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Liver Digest

A weekly update of PLRC happenings

November 7, 2019

PITTSBURGH LIVER RESEARCH CENTER
A partnership of University of Pittsburgh & UPMC

www.livercenter.pitt.edu

Featured Faculty - Dr. Peter Lucas

In this issue

New Process for CME Credit for Seminars

The record-keeping for UPMC's CME accreditation is being migrated to a new on-line system. Beginning with Dr. Tatiana Kisseleva's seminar on November 19, all PLRC seminars will use the new tracking system. In the new system, you will be able to record your attendance at the seminar using your phone. I will provide an SMS code at the seminar for this purpose.

If you would like to receive CME credit for the PLRC seminars, please follow this link for instructions on setting up your account and using the new system: **https://cce.upmc.com/** .

PLRC at AASLD

LOGO for PRESENTATIONS

If possible, please include the PLRC logo in the slides for any presentations you are giving at AASLD. The jpg of the logo is attached. Thank you!

PRESENTATIONS and POSTERS

Many of our members will be presenting their work at the AASLD Liver Meeting November 8-12, 2019, in Boston. We have compiled a list of those presentations, which is **available here**.

COCKTAIL RECEPTION

Please join UPMC Thomas E. Starzl Transplantation Institute, the UPMC Center for Liver Diseases, and the Pittsburgh Liver Research Center for cocktails and hors d'oeuvres while attending The Liver Meeting 2019.

Saturday, November 9
8 to 9:30 p.m.
Boston Marriott Copley Place
Champions Restaurant, 2nd Floor
110 Huntington Ave. | Boston

Upcoming Conference

2019 Annual Update in Medical Hepatology
December 7, 2019
University Club
The program and list of speakers is available **here**.
To register, please follow the link: **https://cce.upmc.com/2019-annual-update-medical-hepatology**

Faculty Highlights

PLRC members collaborating on manuscripts are noted in red.

Original Article:
Grings M, Seminotti B, Karunanidhi A, Ghaloul-Gonzalez L, Mohsen AW, Wipf P, Palmfeldt J, **Vockley J**, Leipnitz G. ETHE1 and MOCS1

deficiencies: Disruption of mitochondrial bioenergetics, dynamics, redox homeostasis and endoplasmic reticulum-mitochondria crosstalk in patient fibroblasts. Sci Rep. 2019 Sep 2;9(1):12651. doi: 10.1038/s41598-019-49014-2. PubMed PMID: 31477743; PubMed Central PMCID: PMC6718683.

ABSTRACT

Ethylmalonic encephalopathy protein 1 (ETHE1) and molybdenum cofactor (MoCo) deficiencies are hereditary disorders that affect the catabolism of sulfur-containing amino acids. ETHE1 deficiency is caused by mutations in the ETHE1 gene, while MoCo deficiency is due to mutations in one of three genes involved in MoCo biosynthesis (MOCS1, MOCS2 and GPHN). Patients with both disorders exhibit abnormalities of the mitochondrial respiratory chain, among other biochemical findings. However, the pathophysiology of the defects has not been elucidated. To characterize cellular derangements, mitochondrial bioenergetics, dynamics, endoplasmic reticulum (ER)-mitochondria communication, superoxide production and apoptosis were evaluated in fibroblasts from four patients with ETHE1 deficiency and one with MOCS1 deficiency. The effect of JP4-039, a promising mitochondrial-targeted antioxidant, was also tested on cells. Our data show that mitochondrial respiration was decreased in all patient cell lines. ATP depletion and increased mitochondrial mass was identified in the same cells, while variable alterations in mitochondrial fusion and fission were seen. High superoxide levels were found in all cells and were decreased by treatment with JP4-039, while the respiratory chain activity was increased by this antioxidant in cells in which it was impaired. The content of VDAC1 and IP3R, proteins involved in ER-mitochondria communication, was decreased, while DDIT3, a marker of ER stress, and apoptosis were increased in all cell lines. These data demonstrate that previously unrecognized broad disturbances of cellular function are involved in the pathophysiology of ETHE1 and

MOCS1 deficiencies, and that reduction of mitochondrial superoxide by JP4-039 is a promising strategy for adjuvant therapy of these disorders.

For full text, please **click here**.

Original Article:

Rachakonda VP, DeLany JP, Kershaw EE, **Behari J**. Impact of Hepatic Steatosis on Resting Metabolic Rate and Metabolic Adaptation in Response to Intentional Weight Loss. Hepatol Commun. 2019 Aug 21;3(10):1347-1355. doi: 10.1002/hep4.1414. eCollection 2019 Oct. PubMed PMID: 31592493; PubMed Central PMCID: PMC6771160.

ABSTRACT

Weight loss is the primary intervention for nonalcoholic fatty liver disease (NAFLD). A decrease in resting metabolic rate (RMR) out of proportion to the degree of weight loss may promote weight regain. We aimed to determine the impact of hepatic steatosis on weight loss-associated changes in RMR and metabolic adaptation, defined as the difference between predicted and measured RMR after weight loss. We retrospectively analyzed prospectively collected data from 114 subjects without diabetes (52 with NAFLD), with body mass index (BMI) >35, and who enrolled in a 6-month weight loss intervention. Hepatic steatosis was determined by unenhanced computed tomography scans by liver:spleen attenuation ratio <1.1. RMR was measured by indirect calorimetry. At baseline, patients with hepatic steatosis had higher BMI, fat mass (FM), fat-free mass (FFM), and RMR (RMR, 1,933 kcal/day; 95% confidence interval [CI], 841-2,025 kcal/day; versus 1,696; 95% CI, 1,641-1,751; P < 0.0001). After 6 months, the NAFLD group experienced larger absolute declines in weight, FM, and FFM, but percentage changes in weight, FFM, and FM were similar between groups. A greater decline in RMR was observed in patients with NAFLD (-179 kcal/day; 95% CI, -233 to

-126 kcal/day; versus -100; 95% CI, -51 to -150; P = 0.0154) for the time × group interaction, and patients with NAFLD experienced greater metabolic adaptation to weight loss (-97 kcal/day; 95% CI, -143 to -50 kcal/day; versus -31.7; 95% CI, -74 to 11; P = 0.0218) for the prediction × group interaction. The change (Δ) in RMR was significantly associated with ΔFM, ΔFFM, and baseline RMR, while metabolic adaptation was significantly associated with female sex and ΔFM only. Conclusion: Hepatic steatosis is associated with a greater reduction in FM, which predicts RMR decline and a higher metabolic adaptation after weight loss, potentially increasing the risk of long-term weight regain.

For full text, please **click here**.

Original Article:

Kitsios GD, Yang L, Manatakis DV, Nouraie M, Evankovich J, Bain W, Dunlap DG, Shah F, Barbash IJ, Rapport SF, Zhang Y, DeSensi RS, Weathington NM, Chen BB, Ray P, Mallampalli RK, **Benos PV**, Lee JS, Morris A, McVerry BJ. Host-Response Subphenotypes Offer Prognostic Enrichment in Patients With or at Risk for Acute Respiratory Distress Syndrome. Crit Care Med. 2019 Oct 18. doi: 10.1097/CCM.0000000000004018. PubMed PMID: 31634231.

ABSTRACT

OBJECTIVES: Classification of patients with acute respiratory distress syndrome into hyper- and hypoinflammatory subphenotypes using plasma biomarkers may facilitate more effective targeted therapy. We examined whether established subphenotypes are present not only in patients with acute respiratory distress syndrome but also in patients at risk for acute respiratory distress syndrome (ARFA) and then assessed the prognostic information of baseline subphenotyping on the evolution of host-response biomarkers and clinical outcomes.

DESIGN: Prospective, observational cohort study.

SETTING: Medical ICU at a tertiary academic medical center.

PATIENTS: Mechanically ventilated patients with acute respiratory distress syndrome or ARFA.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: We performed longitudinal measurements of 10 plasma biomarkers of host injury and inflammation. We applied unsupervised latent class analysis methods utilizing baseline clinical and biomarker variables and demonstrated that two-class models (hyper- vs hypoinflammatory subphenotypes) offered improved fit compared with one-class models in both patients with acute respiratory distress syndrome and ARFA. Baseline assignment to the hyperinflammatory subphenotype (39/104 [38%] acute respiratory distress syndrome and 30/108 [28%] ARFA patients) was associated with higher severity of illness by Sequential Organ Failure Assessment scores and incidence of acute kidney injury in patients with acute respiratory distress syndrome, as well as higher 30-day mortality and longer duration of mechanical ventilation in ARFA patients ($p < 0.0001$). Hyperinflammatory patients exhibited persistent elevation of biomarkers of innate immunity for up to 2 weeks postintubation.

CONCLUSIONS: Our results suggest that two distinct subphenotypes are present not only in patients with established acute respiratory distress syndrome but also in patients at risk for its development. Hyperinflammatory classification at baseline is associated with higher severity of illness, worse clinical outcomes, and trajectories of persistently elevated biomarkers of host injury and

inflammation during acute critical illness compared with hypoinflammatory patients. Our findings provide strong rationale for examining treatment effect modifications by subphenotypes in randomized clinical trials to inform precision therapeutic approaches in critical care.

For full text, please **click here**.

Original Article:

Fraum TJ, Cannella R, Ludwig DR, Tsai R, Naeem M, LeBlanc M, Salter A, Tsung A, Shetty AS, **Borhani AA, Furlan A**, Fowler KJ. Assessment of primary liver carcinomas other than hepatocellular carcinoma (HCC) with LI-RADS v2018: comparison of the LI-RADS target population to patients without LI-RADS-defined HCC risk factors. Eur Radiol. 2019 Oct 25. doi: 10.1007/s00330-019-06448-6. PubMed PMID: 31654212.

ABSTRACT

OBJECTIVES: To determine whether the LI-RADS imaging features of primary liver carcinomas (PLCs) other than hepatocellular carcinoma (non-HCC PLCs) differ between patients considered high risk (RF+) versus not high risk (RF-) for HCC and to compare rates of miscategorization as probable or definite HCC between the RF+ and RF- populations.

METHODS: This retrospective study included all pathology-proven non-HCC PLCs imaged with liver-protocol CT or MRI from 2007 to 2017 at two liver transplant centers. Patients were defined per LI-RADS v2018 criteria as RF+ or RF-. Two independent, blinded readers (R1, R2) categorized 265 lesions using LI-RADS v2018. Logistic regression was utilized to assess for differences in imaging feature frequencies between RF+ and RF- patients. Fisher's exact test was used to assess for differences in miscategorization rates.

RESULTS: Non-HCC PLCs were significantly more likely to exhibit nonrim arterial phase hyperenhancement (R1: OR = 2.94; R2: OR = 7.09) and nonperipheral "washout" (R1: OR = 3.65; R2: OR = 7.69) but significantly less likely to exhibit peripheral "washout" (R1: OR = 0.30; R2: OR = 0.10) and delayed central enhancement (R1: OR = 0.18; R2: OR = 0.25) in RF+ patients relative to RF- patients. Consequently, non-HCC PLCs were more often miscategorized as probable or definite HCC in RF+ versus RF- patients (R1: 23.3% vs. 3.6%, $p < 0.001$; R2: 11.0% vs. 2.6%, $p = 0.009$).

CONCLUSIONS: Non-HCC PLCs are more likely to mimic HCCs on CT and MRI in the LI-RADS target population than in patients without LI-RADS-defined HCC risk factors.

KEY POINTS: • The presence of LI-RADS-defined risk factors for HCC tends to alter the imaging appearances of non-HCC PLCs, resulting in higher frequencies of major features and lower frequencies of LR-M features. • Non-HCC PLCs are more likely to be miscategorized as probable or definite HCC in the LI-RADS target population than in patients without LI-RADS-defined HCC risk factors.

For full text, please **click here**.

Editorial:
Tandon P, **Dunn MA, Duarte-Rojo A.** Resistance Training Reduces Risk of Sarcopenia in Patients With Cirrhosis. Clin Gastroenterol Hepatol. 2019 Oct 4. pii: S1542-3565(19)31079-1. doi: 10.1016/j.cgh.2019.09.030. PubMed PMID: 31589977.

For full text, please **click here**.

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