The Cellular Basis of MASLD and Insulin Resistance

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Abstract:

MASLD is a widespread liver disease that affects people all over the world. In this paper, the development of MASLD on a cellular level is described along with its causes such as insulin resistance, and to a lesser extent, obesity. MASLD is caused by the accumulation and build up of triglycerides or free fatty acids in hepatocytes. The principal focus of the paper is the connection to insulin resistance, which causes higher fat storage in the liver through the excretion of insulin from Beta cells. As the disease progresses, fat stored in hepatocytes can cause the death of hepatic cells, which causes liver scarring and can cause MASLD to progress into MASH or cirrhosis. The damaged hepatocytes then release interleukin-6, causing pro-inflammatory cytokines to increase inflammation levels. Endothelial cells and Hepatic stellate cells can both cause angiogenesis, disrupting the liver's vascular structure and leading to cirrhosis. Other causes of MASLD include gut microbial dysbiosis, which can slow the metabolism, as well as overnutrition and a sedentary lifestyle. Treatments for MASLD include lifestyle adjustments like diet and exercise, surgeries, and drug therapies. New drug therapies are being researched and tested.

Introduction:

Metabolic dysfunction-associated Steatotic Liver Disease (MASLD) is a type of liver injury that affects approximately 30% of adults worldwide and is characterized by the excess deposition of triglycerides in liver cells called hepatocytes (He et al., 2024; Miao et al., 2024).

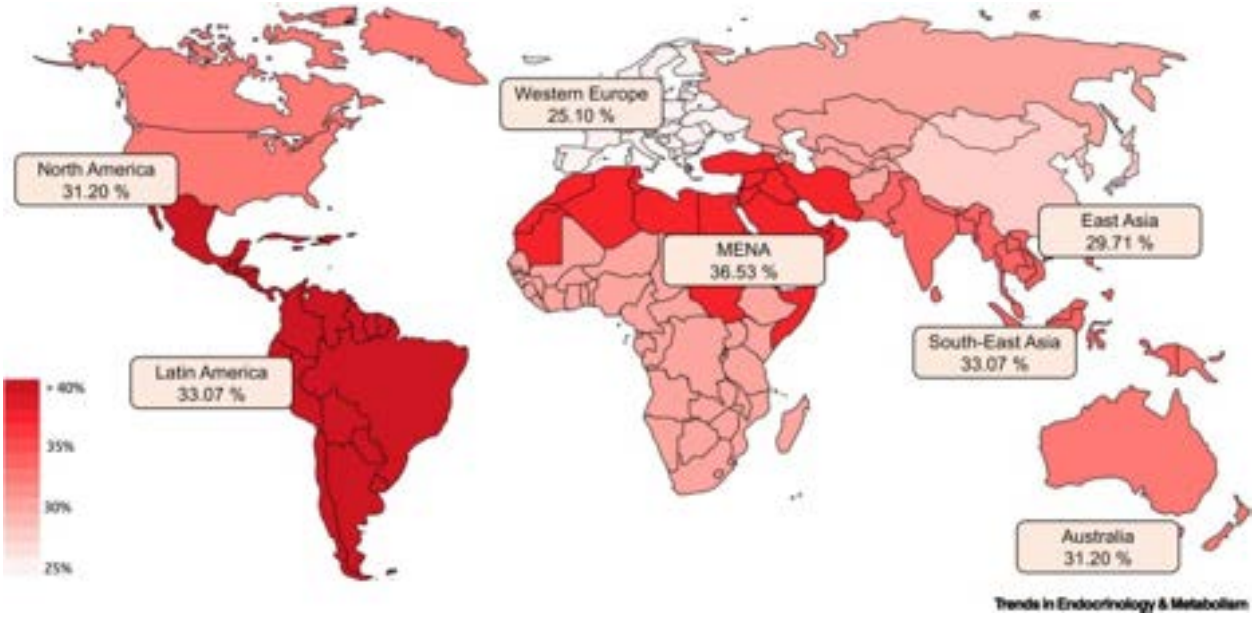

Figure 1: This figure was taken from Miao et. al, 2024. This figure shows the global prevalence of MASLD. The darker the shade of red, the higher the MASLD prevalence.

MASLD is a condition that presents itself with little to no symptoms in most cases. However, in rare cases, some patients will experience symptoms such as fatigue and pain. Long term, the disease negatively affects one's quality of life as it prevents weight loss and can cause permanent scarring of the liver, called cirrhosis (Chan et al., 2023). Cirrhosis can negatively affect quality of life by causing fluid to collect in the abdomen, the buildup of toxins in the blood (Mandiga et al., 2024), and variceal bleeding (Volk, 2020). MASLD's mortality rate has increased in the past few years with an annual percent change of 10% between 1999 and 2022 (Ilyas et al., 2023).

MASLD's development is not simple, and many pathogenic molecular pathways can lead to its occurrence. MASLD has many causes such as gut microbial dysbiosis (Hrncir, 2022), insulin resistance (Nogueira & Cusi, 2024), and obesity (Yin et al., 2023). Despite this multitude of causes, patients who have one of these conditions are not guaranteed to develop MASLD. Rather, these causes are interconnected, making it difficult to pinpoint one condition as the sole cause for the disease (Yanai et al., 2023). For example, gut microbial dysbiosis results in the gut barrier being compromised, which negatively impacts the immune system and metabolism (Hrncir, 2022). Insulin resistance, which is when cells stop responding to insulin signaling, can sometimes be the driver for this dysbiosis to occur. Additionally, insulin resistance can both cause and be caused by obesity, showing the cause and effect relationship between both conditions. Due to the complex nature of the causes of MASLD, it is important for all causes to be considered together as triggers for the disease rather than just individually.

MASLD is often initiated by hepatic lipid accumulation which triggers lipotoxicity in the liver. Lipids accumulate in the liver due to an increased hepatic uptake due to metabolic issues, as well as the transformation of carbohydrates into lipids due to de novo fatty acid synthesis, or a decrease in the beta-oxidation and export of lipids (Geisler & Renquist, 2017). Over time, the disease can progress further, leading to conditions such as Metabolic dysfunction-associated steatohepatitis (MASH), which is when the liver becomes inflamed due to excess fat cells. MASH can then progress into liver cirrhosis. The disease can be reversed at every stage up until the development of cirrhosis which permanently scars the liver (Eskridge et al., 2023). Due to this possibility, it is important to treat MASLD early on before it progresses to irreversible stages. Therefore it's important to understand how MASLD develops and works on a cellular level. In this paper, I will discuss MASLD and its causes and explore how it develops into the later stages, going individually through each cell type in the liver.

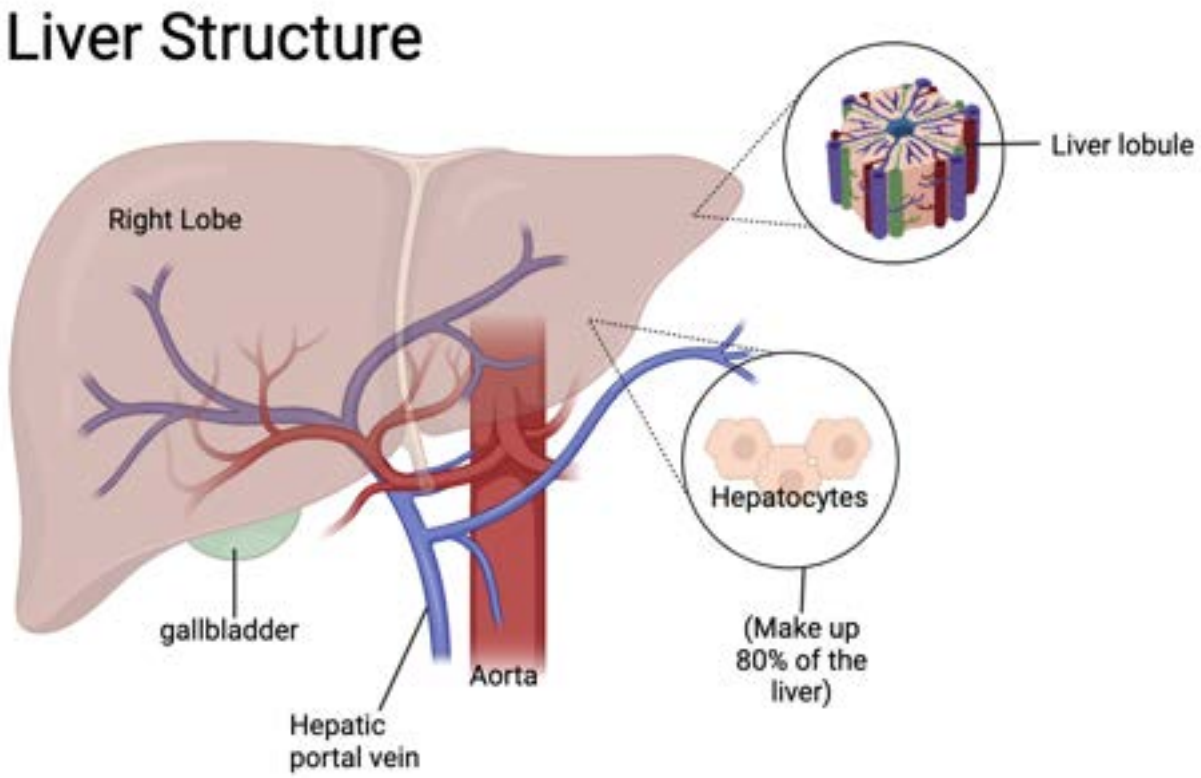

Figure 2: This figure shows the internal structure of the liver and shows the common vascular structure of the liver. The main tissue of the liver is made up of hepatocytes, as shown, which make up 80% of the liver. Hepatocytes make hepatic lobules which contain liver tissue and a portal triad.

Insulin Resistance

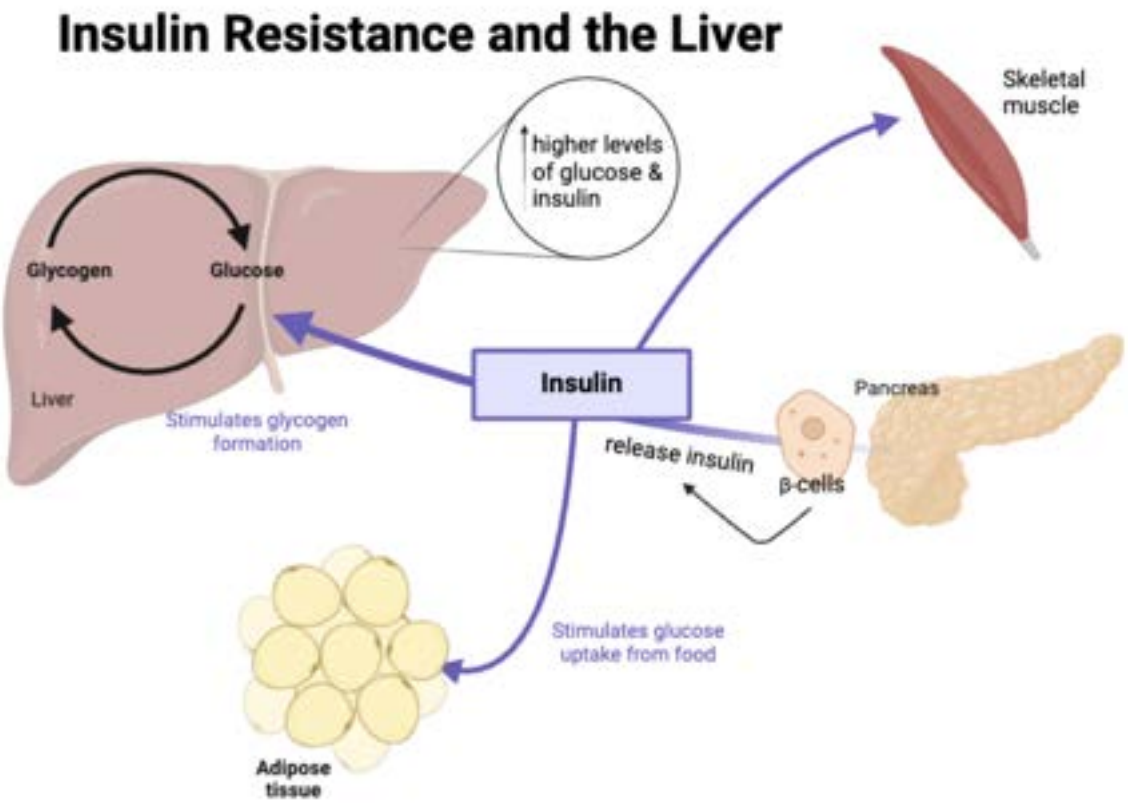

Figure 3: This figure shows that insulin resistance is connected to the skeletal muscle, adipose tissue, and the liver because Beta-cells from the pancreas release insulin and increase the levels of glucose and insulin in the body.

Insulin resistance can be a main cause of MASLD. Insulin resistance involves 3 main sites: skeletal muscle, liver tissue, and adipose tissue. When cells in the muscles, fat, and liver stop responding to insulin signaling, both the level of glucose and insulin in the blood rises(Chen et al., 2021). Insulin signaling is a vital bodily function because it promotes glucose uptake in cells, which regulates the stability of glucose levels and the formation and breakdown of fat and glycogen (Freeman et al., 2024). In combination with health issues such as obesity, the progression of MASLD can be exacerbated by insulin resistance. The reason why insulin resistance is crucial in MASLD development is because it promotes the accumulation of fat through metabolic inflexibility (Smith et al., 2018). Metabolic inflexibility is caused by high insulin levels signaling the liver to store excess glucose as glycogen, which causes it to be stored as fat in the liver by depositing triglycerides in hepatocytes (Galgani et al., 2008). As this occurs, the liver slowly becomes less sensitive to insulin and pumps additional glucose into the blood, triggering the pancreas to release insulin as well to bring glucose levels down. Due to glucose intolerance, high insulin levels create a vicious cycle of excess fat storage prompting higher insulin resistance (Freeman et al., 2024). During insulin resistance, beta cells, which produce insulin, suffer from fatigue as they are not able to produce enough insulin to counteract the body's heightened resistance against it. This causes beta cell death, further worsening glucose metabolism through glucose intolerance (Chen et al., 2021). Additionally, patients suffering from

obesity or high cholesterol are at a higher risk of developing insulin resistance and thus consequently developing MASLD. Overall, insulin resistance is key to the development of MASLD.

The causes of insulin resistance can vary. In many cases, insulin resistance can be caused by genetic mutations. For example, insulin resistance can result from mutations in the insulin receptor (INSR) gene. Insulin resistance can also develop due to lifestyle and diet choices. When the body has insulin resistance, it rarely taps into its fat stores and instead relies on a high production of free fatty acids (FFAs) for energy, which encourages the consistent production and storage of fat without utilization. Because of the heightened accumulation of fat, insulin resistance ends up causing lipotoxicity, a metabolic syndrome that leads to cellular dysfunction and death.

Other causes:

Gut microbial dysbiosis (GMD) plays a role in the pathogenesis of MASLD. Specifically, this issue can compromise the gut barrier, which can negatively impact the metabolism, resulting in slower metabolism (Hrncir, 2022). Additionally, GMD can lead to molecules from the diet flooding into the liver, which increases fat deposition and insulin resistance. Due to the diet being flooded, a dysbiotic gut microbiome is linked to insulin resistance through T2D (type 2 diabetes). It is due to this that the causes of MASLD can vary and also become intertwined with one another. Obesity and diabetes co-occur with MASLD at a high rate (Younossi et al., 2024). Some environmental causes which explain the prevalence of MASLD have to do with social context and lifestyle habits which contribute to the accumulation of fat in the liver. Examples of this include overnutrition and sedentary lifestyles (Valenti & Romeo, 2016). MASLD occurs frequently all over the world.

MASLD Cell By Cell

MASLD usually begins with the presence of other metabolic disorders, which together lead to the buildup of triglycerides in the liver (Geisler & Renquist, 2017). These disorders such as obesity and insulin resistance are often caused by overnutrition combined with sedentary lifestyles, leading patients to slowly gain weight and accumulate fat within their livers (Valenti & Romeo, 2016). Insulin resistance causes the cells to stop responding to insulin signaling. As a result, the conversion of lipid triglycerides into glycerol and free fatty acids (FFAs) by hydrolysis increases (Yanai et al., 2023). As the amount of FFAs increases it causes the dysfunction of adipose tissue (AT) which results in the release of adipokines, leading to a low-grade state of inflammation within the liver (Méndez-Sánchez et al., 2020). Every cell type in the liver is affected to an extent by MASLD, and I will now go through them one by one. MASLD clearly has complex causes, which will be further explored in the scope of this paper.

Hepatocytes:

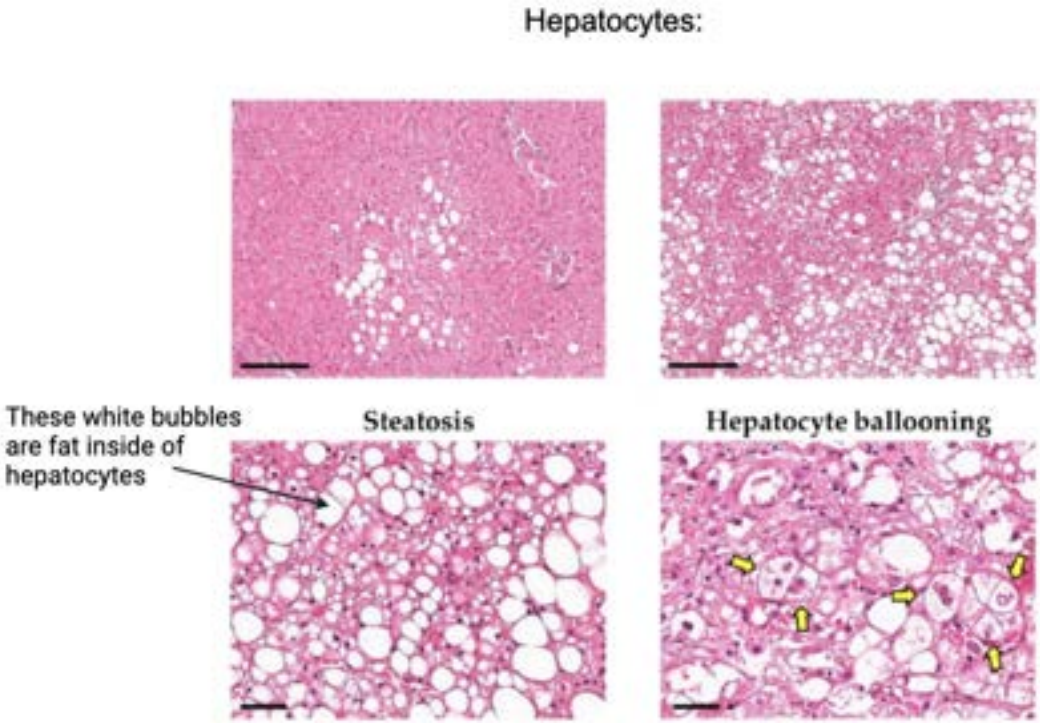

Figure 4: This figure shows what unhealthy hepatocytes look like when triglycerides and FFAs are deposited into them. The white bubbles present inside of the pink hepatocytes represent how fat accumulates in the liver.

Hepatocytes are involved in some of the liver's key functions. They monitor the blood's contents and remove any potentially toxic substances before they can reach the rest of the body.

Hepatocytes are the most abundant cell type in the liver, making up 80% of its volume (Gao et al., 2008). Lipids get stored in the cytosol of hepatocytes when fat accumulates in the liver. The apoptosis and necrosis of hepatocytes is a symptom of patients with MASLD (Shuh et al., 2013). As MASLD develops, hepatocytes develop lobular inflammation and suffer a form of cell death called balloon degeneration (Lu et al., 2021). These are clear indicators of the liver suffering scarring and liver fibrosis which is caused by the release of Tumor Necrosis factor alpha (TNF-α) and Interleukin 6 (IL-6), proinflammatory cytokines (Méndez-Sánchez et al., 2020).

TNF-α is part of two major pathways, but only one of those pathways has a key role in the liver: the NF-κB pathway. The end result of the pathway is the production of pro-inflammatory cytokines and chemokines(Soto et al., 2024). TNF-α is a part of the targeted cell death of hepatocytes. As it is released by the Kupffer cells, it proliferates or undergoes apoptosis after binding to hepatocytes. (Shuh et al., 2013)

When the liver is damaged, hepatocytes release Interleukin-6, which is an inflammatory cytokine (M.-J. Wang et al., 2024). Because of how IL-6 is released, it has been singled out as a possible biomarker for the prognosis of MASLD along with C-reactive protein, IL-1β, and TNF-α

(Ding et al., 2023). IL-6 is produced by T-cells and B-cells, macrophages, and fibroblasts. The purpose of IL-6 is mainly to differentiate between B-cells and induce the synthesis of acute phase reactants. IL-6 also modulates the growth and activation of cells during inflammatory and immune responses. Elevated levels of C-reactive protein indicate insulin resistance, showing how they can serve as a possible biomarker for the development of MASLD. Meanwhile, Adipocyte-derived IL-1β has been shown to directly influence insulin resistance within the liver, enabling the accumulation of lipids (Barbier et al., 2019).

Kupffer Cells

In a healthy liver, Kupffer cells are phagocytic, meaning they play a role in consuming foreign material and debris that may enter the liver. Kupffer cells do this by consuming bacteria and other foreign materials that enter hepatic sinus blood, thereby keeping it clear. This process that Kupffer cells perform helps to defend the liver against infections. Once the fat accumulation in the liver progresses to the point of MASLD, the liver is damaged through lipotoxicity. As a result, Kupffer cells will activate the immune response and will colonize the site of the damaged tissue (Park et al., 2023).

The secretion of inflammatory cytokines and chemokines by Kupffer cells plays a pivotal role in initiating MASLD pathogenesis (Park et al., 2023). For example, Kupffer cells release TNF-α which plays an important role in the proliferation of hepatocytes. TNF-α signals and initiates apoptosis, a form of programmed cell death. The lipotoxicity also causes stress on cell organelles such as the endoplasmic reticulum and the mitochondria which results in the formation of reactive oxygen species (ROS), causing damage to DNA, RNA, and proteins. The formation of ROS can also cause apoptosis, contributing further to liver injury (Méndez-Sánchez et al., 2020).

Endothelial Cells:

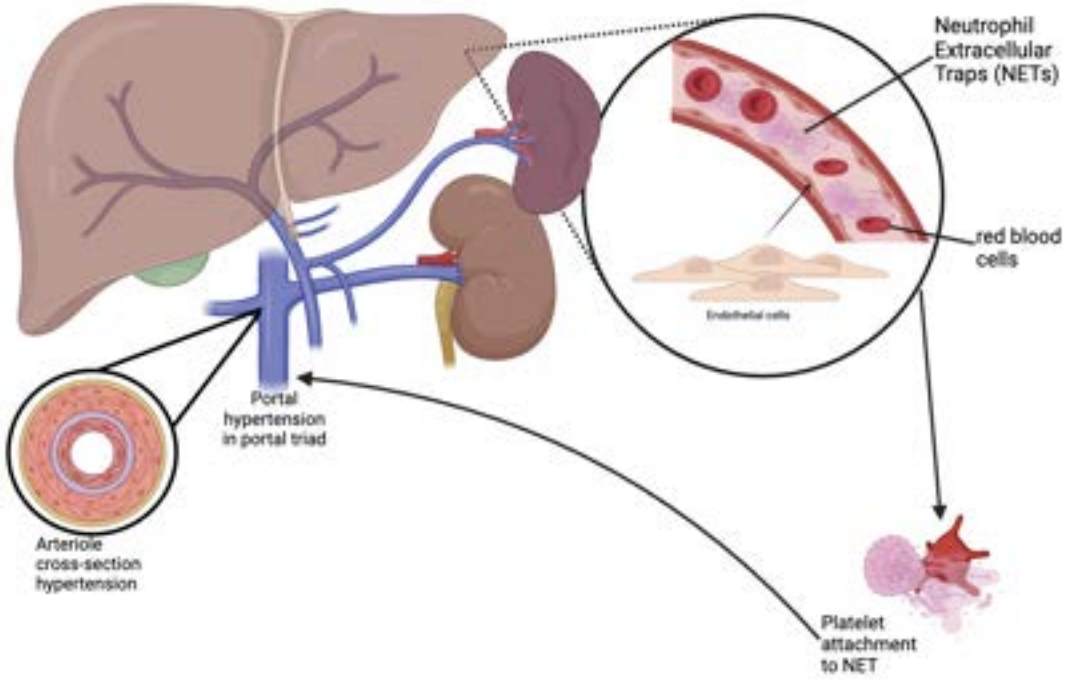

Figure 5: The figure shows how Neutrophil Extracellular Traps attach to platelets and cause portal hypertension in the hepatic portal vein which can cause low levels of oxygen in the blood.

Endothelial cells normally form a single cell layer that line the body's blood vessels and control exchanges between the bloodstream and surrounding tissues. Endothelial cells signal to organize the development and growth of connective tissue cells which form the layers of the blood vessel wall. These cells also play an important role in the progression of MASLD to non alcoholic steatotic hepatitis (NASH). Hepatic sinusoidal endothelial cells (HSECs) are involved in the development of MASLD when interacting with neutrophil extracellular traps(Minciuna et al., 2024). HSECs are responsible for causing angiogenesis during MASLD. Angiogenesis is the creation of new blood vessels, which can be harmful by further driving inflammation and fibrosis. Neutrophil Extracellular Traps (NETs) are a type of white blood cell which protect against infection, particularly by large pathogens. NETs coupled with platelet attachment contribute to portal hypertension in the portal triad of the liver, which is a serious complication in advanced stages of liver disease (Minciuna et al., 2024). As the blood vessels running through the portal triad get compressed by portal hypertension, blood flow is restricted and can lead to internal bleeding. In some cases, portal hypertension can affect the lungs, causing expansion of lung capillaries and consequently hypoxemia, which is when the concentration of oxygen in the blood is abnormally low. This is called hepatopulmonary syndrome (Singh et al., 2012).

Hepatic Stellate Cells:

Hepatic stellate cells (HSC) are significant in the deterioration of the liver as it progresses from the stages of steatotic liver disease (STIL) to metabolic dysfunction-associated steatohepatitis (MASH) and even to cirrhosis and liver cancer.

In a healthy liver hepatic stellate cells play a vital role in preserving liver health by contributing to hepatic development, regeneration, and immune responses (M. Wang et al., 2022). For example, HSCs are involved in injury response as they store retinoids including vitamin A and its metabolites prior to any injury occurring. This is helpful because retinoids regulate cell differentiation, proliferation, and apoptosis (Koyama et al., 2015).

When HSCs are activated during steatosis-induced angiogenesis in the liver, MASLD progresses into later stages of the condition, similar to endothelial cells (Lei et al., 2021; Minciuna et al., 2024).

Disease Progression:

Due to the usually slow progression of obesity and insulin resistance, MASLD can go unnoticed and can progress into later stages of liver disease such as MASH (Soto et al., 2024). When a doctor is deciding whether or not MASLD has progressed to MASH, the standard of care is to perform a liver biopsy (Yin et al., 2023). Then, the level of fat deposits in the liver can be observed in comparison to the initial diagnosis, as well as noting whether or not the liver is inflamed. MASH can further progress if left untreated into fibrosis, which is scarring in the liver (Eskridge et al., 2023). Doctors can diagnose liver fibrosis by using ultrasound elastography (Yin et al., 2023). Fibrosis on its own is no cause for concern, but as scarring increases, the liver can progress into cirrhosis, at which point the disease becomes life threatening.

Treatments:

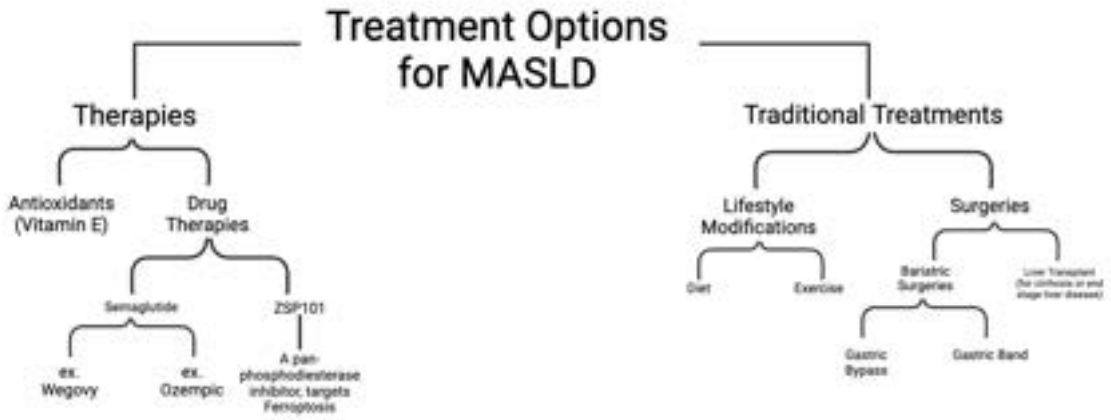

Figure 6: The figure shows treatments for MASLD, with traditional treatments as well as drug therapies showcased.

Treatments for MASLD:

Past treatments for MASLD have involved recommending diet and exercise to patients in hopes of helping patients to lose weight so that conditions like obesity and insulin resistance could be reversed, eventually leading to the fat in the liver also being reversed. However, diet and exercise do not always work to cure MASLD patients. Currently, more drug trials have taken place which propose the possibility for patients to be able to take medication to aid them in reversing this condition. Studies have been done using semaglutide, a medicine used to treat obesity and type 2 diabetes, to find out if it can be effective in also treating MASLD (Vazquez, n.d.). Examples of popular drugs containing semaglutide are Wegovy and Ozempic. These drugs inhibit a patient's appetite, helping them to lose weight and subsequently reverse their fatty liver more quickly. There are pros and cons to every treatment, including semaglutide. Semaglutide can improve liver enzymes, reduce stiffness in the liver, and improve metabolic parameters in patients. However, there are also downsides to this treatment. A major concern is that patients can possibly suffer from gastrointestinal adverse effects and contract gallbladder related diseases (Bandyopadhyay, n.d.).

There are also some potential treatments that target MASLD on a cellular level. ZSP1601 is an inhibitor for pan-phosphodiesterase that has been found to be effective in treating MASLD (Hu et al., 2023). Ferroptosis is a type of cell death that results from accumulation and lipid peroxidation in cells. It is genetically and biochemically distinct from other forms of regulated cell death such as apoptosis. Due to this, it is highly involved in the pathogenesis of MASLD. New drugs are targeting ferroptosis by focusing on the iron overload associated with it (Zhu et al., 2023). A study suggests that a combination of antioxidants and hypoglycemic drugs can be useful in managing the condition (Yin et al., 2023).

Conclusion

To conclude, it is important to continue research on MASLD and insulin resistance because of its high frequency and increasing death toll. MASLD's pathogenesis is complex and includes many causes such as obesity, insulin resistance, and diabetes, as stated earlier. Insulin resistance occurs when cells in the body stop responding to insulin signaling. Over time, this leads to lipotoxicity. Many patients don't have just one of these causes. Instead, they are highly intertwined, so due to this it is unclear how exactly each cause comes about. In some instances, insulin resistance causes obesity which then causes MASLD. But in other cases, obesity causes insulin resistance which then causes MASLD.

Overall, the pathomechanisms of MASLD involve nearly every cell type in the liver and also include inflammatory pathways such as the NF-Kb pathway which is instrumental in increasing the inflammation in the liver.

Though MASLD is a liver disease, it does not only affect the liver. Liver cell types are not the only cells affected by the disease. Other cell types are also involved such as dendritic cells and mast cells. When studying the effects of MASLD on the body, it is also important to consider other organs that are involved in MASLD such as the pancreas, which is responsible for insulin secretion. This is due to the fact that beta cells are found in the pancreas in cell clusters called islets. Additionally, it is also important to consider MASLD in a larger context in conjunction with other diseases such as obesity and diabetes. By researching MASLD this way, methods of treating MASLD are expanding, with new medications being tested and approved in comparison to long-standing treatment options such as gastric bypass surgery or weight loss.

Recent clinical trials have been successful in showing how new treatments such as the pan-phosphodiesterase inhibitor ZSP101 can be successful in lessening the amount of fat in the liver. Additionally, antioxidants can be used to combat the oxygen reactive species that can worsen inflammation.

Another possible way to combat MASLD could be to target the angiogenesis that can worsen the disease. In many cases, angiogenesis has been targeted to treat cancers, so it is not far off to conclude that such treatments could also be adjusted for the treatment of MASLD. To conclude, MASLD is a widespread liver condition that affects many people around the world, thus compounding the need for more research focus on this problem.

Bibliography:

Bandyopadhyay, S. (n.d.). *Role of semaglutide in the treatment of nonalcoholic fatty liver disease or non-alcoholic steatohepatitis: A systematic review and meta-analysis—ScienceDirect*. Retrieved August 6, 2024, from https://www.sciencedirect.com/science/article/abs/pii/S1871402123001455?via%3Dihub

Barbier, L., Ferhat, M., Salamé, E., Robin, A., Herbelin, A., Gombert, J.-M., Silvain, C., & Barbarin, A. (2019). Interleukin-1 Family Cytokines: Keystones in Liver Inflammatory Diseases. *Frontiers in Immunology*, *10*. https://doi.org/10.3389/fimmu.2019.02014

Chan, W.-K., Chuah, K.-H., Rajaram, R. B., Lim, L.-L., Ratnasingam, J., & Vethakkan, S. R. (2023). Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD): A State-of-the-Art Review. *Journal of Obesity & Metabolic Syndrome*, *32*(3), 197–213. https://doi.org/10.7570/jomes23052

Chen, X., Xiao, J., Pang, J., Chen, S., Wang, Q., & Ling, W. (2021). Pancreatic β-Cell Dysfunction Is Associated with Nonalcoholic Fatty Liver Disease. *Nutrients*, *13*(9), 3139. https://doi.org/10.3390/nu13093139

Ding, Z., Wei, Y., Peng, J., Wang, S., Chen, G., & Sun, J. (2023). The Potential Role of C-Reactive Protein in Metabolic-Dysfunction-Associated Fatty Liver Disease and Aging. *Biomedicines*, *11*(10), 2711. https://doi.org/10.3390/biomedicines11102711

Eskridge, W., Cryer, D. R., Schattenberg, J. M., Gastaldelli, A., Malhi, H., Allen, A. M., Noureddin, M., & Sanyal, A. J. (2023). Metabolic Dysfunction-Associated Steatotic Liver Disease and Metabolic Dysfunction-Associated Steatohepatitis: The Patient and Physician Perspective. *Journal of Clinical Medicine*, *12*(19), 6216. https://doi.org/10.3390/jcm12196216

Freeman, A. M., Acevedo, L. A., & Pennings, N. (2024). Insulin Resistance. In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK507839/

Galgani, J. E., Moro, C., & Ravussin, E. (2008). Metabolic flexibility and insulin resistance. *American Journal of Physiology - Endocrinology and Metabolism*, *295*(5), E1009–E1017. https://doi.org/10.1152/ajpendo.90558.2008

Gao, B., Jeong, W.-I., & Tian, Z. (2008). Liver: An organ with predominant innate immunity. *Hepatology*, *47*(2), 729–736. https://doi.org/10.1002/hep.22034

Geisler, C. E., & Renquist, B. J. (2017). Hepatic lipid accumulation: Cause and consequence of dysregulated glucoregulatory hormones. *The Journal of Endocrinology*, *234*(1), R1–R21. https://doi.org/10.1530/JOE-16-0513

He, Q.-J., Li, Y.-F., Zhao, L.-T., Lin, C.-T., Yu, C.-Y., & Wang, D. (2024). Recent advances in age-related metabolic dysfunction-associated steatotic liver disease. *World Journal of Gastroenterology*, *30*(7), 652–662. https://doi.org/10.3748/wjg.v30.i7.652

Hrncir, T. (2022). Gut Microbiota Dysbiosis: Triggers, Consequences, Diagnostic and Therapeutic Options. *Microorganisms*, *10*(3), 578. https://doi.org/10.3390/microorganisms10030578

Hu, Y., Li, H., Zhang, H., Chen, X., Chen, J., Xu, Z., You, H., Dong, R., Peng, Y., Li, J., Li, X., Wu, D., Zhang, L., Cao, D., Jin, H., Qiu, D., Yang, A., Lou, J., Zhu, X., … Ding, Y. (2023). ZSP1601, a novel pan-phosphodiesterase inhibitor for the treatment of NAFLD, A randomized, placebo-controlled phase Ib/IIa trial. *Nature Communications*, *14*(1), 6409. https://doi.org/10.1038/s41467-023-42162-0

Ilyas, F., Ali, H., Patel, P., Sarfraz, S., Basuli, D., Giammarino, A., & Satapathy, S. K. (2023).

Increasing nonalcoholic fatty liver disease–related mortality rates in the United States from 1999 to 2022. *Hepatology Communications*, *7*(7), e00207. https://doi.org/10.1097/HC9.0000000000000207

Koyama, Y., Wang, P., Brenner, D. A., & Kisseleva, T. (2015). Stellate Cells, Portal Myofibroblasts, and Epithelial-to-Mesenchymal Transition. In *Stellate Cells in Health and Disease* (pp. 87–106). Elsevier. https://doi.org/10.1016/B978-0-12-800134-9.00006-3

Lei, L., Mourabit, H. E., Housset, C., Cadoret, A., & Lemoinne, S. (2021). Role of Angiogenesis in the Pathogenesis of NAFLD. *Journal of Clinical Medicine*, *10*(7). https://doi.org/10.3390/jcm10071338

Lu, Q., Tian, X., Wu, H., Huang, J., Li, M., Mei, Z., Zhou, L., Xie, H., & Zheng, S. (2021). Metabolic Changes of Hepatocytes in NAFLD. *Frontiers in Physiology*, *12*, 710420. https://doi.org/10.3389/fphys.2021.710420

Mandiga, P., Kommu, S., & Bollu, P. C. (2024). Hepatic Encephalopathy. In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK430869/

Méndez-Sánchez, N., Valencia-Rodríguez, A., Coronel-Castillo, C., Vera-Barajas, A., Contreras-Carmona, J., Ponciano-Rodríguez, G., & Zamora-Valdés, D. (2020). The cellular pathways of liver fibrosis in non-alcoholic steatohepatitis. *Annals of Translational Medicine*, *8*(6), 400. https://doi.org/10.21037/atm.2020.02.184

Miao, L., Targher, G., Byrne, C. D., Cao, Y.-Y., & Zheng, M.-H. (2024). Current status and future trends of the global burden of MASLD. *Trends in Endocrinology & Metabolism*, *0*(0). https://doi.org/10.1016/j.tem.2024.02.007

Minciuna, I., Taru, M. G., Procopet, B., & Stefanescu, H. (2024). The Interplay between Liver Sinusoidal Endothelial Cells, Platelets, and Neutrophil Extracellular Traps in the Development and Progression of Metabolic Dysfunction-Associated Steatotic Liver Disease. *Journal of Clinical Medicine*, *13*(5), 1406. https://doi.org/10.3390/jcm13051406

Nogueira, J. P., & Cusi, K. (2024). Role of Insulin Resistance in the Development of Nonalcoholic Fatty Liver Disease in People With Type 2 Diabetes: From Bench to Patient Care. *Diabetes Spectrum*, *37*(1), 20–28. https://doi.org/10.2337/dsi23-0013

Park, S.-J., Garcia Diaz, J., Um, E., & Hahn, Y. S. (2023). Major roles of kupffer cells and macrophages in NAFLD development. *Frontiers in Endocrinology*, *14*, 1150118. https://doi.org/10.3389/fendo.2023.1150118

Shuh, M., Bohorquez, H., Loss, G. E., & Cohen, A. J. (2013). Tumor Necrosis Factor-α: Life and Death of Hepatocytes During Liver Ischemia/Reperfusion Injury. *Ochsner Journal*, *13*(1), 119–130.

Singh, A., Girdhar, A., Usman, F., Cury, J., & Bajwa, A. (2012). A rare cause of hypoxia in a patient with liver cirrhosis. *Respiratory Medicine Case Reports*, *6*, 5–6. https://doi.org/10.1016/j.rmcr.2012.07.001

Smith, R. L., Soeters, M. R., Wüst, R. C. I., & Houtkooper, R. H. (2018). Metabolic Flexibility as an Adaptation to Energy Resources and Requirements in Health and Disease. *Endocrine Reviews*, *39*(4), 489–517. https://doi.org/10.1210/er.2017-00211

Soto, A., Spongberg, C., Martinino, A., & Giovinazzo, F. (2024). Exploring the Multifaceted Landscape of MASLD: A Comprehensive Synthesis of Recent Studies, from Pathophysiology to Organoids and Beyond. *Biomedicines*, *12*(2), 397. https://doi.org/10.3390/biomedicines12020397

Valenti, L., & Romeo, S. (2016). Destined to develop NAFLD? The predictors of fatty liver from birth to adulthood. *Journal of Hepatology*, *65*(4), 668–670.

https://doi.org/10.1016/j.jhep.2016.06.010
Vazquez, J. (n.d.). *Clinical Trial Studying Possible New Treatment Option for Patients with NAFLD*. UC San Diego Health. Retrieved July 26, 2024, from https://health.ucsd.edu/news/press-releases/2023-08-23-clinical-trial-studying-possible-new-treatment-option-for-patients-with-nafld/
Volk, M. L. (2020). Burden of Cirrhosis on Patients and Caregivers. *Hepatology Communications*, *4*(8), 1107–1111. https://doi.org/10.1002/hep4.1526
Wang, M., Li, L., Xu, Y., Du, J., & Ling, C. (2022). Roles of hepatic stellate cells in NAFLD: From the perspective of inflammation and fibrosis. *Frontiers in Pharmacology*, *13*. https://doi.org/10.3389/fphar.2022.958428
Wang, M.-J., Zhang, H.-L., Chen, F., Guo, X.-J., Liu, Q.-G., & Hou, J. (2024). The double-edged effects of IL-6 in liver regeneration, aging, inflammation, and diseases. *Experimental Hematology & Oncology*, *13*(1), 62. https://doi.org/10.1186/s40164-024-00527-1
Yanai, H., Adachi, H., Hakoshima, M., Iida, S., & Katsuyama, H. (2023). Metabolic-Dysfunction-Associated Steatotic Liver Disease—Its Pathophysiology, Association with Atherosclerosis and Cardiovascular Disease, and Treatments. *International Journal of Molecular Sciences*, *24*(20), 15473. https://doi.org/10.3390/ijms242015473
Yin, X., Guo, X., Liu, Z., & Wang, J. (2023). Advances in the Diagnosis and Treatment of Non-Alcoholic Fatty Liver Disease. *International Journal of Molecular Sciences*, *24*(3), Article 3. https://doi.org/10.3390/ijms24032844
Younossi, Z. M., Golabi, P., Price, J. K., Owrangi, S., Gundu-Rao, N., Satchi, R., & Paik, J. M. (2024). The Global Epidemiology of Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis Among Patients With Type 2 Diabetes. *Clinical Gastroenterology and Hepatology*, *0*(0). https://doi.org/10.1016/j.cgh.2024.03.006
Zhu, B., Wei, Y., Zhang, M., Yang, S., Tong, R., Li, W., & Long, E. (2023). Metabolic dysfunction-associated steatotic liver disease: Ferroptosis related mechanisms and potential drugs. *Frontiers in Pharmacology*, *14*. https://doi.org/10.3389/fphar.2023.1286449