediates via ALK2 and/or ALK3 and thus indicate these BMP-type 2 receptors as potential therapeutic targets.

10. Assessment of serum neuropilin 1 as a single serum marker for HCC in cirrhotics

Mostafa Elkady (Benha, EG)

Introduction: Hepatocellular carcinoma (HCC) is a global health problem. It is the second most common cause of cancer-related mortality and the sixth most common cause of cancer worldwide. Risk factors for HCC include chronic viral hepatitis, alcoholic and non-alcoholic fatty liver disorders and other forms of chronic hepatitis inflammatory illnesses. The aim of the current work was to study the clinical usefulness of serum neuropilin 1 (NRP1) as a diagnostic marker for HCC.

Methods: This cross-sectional study was conducted on 90 individuals divided into three groups: Group I: thirty patients with HCC, Group II: thirty patients with liver cirrhosis (LC), Group III: thirty apparently healthy subjects. All patients were subjected to full medical history taking, thorough clinical examination and determination of the serum level of NRP1.

Results: NRP1 level was significantly higher in HCC when compared to LC group. Also, NRP1 level was significantly higher in HCC and LC groups when compared to control group. ROC curve of serum NRP1 showed sensitivity was 93.3%, specificity 80%, PPV of 82.4% and NPV of 92.3% with AUC of 0.842 at cut-off value of 4030 pg/ml.

Discussion/Conclusion: Serum NRP1 was significantly high in HCC. It could be used as a potential diagnostic biomarker for HCC.

11. Assessment of serum vitamin D in patients with non-alcoholic fatty liver disease

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Introduction: Non-alcoholic fatty liver disease (NAFLD) has an increasing prevalence worldwide. It is closely associated with metabolic syndrome, as NAFLD and low serum vitamin D are associated with obesity (high BMI). The aim of this study is to assess the association between non-alcoholic fatty liver disease and serum level of vitamin D.

Methods: This cross-sectional study was conducted on 95 subjects divided into 2 groups (1st group 45 patients with sonographically proven non-alcoholic fatty liver disease (NAFLD) and 2nd group 50 healthy subjects). All the patients were evaluated by thorough full history taking, clinical examination, routine laboratory investigations, lipid profile, abdominal ultrasound and serum level of vitamin D by ELISA.

Results: Mean weight, body mass index, and waist circumference were significantly higher in patients with NAFLD than those without also they were significantly higher in patients with severe steatosis (p-value 0.001, 0.000, 0.002, respectively). Incidence of diabetes mellitus, hypertension and cardiovascular disease were significantly higher in patients with non-alcoholic fatty liver disease than those without (p-value 0.001, 0.003 and 0.009, respectively). Serum level of vitamin D was significantly lower in NAFLD patients than those without also their values were lower in overweight NAFLD patients than those with normal body mass index but with no significant difference.

Discussion/Conclusion: Serum level of vitamin D was highly deficient in patients with non-alcoholic fatty liver disease than those without and its level significantly decreased with increasing grades of non-alcoholic fatty liver disease.

12. Predictive factors of rebleeding and mortality in cirrhotic patients with acute variceal bleeding

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Introduction: Upper gastrointestinal bleeding due to portal hypertension is a serious complication of cirrhosis with a mortality rate that can reach 25% during the first 6 weeks. Without secondary prophylaxis, bleeding recurrence within a year is around 60%. The aim of our study was to identify the predictive factors of rebleeding and early mortality in cirrhotic patients after acute variceal bleeding.

Methods: A retrospective study was conducted on all cirrhotic patients with upper gastrointestinal bleeding due to portal hypertension who were admitted to our department between 2016 and 2021. Univariate analysis was performed to search an association between bleeding recurrence, mortality, and the clinical, biological and socio-demographic characteristics of our patients. The variables studied were compared with the Pearson chi-square test with a significance threshold set at $p < 0.05$.

Results: A total of 34 patients were enrolled. The mean age was 65 years old (54–82 years old) with a sex ratio (H/F) of 0.7. The cirrhosis was mainly post viral (47.1%). It was related to an auto immune hepatitis in 11,8% and to non-alcoholic steatohepatitis in 17.6% of cases. Its etiology remained unknown in 23.5% of cases. the source of bleeding was esophageal varices in 20 patients (58.8%), gastric varices in 10 patients (29.4%) and hypertensive gastropathy in 4 patients (11.8%).

Eighteen patients (53%) underwent endoscopic hemostasis: 14 had endoscopic band ligation and 4 had endoscopic glue therapy. Twelve patients (35.3%) presented rebleeding with an average delay of 3.6 months (1–12 months). Eight patients (23.5%) died in the following year.

A significant correlation was found between rebleeding and low prothrombin level < 50% ($p = 0.018$) and a high total bilirubinemia (> 17) ($p = 0.05$). No significant correlation was found between rebleeding and the following factors: low platelet count (< 80,000) ($p = 0.114$), high international normalized ratio (INR) > 2 ($p = 0.2$), high Meld score > 20 ($p = 0.8$) or advanced cirrhosis Child-Pugh grade C ($p = 0.4$). Univariate analysis showed that six variables were predictors of death: advanced age (> 60 years) ($p = 0.031$), advanced Child-Pugh grade C cirrhosis ($p = 0.03$), low serum sodium (< 130 mEq/l) ($p = 0.05$), hypochloremia ($p = 0.011$), thrombocytopenia ($p = 0.035$) and high MELD score > 20 ($p = 0.035$).

Discussion/Conclusion: In our study, the predictive factors of rebleeding in cirrhotic patients were hyperbilirubinemia and low prothrombin level. Those correlated with early mortality were advanced age and severity of liver failure, with most deaths occurring in Child-Pugh grade C patients, as well as ionic disorders.

13. Prognostic value of hypochloremia in cirrhotic patients

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Introduction: Cirrhosis is frequently complicated by electrolyte abnormalities. Due to the high prevalence of hyponatremia, the major focus has been concentrated on the clinical significance of serum sodium levels. However, very little is known about the prognostic implications of serum chloride in patients with cirrhosis.

The aim of this study was to investigate whether serum chloride levels were associated with a worse prognosis and mortality in patients with cirrhosis.

Methods: A retrospective study was conducted on all patients with cirrhosis who were admitted to our department between 2016 and 2021. Clinical and biological data as well as evolutive characteristics were collected from medical files. Hypochloremia was defined by serum chloride levels below 99 mEq/dl. The variables studied were compared with the Pearson chi-square test with a significance threshold set at $p < 0.05$. Survival was assessed with Kaplan Meier.

Results: A total of 82 patients were enrolled. The mean age was 49 years old (39–89 years old) with a sex ratio of 1. The cirrhosis was mainly post viral (61%). It was related to an autoimmune, alcoholic or non-alcoholic steatohepatitis in 2.4%, 2.4% and 9.8% respectively. Its

etiology remained unknown in 24.4% of cases. Twenty-four patients (29.3%) had hypochloremia. Hypochloremia was a predictive factor of hepatorenal syndrome ($p = 0.003$) and ascitic fluid infection occurrence ($p = 0.02$). No significant correlation was found between hypochloremia and oedemato-ascitic decompensation ($p = 0.231$), variceal bleeding ($p = 1$) and hepatic encephalopathy ($p = 0.247$). The median survival in cirrhotic patients with hypochloremia was 5 months, while it was estimated at 22 months in patients with normal chloride levels. Hypochloremia was correlated to higher mortality ($p < 0.001$).

Discussion/Conclusion: In our study, serum chloride was associated with certain complications and short-term mortality in cirrhotic patients. Thus, serum chloride should be incorporated into disease severity and prognosis and could better predict mortality in cirrhosis.

14.A new mouse model to study the pathogenesis of PSC

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Introduction: Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease of unknown origin characterized by inflammation and fibrosis of the intra- and extrahepatic bile ducts. Although the exact underlying etiology is not fully understood, emerging evidence suggests that the pathology is a multifactorial disorder involving genetic, immunological, and environmental factors. Among them gut dysbiosis, translocation of bacteria or bacterial derived products and altered bile acids have been highly associated with PSC, yet its underlying mechanism remains unknown.

Results: We established and characterized a new genetic mouse model combining key features of PSC and Inflammatory bowel disease (IBD) to better capture the nature of the microbiome-gut-liver axis in PSC. To this end we crossed mice with an intestinal epithelial cell specific deletion of caspase-8 (established mouse model for IBD) with Mdr2 deficient mice (both models on C57BL/6 background). These double deficient mice are characterized by an enhanced infiltration of T lymphocytes into the liver accompanied by a strong inflammatory response in the liver as well as severe periportal fibrosis. Beside this, we identified a strong bacterial signature characterized by strong expression of NLRP3 and pyroptosis related proteins.

Furthermore, we verified the results in organoid experiments. Therefore, we exposed biliary organoids to supernatant derived from control and caspase-8 deficient intestinal organoids stimulated with the proinflammatory cytokine TNF. Interestingly, the supernatant of intestinal organoids lacking caspase-8 activated different cell death cascades in ductal organoids similar to the results in the mouse model.

Discussion/Conclusion: In summary our data suggest that this new mouse model, combining PSC and IBD can represent the liver disease more effectively than other models before. This might open novel avenues to better understand the pathogenesis of IBD-associated PSC to further identify novel targets or test therapies.

15.* MicroRNA-ITGA6/Has2 signaling regulates liver fibrosis

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Introduction: Liver fibrosis and cirrhosis are chronic liver diseases which contribute to the deaths of millions of individuals annually and together represent a major healthcare burden, globally. On the cellular level, the activation of quiescent hepatic stellate cells (HSCs) into

pro-fibrotic myofibroblasts is one of the key drivers of fibrogenesis. HSCs change their transcriptional and epigenetic signature and change their microRNA (miRNA) expression pattern. However, identification and in vivo functional analyses of miRNAs, which can modulate pro-fibrotic myofibroblasts remain to be investigated. We aimed to identify miRNAs that can suppress the activation of myofibroblasts in vitro and to analyze anti-fibrotic potential of the identified miRNAs in vivo.

Methods: Based on multiple miRNA screens in primary human myofibroblasts, we identified two miRNAs, as suppressors of the pro-fibrogenic profile of myofibroblasts in vitro. Further, we overexpressed these two miRNAs via adeno-associated viral vectors in various murine models of liver fibrosis.

Results: Overexpression of these miRNAs ameliorated periportal and pericentral liver fibrosis. To elucidate the molecular mechanisms, we performed microarray analyses. As a result, hyaluronan synthase 2 (HAS2) and integrin alpha-6 (ITGA6) were discovered as the targets of the identified miRNAs.

Discussion/Conclusion: Taken together, our findings provide evidence that miRNA modulation in myofibroblasts presents a promising approach for the treatment of liver fibrosis. These findings open new avenues for the development of novel therapeutics, that employ miRNAs alone, or in combination with other drugs currently in clinical trials, for the treatment of liver diseases.

16. Relevance of microRNAs in SARS-CoV-2 infection of pri-mary human hepatocytes

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Introduction: Entry factors angiotensin converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) facilitate severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) entry into the host cells. Despite SARS-CoV-2's preference for respiratory system, extrapulmonary organ involvement has been suggested. Recent studies report that SARS-CoV-2 leads to direct hepatic impairment in COVID-19 patients, necessitating further investigations about hepatic involvement. ACE2 and TMPRSS2 are expressed in primary human hepatocytes (PHH), suggesting a possible susceptibility to SARS-CoV-2. Despite this, data on infection and factors modulating functional regulation of SARS-CoV-2 infection in PHH are lacking. microRNAs (miRNAs) are approximately 22 nucleotide-long non-coding RNAs that have been shown to regulate various cellular processes including virus-host interactions. We aimed to study the susceptibility of PHH to SARS-CoV-2 and to evaluate the potential of miRNAs in modulating viral infection.

Methods: We investigated the role of miRNAs to regulate SARS-CoV-2 infection in PHH in vitro. To strengthen our findings, we analysed liver autopsies from COVID-19 patients.

Results: We demonstrate that PHH can be readily infected with SARS-CoV-2, resulting in robust replication and sustained host responses as indicated by the upregulation of several interferon-stimulated genes. In silico analyses unravelled miR-200c-3p, miR-429 and miR-141-3p as candidate miRNAs targeting ACE2 and, let-7c-5p targeting TMPRSS2. Expression of these miRNAs reduced SARS-CoV-2 infection in PHH. Furthermore, expression of several endogenous miRNAs was altered upon SARS-CoV-2 infection in PHH and human liver autopsies.

Discussion/Conclusion: Our results show that PHH are susceptible towards SARS-CoV-2 and cellular miRNAs can diminish SARS-CoV-2 viral burden.

17. A case of colon cancer complicated with synchronous HCC

Elif Sitre Koc (Beykoz, TR), Cem Aygun (Istanbul, TR), Aziz Yazar (Istanbul, TR), Nurdan Tozun (Istanbul, TR)

Introduction: Colorectal cancer (CRC) is the third most common cancer type worldwide and second most common cause of cancer death. PET-CT can be useful for the staging of CRC. In PET scan, more than 1/3 of patients are diagnosed with extracolonic tumors that locate in liver. Findings that are not compatible with metastasis should be further examined by laboratory, imaging and pathology for extracolonic secondary primary cancers.

Case: A 67-year-old patient presented to the gastroenterology clinic with complaints of rectal bleeding and changes in defecation pattern with a-2-month history. Laboratory tests revealed nothing abnormal except elevated GGT (357 IU/l) level. Serological examination revealed negative HBsAg, anti-HIV tests and positive anti-HCV test. Colonoscopy which showed a tumoral lesion with a diameter of 3 cm in the rectosigmoid region suggesting malignancy was performed. For further examination a PET CT scan was performed and identified two lesions; a 56 x 12 mm lesion located in segment 5 and 22 x 10 mm lesion located in segment 7. Additionally, lobulated liver contour and hypertrophy of the caudate lobe were detected.

These findings were found to be suspicious for HCC, and histopathological evaluation whose results were compatible with HCC was performed. In biopsy samples, the tumor was moderately differentiated, infiltrated into the liver parenchyma, and venous invasion was positively noted. Due to the HCV RNA value resulted in 468,300 IU/ml, the patient was put on velpatasvir 100 mg/sofosbuvir 400 mg therapy for chronic hepatitis C. For the rectosigmoid cancer was low anterior resection after neoadjuvant chemotherapy was carried out. Since hepatic lesions were not appropriate for surgery, Transarterial Chemoembolization (TAKE) was preferred. In the follow-up, HCV RNA became negative and AFP level decreased to normal range.

Discussion/Conclusion: Risk of extracolonic secondary primary cancers in patients with CRC is not rare. In these situations, further laboratory, imaging and histo-pathological examination should be performed.

18. Predictive value of red cell distribution width to platelet ratio for liver fibrosis

Elif Sitre Koc (Beykoz, TR), Cem Aygun (Sarıyer, TR), Eser Kutsal (Sarıyer, TR), Nurdan Tozun (Sarıyer, TR)

Introduction: As a substitute of Fibroscan, serum markers and blood tests are used in many centers as non-invasive methods. Fibroscan is a rapid, reliable, non-invasive method that assess liver fibrosis although availability is a problem in some clinics. In this study, we aimed to predict the value of RDW/PLT to predict liver fibrosis as well as to evaluate the relationship between Fibroscan examination results and routine laboratory tests and APRI score.

Methods: A total of 209 patients (116 with NAFLD, 64 with chronic hepatitis B, 29 with hepatitis C) who were screened with Fibroscan were enrolled in the study. Along with the demographic characteristics of patients, liver function tests and Fibroscan results were evaluated retrospectively.

Results: Of the patients evaluated, 86 were female, 123 were male. The average age and the mean BMI were 52 3 13.4 and 28.6 3 5.2, respectively. The mean laboratory values of the patients were ALT: 65.4 3 52.5, AST: 41.6 3 33.9, GGT: 81.2 3 104.4, total bilirubin: 1.1 3 2.5, albumin: 3.9 3 0.5, INR: 1.1 3 0.2 and hepatic steatosis (CAP): 278.2 3 69. ALT and AST values were significantly higher in severe steatosis group (CAP ≥ 300) as compared with the mild-to-moderate group (CAP < 300) (p-values 0.001, 0.03 respectively); however, there were no statistically significant difference between GGT, APRI and RDW/PLT values. Additionally, AST, APRI, RDW/PLT values were found to be statistically significantly higher in the group with advanced fibrosis (kPa ≥ 13) when compared with the others (kPA < 13) (p-values < 0.01).

Discussion/Conclusion: AST, APRI and RDW/PLT values were significantly higher in advanced liver fibrosis group of patients regardless of etiology. In severe steatosis group, a significant difference was detected only for ALT and AST values.

19.* Comparing survival in liver transplant recipients with hepa-tocellular carcinoma

Elif Sitre Koc (Istanbul, TR), Ali Ozer (Sarıyer, TR), Fatih Oguz Onder (Sarıyer, TR)

Introduction: Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer and driven by multiple etiological factors, such as hepatitis infections, non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease and inherited diseases. Surgery is the only curative treatment and liver transplantation (LT) offers long-term outcome for certain patients. The aim of this study was to assess whether there is difference in survival among patients who underwent liver transplantation due to NAFLD, hepatitis or metabolic induced HCC.

Methods: A total of 202 patients (38; 18.8% with NASH) who were diagnosed with HCC and underwent LT were enrolled in the study. Along with the demographic characteristics of patients, tumor characteristics follow-up results were evaluated.

Results: Patients with NASH were significantly older (61.9 3 7.5 vs. 57.3 3 8.1; p = 0.001). Diagnoses of DM and HT were more prevalent in NASH group (p < 0.001). There were no significant differences between groups for tumor characteristics, including Milan criteria, grade, lympho-vascular invasion, neural invasion. Overall, 42 (20.7%) of the HCC patients relapsed during follow-up. Kaplan-Meier analysis of HCC-free survival (p = 0.38) and overall survival (p = 0.68) were similar between groups. Effects of various factors on survival was analyzed with Cox proportional-hazards regression. Vascular invasion in the tumor was significantly associated with HCC free survival (HR = 24.5; 95% CI: 3.9–154; p = 0.0007) and overall survival (HR = 2.8; 95% CI: 1.0–7.68; p = 0.04).

Discussion/Conclusion: HCC-free and overall survival of patients with NASH are similar compared to other HCC patients after liver transplantation.

20.* Tick-tock – Circadian regulation of liver metabolism represented in a kinetic model

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Introduction: The circadian rhythm is a decisive regulator for metabolic homeostasis especially in the liver. The importance of diurnal control is highlighted by the increased risk of liver diseases, obesity and metabolic syndrome due to disturbance of circadian rhythms. However, time resolved in vivo studies of liver metabolism are rare and molecular resolved,

kinetic models can be used for metabolic phenotyping based on proteomic data, enabling linking circadian rhythmicity of protein abundances to metabolic regulation.

Methods: We investigated the rhythmicity of liver metabolism in male C57BL/6N mice using kinetic models for liver samples isolated every three hours. Additionally, we correlated plasma metabolite profiles with metabolic liver functions.

Results: Our analysis revealed a rhythm of 12 hours for lipid metabolism, ethanol detoxification and partly carbohydrate metabolism in the liver. However, gluconeo-genetic capacity, fructose and urea synthesis capacity were obviously not underlying circadian regulation. We could show a correlation between plasma fatty acid concentrations and fatty acid liver metabolism. Concerning detoxification capacities, ethanol utilization capacity was highly associated with plasma glucose concentrations, but no significant correlations with plasma metabolites could be found for urea synthesis and ammonia uptake capacities.

Discussion/Conclusion: The model helps to better understand whether circadian rhythms are intrinsic and independent of nutrient availability or follow diurnal dietary patterns. By accounting for the circadian regulatory properties of all enzymes, our model integrates the accumulated knowledge from decades of biochemical research and allows quantitative predictions of system behavior as a function of circadian rhythmicity.

21.* Cell plasticity of liver cancer cells is blunted by fasting in combination with the cocktail metformin-sorafenib

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Introduction: Sorafenib and metformin, two gold standard treatments of liver cancer, are reported to have synergistic effect. Since fasting has emerged as a feasible strategy for this type of cancer in the clinical practice, this study aimed to explore the functional effect on cancer cell plasticity by the combination of Nutrient Restriction (NR) with the cocktail sorafenib-metformin (NR:SM).

Methods: To this end, we have carried out proliferative assays in three liver cancer cell lines with increasing tumorigenicity (HepG2, Hep3B, and SNU-387) to test the carcinogenic response to 80% NR in the presence or absence of metformin alone (0.5–10 mM), sorafenib alone (1–5 mM), or their combination. Metabolic plasticity was also determined by the analysis of Mitochondrial and Glycolytic activity, cell cycle dynamics, and the activation of apoptotic and mTOR pathways, the latest considered a well-known metabolic-hub involved in anabolism.

Results: Our results show that metformin and sorafenib reduce cellular proliferation, with fasting boosting their synergistic effect. Early apoptotic events were also increased by NR:SM when compared to NR, Metformin alone, or sorafenib alone. The pro-apoptotic Bcl-xL/Bcl-xL ratio as well as the expression of the anti-apoptotic BCL-2 levels were found increased and decreased respectively, after NR:SM treatment. Consistent with this, NR:SM induced a higher retention of liver cancer cells in SubG1 phase, suggesting the presence of DNA fragments produced by cellular apoptosis. Remarkably, dynamic analysis of mitochondrial function indicated that mitochondrial ATP-linked respiration, Maximal respiration, and spare respiratory capacity was blunted by NR:SM, indicating a potential reprogramming towards a quiescent state in these cells. Basal glycolysis, glycolytic reserve, and glycolytic capacity, together with a reduction of key enzymes involved in Glycogenesis and Glycolytic pathways, were dramatically diminished after NR:SM intervention. Activa-

tion of AMPK pathways and enhancement of autophagy, determined by the LC3B/LC3A ratio were also found in NR:SM treated cells.

Discussion/Conclusion: Taken together, our results demonstrate that in vitro implementation of NR boosts the anti-cancer effect of the cocktail sorafenib:metformin, likely by the modulation of metabolic and cancer cell plasticity. In sum, our results suggest that this strategy may represent a promising therapeutic tool in this tumor pathology.

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22. Low-density granulocytes expressing myeloperoxidase as novel markers of autoimmune hepatitis

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Introduction: Due to their proinflammatory property, low-density granulocytes (LDGs) expressing myeloperoxidase (MPO) (LDGs MPO+) are discussed as potential cells directly involved in the pathogenesis of autoimmune hepatitis (AIH), however this issue remains unclarified. Thus, we decided to assess the diagnostic usefulness of the LDGs percentage, including the fraction of LDGs MPO+ as markers of systemic inflammation in AIH. We looked for the existing correlations between LDGs and indirect indices of liver fibrosis, as well.

Methods: The study consisted of 45 participants: 25 patients with AIH and 20 controls. Mononuclear cells, isolated from peripheral blood, were labeled with monoclonal antibodies conjugated to the appropriate fluorochromes (CD15-FITC, CD14-PE, CD10-PE-Cy5, MPO+) and then analyzed on a Navios Flow Cytometer (Beckman Coulter). Indirect markers of liver fibrosis were also obtained: AAR, APRI, FIB-4 and GPR (GGT to PLT ratio).

Results: Patients with AIH presented a significantly higher median percentage of LDGs (1.2 vs. 0.1; $p = 0.0001$) and LDG MPO+ (0.8 vs. 0.3; $p = 0.0017$) compared to controls. Furthermore, the percentage of LDGs was characterized by 100% of sensitivity and 55% of specificity [area under the curve (AUC) = 0.84; $p < 0.0001$], while the percentage of LDGs MPO+ was 92% of sensitivity and 55% of specificity (AUC = 0.78; $p = 0.0001$) in the detection of AIH. Moreover, LDGs MPO+ correlated positively with APRI ($p < 0.05$).

Discussion/Conclusion: These novel findings indicate a potential great diagnostic value of LDGs MPO+ in the evaluation of inflammatory process in the course of AIH. Subsequently, the relationship between LDGs MPO+ and APRI might be perceived as the proof of a close dependency between hematological parameters and indirect markers of liver fibrosis. Presented results seem to open the unexplored area of diagnostic opportunities in AIH patients.

23. Metabolic-associated fatty liver disease, microRNAs and hematological indices – A novel diagnostic pathway in hepatology?

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Introduction: MicroRNAs (miRNAs) were found to participate in the progression of various liver pathologies. On the other hand, there are attempts to verify the role of hematological indices in patients with liver disorders, as well. Our goal was to assess the relationships between selected miRNAs and hematological indices in the course of MAFLD.

Methods: One hundred ninety-seven persons were enrolled in the study: 97 with MAFLD and 100 healthy volunteers in the control group. Serological expression of miR-126-3p, miR-197-3p and miR-1-3p was evaluated in all examined patients. Hematological markers were also assessed: mean platelet volume (MPV), platelet distribution width (PDW), plateletcrit (PCT), mean platelet volume to platelet ratio (MPR) and platelet to lymphocyte ratio (PLR). Then correlations between evaluated indices were performed. A diagnostic value of miRNAs together with proposed cut-off in the research group were measured with area under the curve (AUC).

Results: The expression of examined miRNAs (miR-126-3p, miR-197-3p and miR-1-3p) in NAFLD group differed significantly in comparison to controls; a concentration of miR-126-3p and miR-1-3p was higher and miR-197-3p – lower ($p < 0.0001$). Furthermore, miR-197-3p correlated positively with PLR and negatively with PDW ($p < 0.05$). MiR-126-3p turned out to be the most powerful diagnostic marker among assessed miRNAs in examined MAFLD group with AUC of 0.716 for the cut-off > 9.49 amol/Ql ($p < 0.0001$); AUC of miR-197-3p was 0.672 for the cut-off < 0.32 amol/Ql ($p < 0.0001$).

Discussion/Conclusion: To the best of our knowledge, serological expression of miR-126-3p, miR-197-3p and miR-1-3p was mostly explored in patients with hepatocellular injury and hepatocellular carcinoma. Our investigation seems to be the first one that shows a direct linkage between miRNAs and hematological indices in MAFLD patients.

24.* Expression and transcriptional regulation of fibroblast growth factor receptors in hepatocellular carcinoma

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Introduction: Fibroblast growth factor receptors (FGFRs) are receptor tyrosine kinases and are created from four genes (FGFR1/2/3/4). Alternative splicing of FGFR1-3 generates b- and c-isoforms that differ in ligand binding and contribute to diversity of FGF signalling. FGFR inhibition has been shown to inhibit progression of hepatocellular carcinoma (HCC) in experimental models. However, interventions with mostly unspecific FGFR pan-inhibitors provided only modest benefits for patients in non-selected cohorts. The aim of this study was to analyze the expression and transcriptional regulation of FGFR variants in HCC.

Methods: RT-qPCR was used to analyze FGFR mRNA expression. Correlations between FGFRs were analyzed by using GEPIA database. Gene knockdown was mediated by specific siRNAs.

Results: COSMIC database analysis showed that genetic FGFR aberrations are rare in HCC (less than 4% in 2090 patients). Still, quantitative PCR analysis revealed that expression levels of FGFR1, FGFR3 and FGFR4 were upregulated in human HCC cell lines (Hep3B, HepG2, Huh7, PLC) compared to primary human hepatocytes. Similarly, FGFR1, FGFR3 and FGFR4 were upregulated in most HCC tissues compared to corresponding nontumorous liver. Applying GEPIA database and a dataset of human HCC (LIHC) samples we found that expression of FGFRs significantly correlated with each other pointing to common transcriptional regulation. In search for the molecular mechanisms, we analyzed histone acetylation and identified histone deacetylase 7 (HDAC7) as negative regulator of FGFR expression in HCC cells. Regarding variant-specific FGFR expression, we analyzed the effects of siRNA-mediated knockdown of epithelial splicing regulatory protein 1 (ESRP1) in HCC cells. ESRP1 suppression led to significant upregulation of FGFR2c and FGFR3c but downregulation of the corresponding b-isoforms.

Discussion/Conclusion: Our study provides novel insights into the transcriptional regulation of FGFR variants in HCC that could facilitate biomarker-selected FGFR-targeted therapies. The observed variation in the FGFR expression pattern might also be exploited for personalized FGFR-directed treatment.

25. Platelet-rich plasma (PRP)-driven changes in the gene expression of hepatic glucose metabolism of diabetic mice

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Introduction: Platelet-rich plasma (PRP) has been reported to play a potential role in alleviating diabetes mellitus in recent years.

The present study was conceived to test the hypothesis that PRP could improve experimentally induced diabetes in mice by altering glucose metabolism.

Methods: Thirty (30) healthy male (4–5 weeks old) albino mice were selected and grouped as G1, G2, G3, G4 and G5 (n = 6). G1 was a control group and remained untreated while G2 was given a subcutaneous dose of PRP (0.5 ml/kg body weight) twice a week for four weeks. To G3, G4 and G5 a single intraperitoneal dose of alloxan (200 mg/kg) was given to induce diabetes. G3 was left untreated as diabetic control and PRP treatment (0.5 ml/kg body weight) was given to G4 and G5 for two and four weeks respectively (twice a week). Upon completion of experimentation, dissections of animals were made to excise livers for further processing of gene expression analyses.

Results: A significant downregulation was observed in the expression of hepatic glycogen phosphorylase (GPase) in G3, compared to controls (G1 and G2) and PRP treatment restored it significantly in G4 and G5 while glycogen synthase (Gs) expression showed no significant change among all groups. Additionally, Fbp1, G6pc, and Pklr genes of the gluconeogenesis pathway showed an upregulation while a downregulation was detected in the expression of Pck1 gene in G3. PRP treatment restored the expression of Fbp1 and G6pc genes but Pklr remained unchanged in G4 and G5.

Discussion/Conclusion: Current study revealed that PRP anticipates a reduction in glucose production by modulating glycogen degradation and gluconeogenesis but more detailed investigations are suggested.

26.* Four-and-a-half LIM-domain protein 2 (FHL2) in hepato-cellular carcinoma

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Introduction: The four-and-a-half LIM-domain protein 2 (FHL2) is an adaptor protein that can bind to various proteins, directing the functions of the protein complexes formed. FHL2 has been described to have multiple, often opposing functions in different cells and tissues. Also, in different types of cancer, FHL2 has been associated with both pro- and anti-tumorigenic functions. The aim of this study was to investigate the expression and function of FHL2 in hepatocellular carcinoma (HCC).

Methods: Survival analysis was performed applying the „SurvExpress-Biomarker validation for cancer gene expression" database using the Hoshida Golub Liver GSE10143 dataset as described [PLoS ONE 2013, 8, e74250]. Colony formation and CyQUANT®NF proliferation assay were performed as described [Cancers (Basel) 2019;11(10)] after transfection with siPOOLs (siFHL2) or after adenoviral transduction (FHL2 OE). qRT-PCR analysis was per-

formed with specific primers as described [Gastroenterology 2003;125:1085–1093]. Statistical analysis: Results are expressed as mean 3 SEM. Comparison between groups was made using the Student's unpaired t-test, ordinary one-way ANOVA or ordinary two-way ANOVA, respectively. A p-value < 0.05 was considered statistically significant (*).

Results: FHL2 mRNA and protein expression were significantly reduced in 4 human HCC cell lines compared to primary human hepatocytes. Also in human HCC tissues, FHL2 expression was significantly lower than in corresponding adjacent non-tumorous liver tissue. Analysis of HCC patient data showed that FHL2 expression was lower in high-risk patient group (based on prognostic index) and correlated inversely with patients' survival. To get further insight into the role of FHL2 in HCC, we assessed HCC cells with siRNA-induced FHL2 suppression or adenoviral-mediated over expression of FHL2 in functional in vitro assays. Neither knockdown nor over expression of FHL2 had a significant effect on the proliferation of HCC cells. Furthermore, FHL2 suppression did not affect colony formation and colony growth in clonogenic assays. However, colony formation was significantly inhibited in FHL2 overexpressing cells. Furthermore, FHL2 suppression resulted in reduced expression of pro-inflammatory genes (IL-8 and ICAM-1) and was accompanied by an accumulation of p62 in HCC cells, which is indicative for impaired autophagy. Autophagy is known to affect the response to the multikinase inhibitor sorafenib, and interestingly, we observed that FHL2 depletion enhanced the sensitivity of HCC cells for sorafenib.

Discussion/Conclusion: Expression analyses suggest an anti-tumorigenic role of FHL2 in HCC. However, functional analysis indicate both pro- and anti-tumorigenic effects of FHL2 in HCC cells and a complex role of FHL2 in combination with sorafenib treatment, which requires further investigation.

27. Gut-liver axis dilemma: Genetically determined linkage of NAFLD and intestinal dysbiosis via impaired mesenteric circulation

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Introduction: It is generally accepted that non-alcoholic fatty liver disease (NAFLD) is the most common liver disorder in developed countries (6–35%) with about 30% prevalence in the United States during the last decade as shown in the study using the National Health and Nutrition Examination Survey. Due to multiple similar pathogenesis mechanisms, NAFLD commonly combines with other systemic and metabolic disorders, among them obesity, diabetes (DM), and arterial hypertension (AH). Gut-Liver axis is a complex interplay depicting linkage of liver pathology and changes of intestinal microbiota while having strong clinical and physiological evidence lacks cohesive genetic background explanations i.e. there is a sort of dilemma if Gut-Liver axis results only due to environmental factors or involved mechanisms have possible genetic predisposition. Angiotensin converting enzyme and angiotensin ii receptor type genes attracted our attention following recent data of these mechanisms involvement into the coronavirus-related multi-organ injury, especially liver failure. The aim of this study is to clarify possible associations of NAFLD, changes of intestinal microbiota, changes in the mesenteric blood supply, and ACE (I/D) and AGTR1 (A1166c) genes' polymorphisms.

Methods: Study involves 104 NAFLD patients, among them 50 (48.1%) were women, and 54 (51.9%) men, fully adhering bioethics. Mean age – 53.2 3 8.7 years. NAFLD and systemic/metabolic conditions (AH and DM) diagnosis and management according to AASLD/ACG/AGA, ASC/ESH and ASD Guidelines, respectively. Bowel microbiology study included taxo-

nomic group identification and determination of their population levels with 33.3% variation (statistical tertiation principle) as dysbiosis single step deviation (dysbiosis severity grades I–III). Mesenteric blood vessels were assessed by Doppler US. ACE (I/D) and AGTR1 (A1166c) genes' single nucleotide polymorphisms were studied in RT-PCR.

Results: As mesenteric circulation looks the most proximate and obvious pathogenetic connection between vascular and intestinal systems, sonography demonstrated ischemic changes in mesenteric blood vessels, which were characterized by 1.4–1.94 times decrease of time overage velocity (reliable in D-allele carriers of ACE gene and C-allele of AGTR1 gene, $p < 0.05$), 1.5–3.05 times ($p < 0.05$) increase of peak systolic and end diastolic velocity (independent on genotypes of analyzed genes), and raised peripheral vascular resistance by Gosling index (2–2.35 times, $p < 0.05$). Intestinal microbiota changes (dysbiosis) severity strongly correlated with NAFLD, AH severity in D (ACE) and A (AGTR1) allele's carriers while changes in mesenteric blood vessels also correlated with dysbiosis severity but with weaker dependence on genotypes. AGTR1 gene's CC-genotype carriers had the highest risk of changes in abdominal vessels. Severity of dysbiosis at least moderately or strongly ($r = 0.61–0.83$, $p \leq 0.04–0.001$) but positively correlated with NAFLD, AH and DM severity/grade, respectively.

Discussion/Conclusion: Whereas, presence of direct linkage of bowel and hepatic functioning is apparent, forming Gut-liver axis, its genetic background is less obvious. While genetic predisposition to NAFLD is considered to be a well-established fact, the role of genetic background explaining systemic changes in NAFLD patients, including Diabetes, Hypertension or other comorbidities is somehow controversial. This study shows that both ACE and AGTR1 genes' polymorphisms while having no direct pathogenetic influence on hepatic function, nevertheless determine changes of blood vessels and thus, intestinal microbiota. Following this concept, it causes respective influence on metabolic profile and intestinal metabolism with reliable correlation of dysbiosis and disease severity.

28. Xenobiotic-dependent changes of liver circadian biorhythms and oxidative stress

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I**ntroduction:** Xenobiotics are chemical substances that are not naturally produced or expected to be present within the organism, or metabolically unfamiliar. Xenobiotics are often environmental pollutants and drugs, because they are understood as substances foreign to an entire biological system, i.e. artificial substances, which do not normally exist in nature. Metabolism of xenobiotics happens mostly in the liver and consists of deactivation and excretion. Particular example of a group of enzymes involved in xenobiotic metabolism is hepatic microsomal cytochrome P450, which are very important for the pharmacotherapies because they are responsible for the breakdown of various medications. Several studies raised the problem of how environmental chemicals affect circadian rhythms depicting connections of diurnal rhythms and xenobiotic metabolism in liver. Moreover, while many xenobiotic substances are directly involved into development of oxidative stress and liver dysfunction, understanding of interrelations between xenobiotic influence, oxidative stress, and circadian pattern emphasizing liver, looks underexplored. Consequently, the aim of this study is to clarify the xenobiotic influence on circadian rhythms of liver's pro- and antioxidant systems. Hypothetically, this may peculiarly ameliorate daily schedule for drug therapies resulting in more optimized and successful treatment.

Methods: The was study conducted experimentally in vitro involving 124 (64 – study group, 60 – control) adult Wistar line rats of both genders weighing 203.8 3 26.31 g adhering strict bioethics standards. Para-acetaminophen (paracetamol) was selected as xenobiotic: 1 mg per gram of mass in 2% potato starch gel was administered in study subgroups (16 animals of both genders each equally) every six hours (9:00, 15:00, 21:00 and 3:00). Following exactly 24 h, reduced glutathione (GSH), catalase and superoxide dismutase (SOD) as a potent antioxidative compounds, and thiobarbituric acid reactive substances (TBARS) as a marker of lipid peroxidation in liver were determined each time period. To reduce exposure to light-dependent melatonin synthesis effect during the evening and night periods the experiment was carried out under an infrared illumination. Cosinor.online and circadian.org software plus standard statistical packages were used for statistical calculations of biorhythms indicators: mean, median, amplitude, batiphase, acrophase, mesor and daily curve of data.

Results: Expectedly, GSH activity in liver dropped significantly throughout the day compared to control data: 39.37% at 9:00, 24.56% at 15:00, 14.43% at 21:00, and 24.99% at 3:00, respectively. Xenobiotic influence on SOD circadian pattern was less significant: 12.31% reduction at 9:00, 7.07% at 15:00, 12.86% at 21:00, and 8.78% at 3:00, respectively. Under xenobiotic influence catalase showed various biorhythm fluctuations during the day compared to control group: 9.78% reduction at 9:00, 59.63% reduction at 15:00, 6.38% at reduction 21:00, and 9.45% increase at 3:00. Under xenobiotic influence TBARS values underwent insignificant changes compared to control: insignificant growth (0.03–11.54%) at 15:00, 21:00, and 3:00 accompanied by unchanged value at 9:00. Male animals showed significantly more expressed xenobiotic-dependent circadian reaction caused by para-acetaminophen administration with fluctuations exceeding 21.37–48.83% compared to female group of the same time period. Both mesor and daily amplitude did not significantly differ between study group and control except GSH mesor in male animals (68.25 3 9.48 U versus 105.96 3 6.49 U in control p = 0.0095).

Discussion/Conclusion: Whereas it was clearly foreseen that xenobiotic significantly impact liver's pro- and antioxidant systems, its influence on circadian pattern seems less obvious. Most of GSH circadian characteristics under xenobiotic influence remained unchanged except mesor in male animals. Administration of a toxic dose of paracetamol cause desynchronization of the circadian rhythm of catalase activity with the levelling of a pronounced acrophase, which is characteristic for intact control animals. Its amplitude is decreased almost 96.75% in male animals and 74.65% in female rats. Minor circadian changes of TBARS values depict involvement of different mechanisms into liver's injury in oxidative stress or reflects it independence emphasizing biorhythms. The data from this study may be used for peculiarly ameliorate daily schedule for drug therapies. Moreover, it may be interesting to study other xenobiotic substances to compare their effects, too.

29.* Circadian pattern of pro- and antioxidants in liver

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Introduction: Liver is a major organ attacked by oxygen free radicals, such as hydroxyl radicals, superoxide, and peroxyl radicals, with addition of non-radicals, such as hypochlorous acid, hydrogen peroxide, and ozone, which are generated during the metabolism of oxygen. Parenchymal cells are primary cells subjected to oxidative stress induced injury in the liver, whereas Kupffer cells, hepatic stellate cells and endothelial cells are potentially even more vulnerable because they are more exposed or sensitive to oxidative stress-related molecules.

A sophisticated antioxidant system is present in all mammals aimed to maintain the redox homeostasis in the liver. The oxidative stress does not only trigger hepatic damage by inducing irretrievable alteration of lipids, proteins and nucleic acids and more importantly, modulate regulatory pathways, which control normal biological functions. It is widely accepted that circadian rhythms can participate in lipid, glucose, and cholesterol metabolism and are closely related to homeostasis changes seen in various liver diseases. Desynchronized biorhythms and the influences imparted by external environmental stimuli can significantly influence both pathologic conditions and treatment efficacy. However, little is known about circadian pattern of liver's antioxidant system which can have a strong potential for treatment strategies. Therefore, we aimed on studying the circadian rhythms of liver pro- and antioxidant systems including gender related variations.

Methods: Sixty-eight adult Wistar line rats of both genders (to identify possible gender differences in circadian rhythms) weighing 203.7 3 19.49 g were included into the experimental study adhering strict bioethics standards. Every six hours (9:00, 15:00, 21:00 and 3:00) reduced glutathione (GSH), catalase and superoxide dismutase (SOD) as a potent antioxidative compounds, and thiobarbituric acid reactive substances (TBARS) as a marker of lipid peroxidation in liver were determined. To reduce exposure to light-dependent melatonin synthesis effect during the evening and night periods the experiment was carried out under an infrared illumination. Cosinor.online and circadian.org software plus standard statistical packages were used for statistical calculations of biorhythms indicators: mean, median, amplitude, batiphase, acrophase, mesor and daily curve of data.

Results: GSH activity in liver changed significantly throughout the day: 107.16 3 11.60 U (9:00), 155.03 3 14.11 U (15:00, p = 0.012), 78.29 3 15.12 U (21:00, p1 = 0.0065), and 86.91 3 8.27 U (3:00, p1 = 0.0044), respectively. SOD changes were less significant, depicting lower grade circadian pattern: 49.15 3 2.61 U (9:00), 45.58 3 3.59 U (15:00), 40.02 3 3.69 U (21:00, p = 0.049), and 43.11 3 3.20 U (3:00). Catalase showed much stronger circadian pattern with following levels, respectively: 51.14 3 4.19 Qkat (9:00), 78.36 3 3.82 Qkat (15:00, p = 0.027), 49.97 3 3.10 Qkat (21:00, p1 = 0.0018), and 44.09 3 3.01 Qkat (3:00, p1 < 0.001). TBARS values underwent significant changes as well: 16.30 3 2.41 Qmol/l (9:00), 17.19 3 3.42 Qmol/l (15:00), 31.09 3 4.25 Qmol/l (21:00, p = 0.0033), and 26.14 3 3.16 Qmol/l (3:00, p1 = 0.017). Mesor for male and female animals were 107.14 3 5.98 U and 106.10 3 6.52 U (GSH), 44.21 3 1.07 U and 45.23 3 2.29 U (SOD), 56.17 3 3.12 Qkat and 56.15 3 3.50 Qkat (Catalase), and 22.51 3 1.23 Qmol/l and 24.33 3 2.91 Qmol/l (TBARS), respectively. The circadian peak of activity (acrophase) of GSH and catalase were observed at 15:00, SOD – 9:00, and TBARS reached acrophase at 21:00.

Discussion/Conclusion: Circadian pattern of pro- and antioxidant systems in hepatocytes undergoes significant variations during the day. The highest activity of antioxidant factors and mechanisms is observed mostly at daytime (9:00–15:00), whereas pro-oxidative factors express highest activity at nighttime (21:00–3:00). This data may suggest modification of both diagnostic (time of determination of symptoms and bench indices) and treatment (time of drugs administration) approaches in liver disease.

30. Extrahepatic cancer risk in patients with cirrhosis

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Introduction: Cirrhosis is a well-known risk factor for hepatocellular carcinoma. nevertheless, less is known about the risk of extrahepatic neoplasia (EHN) during cirrhosis.

Our objective was to study the prevalence and the prognostic impact of EHN in patients with cirrhosis.

Methods: We performed a retrospective analysis of data from consecutive patients followed in our department for cirrhosis recruited from January 2012 to December 2020.

Results: A total of 224 patients were included with a mean age of 61.02 3 13.21 years and a sex ratio of 1.60. Viral infection was the most common etiology of cirrhosis (55.2%), followed by non-alcoholic steatohepatitis (21.3%). During an average follow-up period of 17.2 months [1–96], 27 patients had EHN with a percentage of 12%. There were 15 men and 12 women with an average of 71 3 14.8 years. Patients were classified by the Child-Pugh (CP) score: 12 patients with CP A, ten CP B, and five CP C. Breast tumor was the most frequent EHN (7 cases) followed by prostatic adenocarcinoma (5 cases), bladder tumor (2 cases) and pulmonary adenocarcinoma (2 cases). Only seven patients benefited from curative treatment. During follow-up, seven patients developed HCC (25.9%). A significant correlation was noted between the presence of EHN and the occurrence of hepatic encephalopathy ($p = 0.04$), bacterial infection ($p = 0.03$), and variceal bleeding ($p = 0.01$). A total of 14 patients (51.8%) died, including four directly related to complications of cirrhosis and ten related to the advanced stage of their neoplasia. Mortality was significantly correlated with the presence of EHN ($p = 0.006$).

Discussion/Conclusion: In our study, 12% of patients with cirrhosis had EHN. Since one compromised the therapeutic management of the other, the association between EHN and cirrhosis had a poor prognosis with high morbidity and mortality.

31. Prognostic performance of Toronto HCC risk index in patients with hepatocellular carcinoma

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Introduction: Hepatocellular carcinoma (HCC) is a life-threatening complication of cirrhosis. The Toronto HHC risk index (Toronto index) which is a simple score recently proposed for the prediction of HCC, could have a prognostic value.

Our objective was to assess the prognostic performance of the Toronto index at the time of diagnosis of HCC on the prediction of overall one-year survival.

Methods: This was a retrospective study including consecutive cirrhotic patients with HCC followed in our department, between January 2010 and December 2019. Overall survival was assessed by Kaplan-Meier survival analysis using log-rank. Demographic, clinical, and paraclinical data were collected.

Results: A total of 219 cirrhotic patients were included. Sixty-one (27.8%) of them had HCC with a mean age of 64.3 3 10.1 years and a sex ratio of 3.35. The patients were classified according to the BCLC classification: 3.2% stage (0), 33.8% stage (A), 28.9% stage (B), 19.1% stage (C) and 15 % stage (D). At a threshold of 226, the Toronto index had a sensitivity and specificity in predicting HCC of 80.3% and 48% respectively with an area under the ROC curve of 0.69 [95% CI: 0.61–0,76]. Toronto index was statistically associated with BCLC classification ($p = 0.011$). Twenty-one patients (classified as stage BCLC 0 and A) underwent curative radiofrequency treatment (34.4%) and two patients underwent surgical resection (3.2%). Thirteen patients classified as stage B underwent chemoembolization (21.3%) and three patients were treated with sorafenib (4.9%). One-year overall survival was 83.6%. Toronto index was not statistically associated with one-year survival ($p = 0.136$).

Discussion/Conclusion: Despite its good predictive value for the development of HCC, the prognostic performance of the Toronto index is not significant.

32. Gallstones associated with non-alcoholic steatohepatitis (NASH) and metabolic syndrome

Oktay Yener (Istanbul, TR)

Introduction: We aimed to evaluate the prevalence of non-alcoholic steatohepatitis and metabolic syndrome in patients with symptomatic gallstones undergoing laparoscopic or open cholecystectomy.

Methods: A study of 95 patients was performed. Simultaneous liver biopsies were taken during cholecystectomy between 2020 and 2022. There were no postoperative complications. Patients with significant alcohol intake, hepatitis B or C (virus-positive), autoimmune diseases, and Wilson's disease were excluded.

Demographics, liver function tests, lipid profile, and ultrasound findings of patients with and without non-alcoholic steatohepatitis were compared.

Results: A total of 95 patients completed the study. The mean age was 52.15 years, and 29 patients were male and 66 females. Fifty-two patients (55%) had biopsies compatible with non-alcoholic steatohepatitis.

Discussion/Conclusion: Fifty-five percent of patients with gallbladder stones had associated non-alcoholic steatohepatitis. Awareness of this association may result in an earlier diagnosis. The high prevalence of non-alcoholic steatohepatitis in patients with gallbladder stone may justify routine liver biopsy during cholecystectomy to establish the diagnosis and stage and possibly direct therapy.

33. Hepatitis B serology in non-alcoholic steatohepatitis-induced liver cirrhosis and hepatocellular carcinoma

Elif Yorulmaz (Bagcilar, TR)

Introduction: Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease in the world, with an increasing incidence. It has a wide spectrum ranging from simple hepatosteatosis to non-alcoholic steatohepatitis (NASH), liver cirrhosis and hepatocellular carcinoma (HCC). Since exposure to hepatitis B in patients with NASH may cause acute exacerbations, close follow-up with hepatitis B immunoglobulin and antiviral therapy is required in the posttranspalant period. In this study, we aimed to evaluate the pretransplant hepatitis B serology of patients with liver cirrhosis due to NASH and HCC who developed on the basis of cirrhotic NASH.

Methods: 76 NASH-related liver cirrhosis and 22 cirrhotic NASH-related HCC patients were included in the study. Those who were positive for HBV DNA, HCV RNA, delta antibody were excluded from the study. HbsAg, anti-Hbs, anti-Hbc IgG, HbeAg, anti-HbeAg positivity and negativity rates were evaluated before transplantation.

Results: The sex of 67.1% (n = 51) patients with cirrhosis was male and 32.9% (n = 25) female. The gender of the patients with HCC was male, 9.9% (n = 20) and female 9.1% (n = 2). CHILD classification was found 7 (9.2%) A, 53 (69.7%) B, 16 (21.1%) C in the cirrhotic group, 9 (40.9%) A, 8 (36.4%) B, 5 (22.7%) C in the HCC group. HbsAg, anti-Hbs, anti-Hbc IgG, HbeAg, anti-HbeAg were negative in 26 (34.2%) cirrhosis group and 15 (68.2%) in HCC group. HbsAg positivity was detected in 2 (2.6%) patients. Anti-Hbs, anti-Hbc IgG, anti-HbeAg positivity

was detected in 16 (21%) cirrhosis group and 2 (9.1%) in HCC group. Anti-Hbc IgG, anti-HbeAg positivity was found in 4 (5.26%) cirrhosis group. The hepatitis B vaccination rate was 13 (17.1%) in the cirrhosis group and 4 (18.2%) in the HCC group. Isolated anti-Hbc IgG positivity was 8 (10.5%) in the cirrhosis group, 18.2% in the HCC group, anti-Hbc IgG and anti-Hbs positivity was detected 7 (9.2%) in the cirrhosis group and 1 (% 4.5) in the HCC group.

Discussion/Conclusion: In this study, we found that hepatitis B vaccination rates were very low and the rates of exposure to hepatitis B virus were very high in our cirrhosis and HCC patients. Patients with NASH who do not have serological immunity should be included in the vaccination program before they reach the stage of cirrhosis and cancer.

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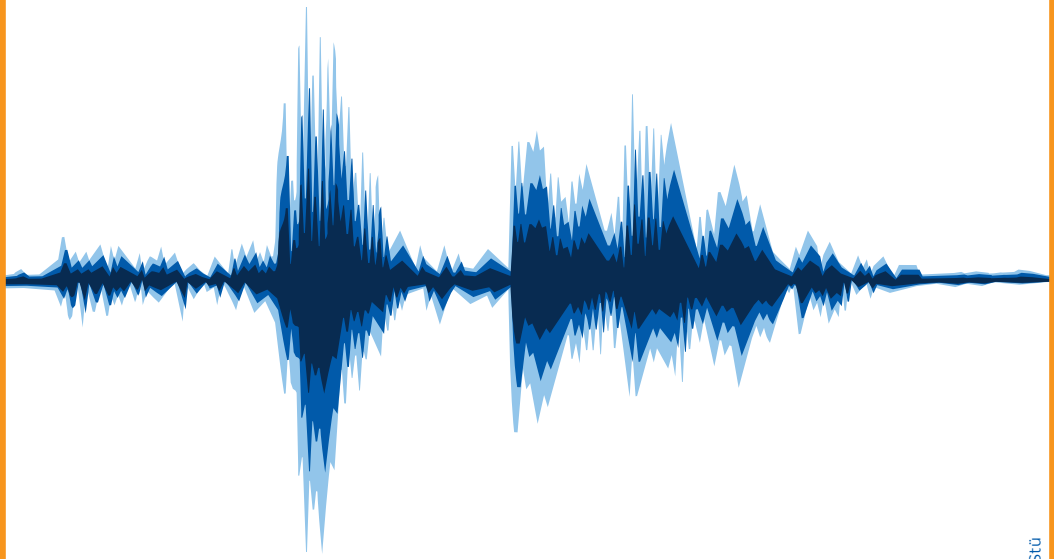

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