

# Joint Symposium -JKT (Basic)

Novel Mechanisms and Therapeutic  
Approaches for MASLD

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## Chairpersons

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**Ki Woo Kim**

Yonsei University, Korea

**Jun Wada**

Okayama University, Japan

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## Speakers

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**Hisanori Goto**

Kanazawa University, Japan

**Chia-Wen Lu**

National Taiwan University, Taiwan

**Eun Hee Koh**

University of Ulsan, Korea



## Hisanori Goto

Kanazawa University, Japan

### • Education

Period	Affiliation	Position
- 2014	Kanazawa University School of Medicine, College of Medical, Pharmaceutical and Health Sciences	M.D.

### • Affiliations / Experience

Period	Affiliation	Position
- 2021-Present	Kanazawa University Hospital	Assistant professor
- 2020	Kanazawa University Hospital	Medical Staff
- 2016	Kyoto University Hospital	Medical Staff
- 2015	National Hospital Organization Kyoto Medical Center	Resident
- 2014	Kyoto University Hospital	Resident

### • Publications

- *Commun Biol.* 25:2:76
- *Diabetes Care.* 45(9):2064-2075
- *Diabetes.* 72(9):1297-1306
- *Am J Pathol.* 194(5):693-707
- *Endocrinology.* 165(7):bqae059

**Joint Symposium-JKT (Basic)**

## **Molecular Pathophysiology Underlying MASH Complicated by Diabetes**

Hisanori Goto (Kanazawa University, Japan)

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Obesity is a significant contributor to MASLD/MASH. Additionally, it has been suggested that diabetes may exacerbate MASLD in East Asian individuals. However, the mechanisms by which diabetes promotes liver inflammation and fibrosis remain unclear. In our longitudinal liver biopsy study of diabetic MASLD subjects, increases in HbA1c, but not BMI were significantly associated with the progression of liver fibrosis (Saori S et al., Diabetes 2023). Gene set enrichment analyses suggest the coordinated downregulation of genes involved in central liver sinusoidal endothelial cells (LSECs) during the progression of liver fibrosis. To further explore the molecular mechanisms by which diabetes exacerbates steatohepatitis, we established a novel murine model of "diabetic steatohepatitis (DiSH)" (Abuduyimiti T, Goto H, et al., Am J Pathol, 2024). Male C57BL/6J mice were fed a 60% high-fat diet (HFD). Liver inflammation and fibrosis were induced using carbon tetrachloride (CCl4), and insulinopenic diabetes was induced by streptozotocin (STZ). The DiSH model (HFD+CCl4+STZ) group exhibited more advanced liver steatosis, hepatocyte ballooning, and regenerative nodules than the non-diabetic MASH model (HFD+CCl4) group. Single-cell RNA-seq analyses revealed a decrease in LSEC clusters in the DiSH model. Pathway analysis of genes with altered expression in LSECs due to the induction of a diabetic state revealed a coordinated increase in the expression of genes linked to senescent phenotype, oxidative stress response, capillary formation, leukocyte migration, and apoptosis in diabetes. Genes involved in ligand-receptor interactions in RAGE/TLR4 signaling were also coordinately upregulated in diabetes. Morphological findings also suggested LSEC injury in the DiSH model. These findings indicate that diabetes may injure LSECs via RAGE/TLR signaling during the development of DiSH. These results imply that diabetic vascular complications underlie DiSH pathology. At the symposium, we will discuss experimental strategies to test this hypothesis and therapeutic strategies aimed at protecting vascular endothelial cells.



## Chia-Wen Liu

National Taiwan University, Taiwan

### • Education

Period	Affiliation	Position
– 2023	Graduate Institute of Clinical Medicine, National Taiwan University College of Medicine	Ph.D.
– 2013	Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University	M.Sc.
– 2007	College of Medicine, National Cheng Kung University	M.D.

### • Affiliations / Experience

Period	Affiliation	Position
– 2024-Present	Department of Family Medicine, College of Medicine, National Taiwan University	Clinical Associate Professor
– 2019	Department of Family Medicine, College of Medicine, National Taiwan University	Clinical Assistant Professor
– 2016	Department of Family Medicine, College of Medicine, National Taiwan University	Clinical Lecturer
– 2013	Department of Family Medicine, National Taiwan University Hospital	Attending Physician

### • Committee Memberships

- Taiwan Association of Family Medicine
- Taiwan Medical Association for the Study of Obesity
- Taiwan Medical Association for Comprehensive Care of Chronic Diseases
- Taiwan Medical Association of Human Nutrition
- Taiwan Academy of Hospice Palliative Medicine

### • Publications

- Lu CW, Yang KC, Chi YC, Wu TY, Chiang CH, Chang HH, et al. Adiponectin-leptin ratio for the early detection of lean non-alcoholic fatty liver disease independent of insulin resistance. *Ann Med.* 2023;55(1):634-42
- CW Lu, YC Lee, CH Chiang, HH Chang, WS Yang, KC Huang. Independent Dose–Response Associations between Fetuin-A and Lean Nonalcoholic Fatty Liver Disease. *Nutrients.* 2021, 13(9), 2928
- Chen PY, Lee YH, Chiang CH, Chang HH, Lu CW\*, Huang KC. Sex Differences and Positive Dose-Response Relationships between Serum Osteocalcin Levels and Low Muscle Strength. *Gerontology.* 2023 Jun;69(9):1056-1064. (\*equal contribution)
- Shen YH, Lee YH, Lee YC, Chang HH, Huang KC, Lu CW. Changes in Circulating Galectin-1 among Adults with Obesity Participating in a Diet and Exercise Program. (Accept)
- CW Lu, YC Lee, CS Kuo, CH Chiang, HH Chang, KC Huang. Association of Serum Levels of Zinc, Copper, and Iron with Risk of Metabolic Syndrome. *Nutrients.* 2021, 13(2), 548

**Joint Symposium-JKT (Basic)**

## **Effects of Exercise Intervention in Obese Mice with Steatotic Liver Disease**

Chia-Wen Liu (National Taiwan University, Taiwan)

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This lecture was intended to share the effects of various exercise modalities on obesity treatment and liver health in high-fat diet-induced obese mice from our team. The exercise interventions included aerobic exercise (AE), resistance exercise (RE), high-intensity interval training (HIIT), and vibration training (VT). Each regimen was conducted over eight weeks: AE involved treadmill running, RE focused on weight-bearing ladder climbing, and HIIT incorporated alternating high and low-intensity treadmill running intervals. Additionally, the study examined the impact of swimming at different temperatures (25°C and 32°C) on obesity treatment.

Metabolic improvements were also observed, with AE significantly reducing total cholesterol (TCHO), low-density lipoprotein (LDL), and triglycerides (TG), and improving glucose tolerance as measured by OGTT. Both AE and VT groups showed improvements in fasting glucose levels, although these changes were not statistically significant. In terms of body composition, AE and VT groups experienced significant reductions in body weight and fat percentage, with AE also increasing lean mass percentage.

The results demonstrated that most of the exercise modalities reduced liver weight and improved liver function, as evidenced by decreased GPT levels. AE notably increased irisin levels, enhancing insulin sensitivity and improving HOMA-IR. Liver proteomic analysis indicated that obesity induced mitochondrial dysfunction, which was mitigated by AE through the regulation of the PKA pathway. Furthermore, western blot analysis revealed significant changes in the expression of liver proteins such as Fetuin A, Galectin-1, and Cathepsin S.



## Eun Hee Koh

University of Ulsan, Korea

### • Education

Period	Affiliation	Position
– 2007	University of Ulsan, Korea	Ph.D.
– 2005	University of Ulsan, Korea	M.S.
– 1999	College of Medicine, Inje University, Korea	M.D.

### • Affiliations / Experience

Period	Affiliation	Position
– 2020–Present	Internal Medicine, College of Medicine, University of Ulsan	Professor
– 2015-2019	Internal Medicine, College of Medicine, University of Ulsan	Associate Professor
– 2015-2016	Baylor College of Medicine	Visiting Researcher
– 2009-2013	Endocrinology and Metabolism, Asan Medical Center	Clinical Assistant Professor

### • Committee Memberships

- Committee of Research, Korean Diabetes Association

### • Publications

- Sang H, Lee KN, Jung CH, Han K, Koh EH. Association between organochlorine pesticides and nonalcoholic fatty liver disease in the National Health and Nutrition Examination Survey 2003-2004. *Sci Rep.* 2022 8;12(1):11590
- Hong CH, Ko MK, Kim JH, Cho H, Lee CH, Yoon JE, Yun JY, Baek IJ, Lee KU, Fernández-Checa JC, Choi JW, Kim S, KoH EH. Sphingosine 1-Phosphate Receptor 4 Promotes Nonalcoholic Steatohepatitis by Activating NLRP3 Inflammasome. *Cell Mol Gastroenterol Hepatol* 2022;13(3):925-947
- Koh EH, Yoon JE, Ko MS, Leem J, Yun JY, Hong CH, Cho YK, Lee SE, Jang JE, Baek JY, Yoo HJ, Kim SJ, Sung CO, Lim JS, Jeong W, Back SH, Baek I, Torres S, olsona-Vilarrasa E, Rosa LC, Garcia-Ruiz C, Feldstein A, Fernandez-Checa J, Lee KU. Sphingomyelin synthase 1 mediates hepatocyte pyroptosis to trigger non-alcoholic steatohepatitis. *GUT* 2021 70(10):1954-1964
- Ko MS, Yun JY, Baek IJ, Jang JE, Hwang JJ, Lee SE, Heo SH, Bader DA, Lee CH, Han J, Moon JS, Lee JM, Hong EG, Lee IK, Kim SW, Park JY, Hartig SM, Kang UJ, Moore DD, Koh EH, Lee KU. (co-corresponding author). Mitophagy deficiency increases NLRP3 to induce brown fat dysfunction in mice. *Autophagy.* 2021 17(5):1205-1221
- Lee YH, Jang HJ, Kim S, Choi SS, Khim KW, Eom HJ, Hyun J, Shin KJ, Chae YC, Kim H, Park J, Park NH, Woo CY, Hong CH, Koh EH, Nam D, Choi JH. Hepatic MIR20B promotes nonalcoholic fatty liver disease by suppressing PPARA. *Elife.* 2021 29;10:e70472

Joint Symposium-JKT (Basic)

## Therapeutic Approaches for Non-Alcoholic Steatohepatitis Utilizing Diverse Metabolites

Eun Hee Koh (University of Ulsan, Korea)

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Nonalcoholic fatty liver disease (NAFLD) has become a major health issue worldwide. Approximately 10–20% of patients with NAFLD develop non-alcoholic steatohepatitis (NASH), an advanced stage of NAFLD that may subsequently progress to liver cirrhosis and hepatocellular carcinoma. The mechanism by which simple steatosis progresses to NASH and liver fibrosis is not completely understood, and an effective treatment for halting the progression of NASH is yet to be discovered. Lipotoxic hepatocyte death may be the primary lesion that causes liver inflammation and fibrosis. Damage-associated molecular patterns released from dying hepatocytes may activate hepatic macrophages, and secretion of proinflammatory and fibrogenic cytokines from macrophages promotes hepatic stellate cells activation. Sphingolipids are ubiquitous building blocks of eukaryotic cell membranes and their metabolites regulate a wide range of cellular processes that are important in immunity, inflammation, and inflammatory disorders. Separate lines of evidence have suggested that changes in sphingolipid metabolism are an important cause of metabolic diseases. In the liver, increased intracellular ceramide, the prototype sphingolipid and the precursor of complex sphingolipids, induces lipotoxic hepatocellular cell death by multiple mechanisms.

Previous studies proposed the two-hit hypothesis for NASH, suggesting that excessive triglyceride accumulation in the liver increases the susceptibility of the liver to injuries mediated by other stimuli such as oxidative stress or pro-inflammatory cytokines. However, subsequent studies have shown that triglyceride accumulation is not harmful by itself to hepatocytes and may actually protect against lipotoxicity. In recent studies, we show that the changes in ceramide/sphingolipid metabolism, which are well-known mediators of hepatocyte injury, are inter-related. In this presentation, I will introduce the role of sphingolipid metabolism in hepatocyte injury and macrophage activation with inflammasome activation.