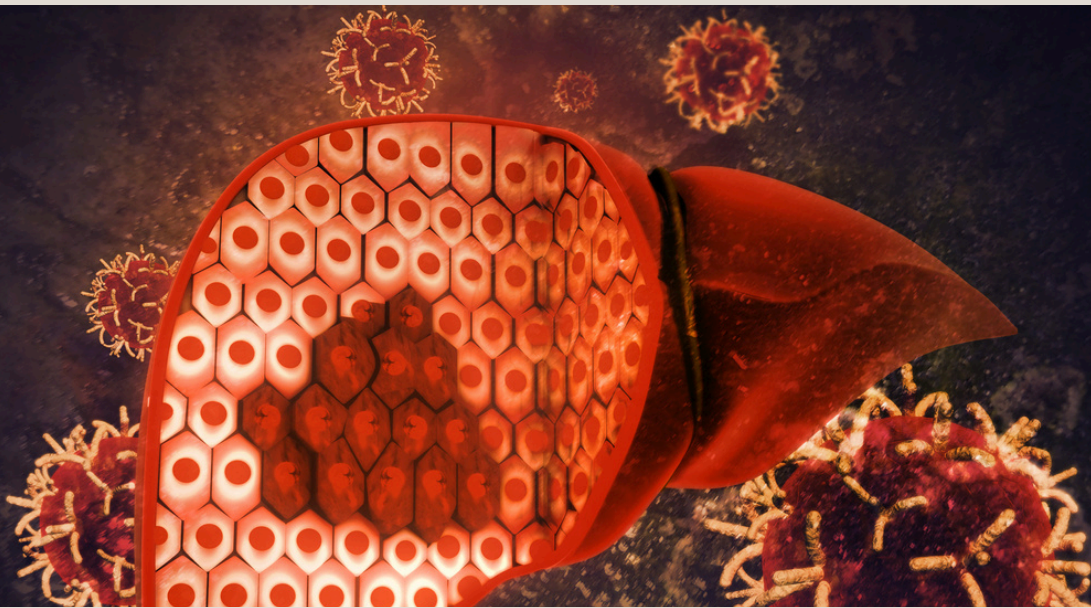




THE HOLE-Y TRUTH / FIGHTING FATTY LIVER:

Unravelling the Immunometabolic Role of Liver Sinusoidal Endothelial Cells (LSECs) in the Pathogenesis of Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD)

[600-RMC/FRGS 5/3 (097/2024)]

By: Dr. Mashani Mohamad

Did you know that over 1 in 4 people worldwide may have fatty liver disease¹ - and most don't even know it? Metabolic dysfunction-associated fatty liver disease (MAFLD) is a chronic liver condition characterised by the accumulation of fat in the liver, accompanied by metabolic abnormalities such as obesity, insulin resistance (IR), type 2 diabetes, or metabolic dysregulation. MAFLD pathologies range from simple steatosis to a more severe inflammatory form known as metabolic dysfunction-associated steatohepatitis (MASH). MASH is marked by hepatocyte injury, fibrosis, and an increased risk of cirrhosis and hepatocellular carcinoma². Because MAFLD often presents with no symptoms in its early stages, many individuals remain unaware of the disease until significant liver damage has already occurred.

The pathogenesis of MAFLD is complex and multifactorial, aligning with the "multiple hit" hypothesis, which encompasses insulin resistance (IR), lipotoxicity, oxidative stress, and chronic low-grade inflammation.² Immunometabolism, the interaction between immune and metabolic processes, has emerged as a key factor in MAFLD progression, although its exact role remains unclear.

The liver is the principal organ for essential functions, including metabolism, immunity and detoxification. Within the liver, liver sinusoidal endothelial cells (LSECs) are uniquely perforated with transcellular fenestrations that provide permeability and transfer of substrates between the sinusoidal blood and hepatocytes, while also maintaining involved ultrastructural changes including a reduction in the number and size of fenestrations (defenestration) leading to a process termed capillarisation (Figure 1). This transition, referred to as sinusoidal endotheliopathy³, marks the morphological and functional transformation of the LSECs.

To date, research on MAFLD pathogenesis has identified several mechanisms primarily involving hepatocytes. However, the significance of LSECs as a dynamic biofilter in MAFLD progression has been largely overlooked. Therefore, this study aims to identify the immunometabolic role of LSECs in the bothf acute and chronic stages of MAFLD. The LSECs ultrastructure will be comprehensively analysed using scanning electron microscopy to identify morphological changes associated with MAFLD. Additionally, metabolomics profiling using Liquid Chromatography Mass Spectrometry (LC-MS), will be performed to explore the crosstalk between sinusoidal endotheliopathy and immunometabolism.

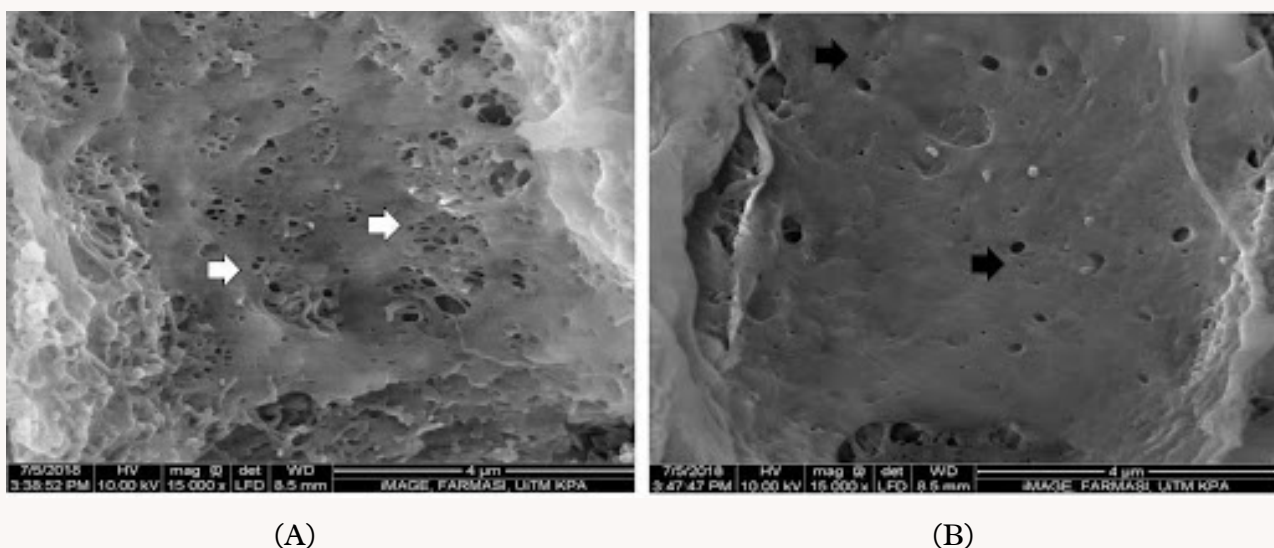


Figure 1: The LSECs observed under SEM, with (A) control liver showing fenestrations clustered into sieve plates (white arrow), while (B) insulin resistance liver results in loss of fenestrations (black arrow)⁴. A comprehensive ultrastructural analysis of LSECs in the MAFLD model has not yet been documented.

The findings of this study aim to uncover novel mechanistic and therapeutic targets that link metabolic dysfunction and immune response in MAFLD. This has the potential to translate to various interventions for the treatment and management of MAFLD, aligning with Sustainable Development Goal 3 3: Good Health & Well-being, and supporting Malaysia's aspirations towards improving national and global health outcomes.

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REFERENCES:

1. Lee, E. C. Z., Anand, V. V., Razavi, A. C., Alebna, P. L., Muthiah, M. D., Siddiqui, M. S., Chew, N. W. S., & Mehta, A. (2024). The Global Epidemic of Metabolic Fatty Liver Disease. *Current Cardiology Reports*, 26(4), 199–210.
2. American Association for the Study of Liver Diseases (AASLD). (2023). Introducing the MASLD nomenclature: Unifying the terminology of liver steatosis. *Hepatology*.
3. Furuta, K., Tang, X., Islam, S., Tapia, A., Chen, Z. B., & Ibrahim, S. H. (2023). Endotheliopathy in the metabolic syndrome: Mechanisms and clinical implications. *Pharmacology & Therapeutics*, 244, 108372.
4. Shukri, N. F., Mukhtar, S. M & Mohamad, M. (2023). Structural Alterations in Liver Endothelium of Rats with Dexamethasone-Induced Insulin Resistance. *Malaysian Journal of Medicine and Health Sciences*, 19 (Supp 7), 75-76.

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