

Review

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Posted Date: 30 October 2025

doi: 10.20944/preprints202510.2378.v1

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Review

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD): New Perspectives on an Evolving Epidemic

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Abstract

A key, but frequently underappreciated parallel between alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD), now also termed metabolic dysfunction-associated steatotic liver disease (MASLD), is the delivery of excessive amounts of calories to the liver via the portal circulation: ethanol in the case of ALD, and nutrient-derived substrates in NAFLD/MASLD. A second, equally salient point is the liver's distinctive dual blood supply. The portal vein provides approximately 80% of hepatic blood flow, delivering deoxygenated but nutrient-rich blood from the gut, while the hepatic artery supplies the remaining 20% yet contributes about half of the organ's total oxygen requirements. Notably, only the hepatic artery possesses myogenic regulatory capacity that allows it to dynamically adjust flow and thus modulate hepatic oxygenation. A third consideration is that the liver receives approximately 25% of total cardiac output, which means that maintaining a stable hepatic blood supply is essential for cardiovascular homeostasis and survival. To this end, the liver has developed a unique and specialized mechanism, the hepatic artery buffer response (HABR), that stabilizes total hepatic blood flow independently of metabolic fluctuations or needs. However, this prioritization of constant flow means that the hepatic arterial blood supply, even with maximal vasodilatation, cannot always ensure that oxygen delivery matches nutrient demand, especially under conditions of caloric excess. An imbalance between oxygen delivery and nutrient availability— "oxygen-nutrient mismatch"—can lead to tissue hypoxia and liver cell damage. Over four decades ago, Lautt postulated that this kind of imbalance might play a role in the pathogenesis of alcohol-related liver disease (ALD). We have extended this paradigm to non-alcoholic fatty liver disease (NAFLD), now also called MASLD, theorizing that analogous mechanisms may be involved. Comorbidities such as obstructive sleep apnea (OSA) are associated with recurrent episodes of nocturnal hypoxemia. The concomitant presence of intermittent hypoxia and increased nutrient flux may synergistically exacerbate hepatocellular injury, providing a plausible mechanistic explanation for the more rapid progression of MASLD observed in patients with OSA and other conditions associated with hypoxemic episodes. The attenuated association between ALD and metabolic syndrome, compared with MASLD, likely stems from inherent differences in substrate metabolism. Carbohydrates, lipids, and proteins are subject to multiple complex cytosolic metabolic pathways that permit alternative, often non-oxidative, fates in states of metabolic dysfunction. In contrast, hepatic ethanol metabolism proceeds via a more linear, obligate oxidative route, offering limited flexibility. Therapeutic strategies that reduce hepatic caloric overload, increase basal hepatic metabolic rate (for example, with Resmiritom), or enhance hepatic oxygenation (such as through hyperbaric oxygen therapy) represent promising approaches for disease modification.

Keywords: nonalcoholic fatty liver disease (NAFLD); metabolic dysfunction-associated steatotic liver disease (MASLD); hepatic blood flow; hepatic artery buffer response (HABR); oxygen-nutrient mismatch

Historical Perspective

Nonalcoholic fatty liver disease (NAFLD) is a relatively recent focus in liver research. The specific term, Non-alcoholic steatohepatitis (NASH) was introduced in 1980 by Ludwig and colleagues at the Mayo Clinic (Ludwig, Viggiano et al. 1980), while Nonalcoholic fatty liver disease, NAFLD, was coined later in 1986 by Schaffner and Thaler (Schaffner and Thaler 1986).

NAFLD describes a condition in which the liver shows changes that are virtually identical to those seen in alcoholic liver disease, including lobular hepatitis, focal necrosis with mixed inflammatory infiltrates, Mallory bodies and fibrosis. The key difference is that patients with NAFLD do not drink alcohol in excess (Saadeh and Younossi 2000).

Over the past few decades, NAFLD has become one of the most common chronic liver diseases globally, tracking with the rise in obesity and metabolic syndrome. It encompasses a spectrum of liver pathology, ranging from simple steatosis (fat accumulation in hepatocytes) to nonalcoholic steatohepatitis (NASH), which is characterized by inflammation, cellular injury, and varying degrees of fibrosis.

Early research often sought to compare the clinical and pathological similarities between NAFLD and alcoholic liver disease (ALD). In both conditions, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are mildly elevated, typically two to three times normal. A key differentiator is the AST: ALT ratio, which is usually less than one with NAFLD, but is greater than two in ALD (Saadeh and Younossi 2000). Increased AST relative to ALT suggests possible mitochondrial damage (Lake-Bakaar 2017), a topic which will be discussed later.

Given the parallel global rise in obesity and metabolic syndrome, but without a similar increase in alcoholic liver disease, the research focus shifted. Clinical scientists began to look more closely at the connection between NAFLD and metabolic syndrome, rather than comparing NAFLD to ALD.

This change in focus is reflected in the recent proposal to rename NAFLD and NASH to metabolic dysfunction-associated steatotic liver disease, MASLD, and metabolic dysfunction-associated steatohepatitis, MASH (Canivet, Boursier et al. 2024). The new names, suggested in 2023, also aimed to move away from any stigma associated with alcohol misuse.

MASLD is now recognized as strongly associated with metabolic syndrome, which includes obesity, insulin resistance or type 2 diabetes mellitus, hypertension and dyslipidemia (Geier, Tiniakos et al. 2021). In contrast, metabolic syndrome has little or no direct link to alcoholic liver disease.

ALD, MASLD, and Calories

Both ALD and NAFLD result from the liver being exposed to more calories than it was designed to manage, and for much longer periods. Alcoholic beverages, especially those made by artificial fermentation, contain far higher levels of alcohol than what naturally occurs in foods. For context, an average adult male would need to consume about seventy kilograms of ethanol, his average body weight, over a decade to develop alcoholic steatohepatitis, ASH.

Gastric alcohol dehydrogenase is an enzyme present in the stomach that is involved in the initial processing of alcohol. Under normal circumstances, it can metabolize only the minute quantities of alcohol that are naturally found in foods such as ripening fruits and vegetables. These trace amounts are easily managed by the enzyme, preventing excess alcohol from reaching the liver.

However, when alcoholic beverages are consumed, the concentration of alcohol is much higher than what the enzyme is equipped to handle. As a result, gastric alcohol dehydrogenase becomes saturated very quickly. Once saturation occurs, the enzyme is no longer effective in protecting the liver from the influx of alcohol. Consequently, the excess alcohol bypasses this initial metabolic barrier and enters the liver.

In cases of obesity, the problem centers around excessive intake of food, particularly ultra-processed foods. Obese individuals consume between 4,000 and 6,000 kilocalories per day.

For reference, ducks or geese raised for foie gras are force-fed similar or slightly larger amounts (around 10,000 kilocalories daily), although over shorter periods.

Nutrients, including food and alcohol are absorbed from the intestines and delivered to the liver via the portal vein. This delivery occurs in direct proportion to the amount consumed, with little feedback to regulate or limit the delivery, once the nutrient has been absorbed.

The Unique Supply and Control of Blood Flow to the Liver

The majority of organs and tissues are perfused by arteries that deliver oxygen and nutrients in fixed ratios and can adjust flow to match metabolic demands (Johnson 1986). However, the liver exhibits notable differences. It is unique in possessing a dual blood supply, with the primary inflow originating from a vein rather than an artery.

Approximately 80% of hepatic blood flow is provided by the portal vein (PV), which drains the intestines. This blood is nutrient-rich and low in oxygen, reflecting its venous origin. Unlike arteries, veins do not possess significant myogenic mechanisms to regulate flow. Consequently, portal vein flow to the liver is unregulated and governed largely by venous pressure.

The remaining 20% of hepatic blood supply is delivered by the hepatic artery (HA). Originating from the systemic circulation, this blood is highly oxygenated. Although the HA contributes only a fifth of the total hepatic blood flow, it supplies at least 50% of the liver's oxygen requirements (Sezai, Sakurabayashi et al. 1993).

The HA contains myogenic elements that modulate flow via vasoconstriction and vasodilation. In organs with a single arterial supply, this would suffice for metabolic regulation; however, in the liver, where 80% of blood arrives via the unregulated PV, the dual supply limits the organ's ability to precisely match blood flow with metabolic demand (Lautt 1980).

Regulation of hepatic blood flow is further distinguished by its scale and significance. Nearly a quarter of the cardiac output flows through the liver. Ensuring this high-volume flow is critical for maintaining cardiovascular and circulatory stability, taking precedence over many other hepatic homeostatic functions.

Perhaps, because of this vital role, the liver has evolved a unique, specialized regulatory mechanism. This involves an interplay between portal blood flow and HA tone. The inverse relationship between HA and PV flow rates was first noted by Burton-Opitz in 1911 (Burton-Opitz 1911) and more fully described and termed hepatic arterial buffering response, HABR by Lautt (Lautt 1980, Lautt 1981). The mechanism of the HABR operates via adenosine washout (Lautt 1996). Briefly, when flow through the hepatic sinusoids decreases, adenosine accumulates and induces vasodilation of the HA. This increases HA flow to compensate for reduced PV flow, thus stabilizing total hepatic perfusion. As a result, overall hepatic blood flow is maintained independently of the liver's immediate oxygen or nutrient demands.

The concept of Oxygen-Nutrient Mismatch in ALD and MASLD

Unlike most organs and tissues, the liver does not intrinsically regulate its own oxygen or nutrient delivery as may be required by transient metabolic demands. Instead, its primary focus is on maintaining a stable overall hepatic blood flow. This approach could result in a discordance between oxygen supply and nutrient influx, particularly when nutrients are presented in excess, predisposing hepatic tissue to hypoxia and subsequent hepatocellular injury.

The hypothesis that an oxygen-nutrient mismatch underlies certain forms of liver pathology was initially articulated by Lautt (Lautt 1985). Lautt postulated that in alcoholic steatohepatitis, increased ethanol supply from chronic alcohol consumption may exceed the oxygen supply via the hepatic artery, thereby resulting in tissue hypoxia and cellular damage.

We have proposed that a parallel mechanism occurs in non-alcoholic steatohepatitis (NASH), or metabolic dysfunction-associated steatotic liver disease (MASLD), wherein excessive nutrient influx—rather than alcohol—surpasses the hepatic artery's oxygen delivery, leading to hypoxic injury (Lake-Bakaar, Robertson et al. 2022). This hypothesis could account for several other

observations associated with MASLD. For example, progression of MASLD is accelerated in patients with comorbid conditions characterized by intermittent hypoxia, such as obstructive sleep apnea.

Also, the flow of oxygenated blood across the hepatic acinus from the portal triad to the central vein, establishes an oxygen gradient that is highest in zone 1 and lowest in zone 3. In both alcoholic liver disease (ALD) and MASLD, maximal parenchymal injury occurs in zone 3, where oxygen concentration is lowest, implicating hypoxia in the pathogenic mechanism.

Clinical studies closely associate the progression of fibrosis in NASH with chronic obstructive sleep apnea and episodic hypoxia (Aron-Wisnewsky, Minville et al. 2012, Aron-Wisnewsky and Pepin 2015, Aron-Wisnewsky, Clement et al. 2016) further implicating hypoxia in its pathogenesis.

Finally, experimental data from animal models and clinical studies in humans consistently demonstrate a link between hepatic steatosis, fibrosis, and recurrent episodes of hypoxia (Drager, Li et al. 2011, Aron-Wisnewsky, Minville et al. 2012, Lemoine 2012, Musso, Olivetti et al. 2012, Aron-Wisnewsky and Pepin 2015, Aron-Wisnewsky, Clement et al. 2016, Ahmed, El-Badry et al. 2018, Liu 2018, Mesarwi, Loomba et al. 2019). Treatment targeting intermittent hypoxia in patients with NASH has been shown to ameliorate disease severity, further supporting a causal relationship (Bajantri 2018, Kim 2018, Sundaram, Halbower et al. 2018, Yu, Wang et al. 2020).

Ethanol vs Macronutrient Metabolism in the Liver

The principal clinical and pathological distinction between alcohol-associated liver disease (ALD) and metabolic dysfunction-associated steatotic liver disease (MASLD)—beyond the absence of significant alcohol intake and the frequent presence of obesity in MASLD—relates to the differential elevations of aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Both conditions typically present with mild elevations of ALT and AST, ranging from two to three times the upper limit of normal. However, ALD is characterized by a disproportionately greater increase in AST relative to ALT. In MASLD (formerly NAFLD), the AST:ALT ratio is usually less than one, whereas in ALD it often exceeds two (Saadeh and Younossi, 2000). This pattern is attributed to the primarily mitochondrial localization of AST in hepatocytes; thus, a predominant increase in AST over ALT in serum, likely implicates mitochondrial injury in ALD (Lake-Bakaar, 2017).

The metabolic processing of ethanol differs fundamentally from that of macronutrients. Unlike carbohydrates, lipids, and proteins, which can be stored post-absorption as glycogen, triglycerides, or within protein reserves, ethanol metabolism is not subject to regulatory storage mechanisms. Ethanol cannot be stored and is instead metabolized immediately, often at the expense of other metabolic processes.

Ethanol catabolism, particularly via the microsomal ethanol oxidizing system (MEOS), generates substantial amounts of reactive oxygen species (ROS). The central enzyme in this pathway, cytochrome P450 2E1 (CYP2E1), is upregulated with chronic alcohol exposure and utilizes oxygen inefficiently, resulting in increased ROS production. These ROS inflict oxidative damage on mitochondrial enzymes, proteins, and DNA. Mitochondrial DNA (mtDNA) is notably more vulnerable to oxidative injury, due to its lack of histone protection. The ensuing mitochondrial damage induces apoptotic cell death, which, due to the nature of apoptosis, causes relatively limited release of intracellular enzymes. Consequently, serum AST concentrations in ALD rarely exceed 300 IU/L.

In contrast, the metabolism of carbohydrates, fats, and proteins involves a variety of interrelated cytosolic pathways and generates far lower quantities of ROS. The induction of MASLD generally requires chronic consumption of supraphysiological amounts of macronutrients relative to caloric needs, often leading to obesity. For alcohol-induced liver injury, the approximate threshold for ALD development is the ingestion of around 70 kilograms of ethanol over a decade for an average 70 kg male. By comparison, the development of MASLD in an obese individual necessitates the consumption of several times the average body weight in macronutrients over the same period.

Treatment of MASLD: Re-Balancing the Oxygen-Nutrient Equation

Diet, Exercise

For years, dietary modification and physical activity have formed the basis of treatment for NASH/MASLD. Although it is tempting to attribute the benefits of these interventions to a reduction in total caloric intake, evidence suggests the picture is more complex. Altering macronutrient composition, for example, by adopting a higher-protein or Mediterranean-style diet in place of a high-carbohydrate one—can improve liver histology, even when total calories are unchanged (Zeng, Varady et al. 2024, Emanuele, Biondo et al. 2025).

The quality of calories is also critical: limiting fructose and saturated fat intake yields particular benefit (Yki-Jarvinen, Luukkonen et al. 2021, Shi, Prough et al. 2023, Burger, Michael Trauner et al. 2025). This suggests that distinct metabolic pathways are involved in hepatic steatosis, inflammation, and fibrosis depending on both the type of nutrients consumed and the mode of exercise performed.

Ultra-processed foods (UPFs) worsen NASH through mechanisms beyond simple caloric excess. Their rapid digestibility leads to quick surges in blood glucose and lipids, taxing hepatic metabolic systems and stimulating *de novo* lipogenesis. Additionally, UPFs are rich in additives such as emulsifiers, preservatives, and artificial sweeteners, all of which can compromise gut barrier function (Zhang, Qiao et al. 2024, Garcia, Monserrat-Mesquida et al. 2025, Geladari, Kounatidis et al. 2025). This increased intestinal permeability (“leaky gut”) allows endotoxins like LPS to reach the liver, driving hepatic inflammation—a central process in NASH pathogenesis.

Exercise, even in the absence of dietary changes, has been shown to reduce liver fat and lower ALT levels (Arita, Cabezas et al. 2025, Channapragada, Batra et al. 2025, Fan, Nie et al. 2025). While these effects may partly reflect changes in net energy balance, regular aerobic or resistance training can induce a caloric deficit even without a reduction in food intake.

Insulin resistance offers a unifying explanation for some of the beneficial effects of diet and exercise that extend beyond changes in calorie consumption. Rapid absorption of refined carbohydrates and fats heightens postprandial insulin responses, exacerbating systemic insulin resistance. This, in turn, impairs hepatic lipid metabolism, promoting steatosis and inflammation. Achieving a 5–10% reduction in body weight is associated with improved insulin sensitivity, which correlates with decreased hepatic steatosis, inflammation, and slower fibrosis progression (Yang, Meng et al. 2025).

Effect of Weight Loss Medications on MASLD

Caloric restriction and reduced macronutrient intake are established lifestyle interventions for the management of NASH/MASLD, contributing to clinically significant weight loss. The use of anti-obesity medications (AOMs) in this context introduces additional complexity, given the altered hepatic metabolism in MASLD, as well as ongoing concerns regarding drug safety and potential hepatotoxicity.

Novel agents such as glucagon-like peptide-1 (GLP-1) receptor agonists, dual GLP-1/glucose-dependent insulintropic polypeptide (GIP) agonists, and triple agonists targeting GLP-1, GIP, and glucagon receptors have demonstrated favorable metabolic profiles.

Among these, GLP-1 receptor agonists—including liraglutide and semaglutide—have consistently been associated with clinically beneficial effects including reductions in hepatic steatosis, improvement in serum liver enzymes, and attenuation of fibrosis progression.

Of note, semaglutide, initially approved for obesity in 2017, recently received regulatory approval for the treatment of MASH in adults with moderate-to-advanced hepatic fibrosis (Bhushan, Sohal et al. 2025, Kumar 2025). Tirzepatide, a dual GLP-1/GIP agonist, has shown superior weight loss effects compared to GLP-1 receptor agonist monotherapy, with emerging but still limited data on hepatic outcomes in MASLD/MASH.

The triple agonist retatrutide has induced the most pronounced metabolic improvements observed to date, although its effects on liver histology have yet to be fully elucidated.

Other AOMs, including bupropion-naltrexone and phentermine-topiramate, should be prescribed with caution due to concerns over hepatotoxic potential.

It is important to recognize that advanced MASLD may significantly alter drug pharmacokinetics, necessitating individualized treatment regimens and close monitoring (Somabattini, Sherin et al. 2024, Concepcion-Zavaleta, Fuentes-Mendoza et al. 2025, Rodriguez and Hartmann 2025)

Influence of Drugs Modulating Hepatic Blood Flow on MASLD

Metabolic dysfunction-associated steatohepatitis (MASH), previously termed non-alcoholic steatohepatitis (NASH), is a progressive form of steatotic liver disease (SLD). MASH has emerged as a significant public health concern, given its increasing prevalence, unpredictable and often accelerated course, and ultimate progression to either decompensated liver failure or hepatocellular carcinoma (HCC).

Pathogenesis is complex with strong ethnic influences and genetic predispositions. The complex pathophysiology involves insulin resistance, lipotoxicity, oxidative stress, and chronic inflammation.

Although, this would appear to offer multiple targets for therapeutic intervention, pharmacotherapy remains elusive. While lifestyle changes remain fundamental, their limitations in achieving sustained improvements highlight the need for effective pharmacological and interventional therapies.

Current pharmacotherapeutic strategies target various pathogenic pathways, including the use of farnesoid X receptor (FXR) agonists. FXR has emerged as a central therapeutic target in NASH/MASLD and obeticholic acid (OCA), an FXR agonist, has demonstrated efficacy in clinical trials. However, the occurrence of adverse events such as severe pruritus has thus far prevented its regulatory approval for NASH.

Preclinical studies, including the isolated perfused porcine liver model, have shown that obeticholic acid increases hepatic artery (HA) flow in a dose-dependent fashion, while concurrently reducing portal vein (PV) flow (Lake-Bakaar, Robertson et al. 2022). Enhancement of HA flow and increasing hepatic oxygen delivery provides a plausible mechanistic explanation for the drug's beneficial effects in NASH.

Concomitant reduction in portal flow, mediated by the hepatic arterial buffer response (HABR), results in a concomitant decrease in portal pressure—an effect with potential therapeutic benefit in chronic liver disease.

Potential Impact of Non-selective Beta-Blockers on MASLD

Non-selective beta-blockers (NSBBs), such as propranolol (Suffert, Beis et al. 2025) and carvedilol (Rajpurohit, Musunuri et al. 2025) remain the standard therapeutic approach for managing portal hypertension. Their primary mechanism for reducing portal pressure has been generally attributed to a decrease in cardiac output via beta-1 adrenergic receptor blockade and a reduction in splanchnic blood flow through beta-2 antagonism (Avram, Minea et al. 2025). An alternative mechanism, as proposed in our current hypothesis, suggests NSBBs may directly induce vasodilation of the hepatic artery, thereby activating the hepatic arterial buffer response (HABR) and consequently reducing portal vein flow. However, this hypothesis remains to be tested.

Long-term NSBB therapy in patients with stable cirrhosis has been associated with a lower incidence of adverse outcomes—including death, hepatocellular carcinoma, and liver transplantation—even after adjusting for baseline disease severity (Almenara, Lozano-Ruiz et al. 2023). In intention-to-treat analyses, carvedilol provided a notable survival benefit, with median survival reaching 7.8 years, compared to 4.2 years in patients treated with variceal band ligation (VBL) ($P = 0.03$). Carvedilol thus confers a significant survival advantage for individuals with

cirrhosis and portal hypertension when compared to VBL (McDowell, Chuah et al. 2021). This survival advantage, previously unexplained, may reflect enhanced hepatic oxygenation mediated by NSBB administration.

Enhancing Hepatic Basal Metabolism in MASLD

Resmetirom is an orally administered, selective agonist of the thyroid hormone receptor-beta (THR- β). Its clinical efficacy derives from its capacity to mimic thyroid hormone activity specifically within hepatic tissue. This selectivity is achieved through hepatic uptake via the OATP1B1 transporter and preferential activation of THR- β over THR- α (Hones, Sivakumar et al. 2022). Given that THR- β receptors are predominantly expressed in hepatocytes, resmetirom induces a localized, liver-specific hyperthyroid state, thereby minimizing the off-target, systemic side effects typical of conventional thyroid hormone therapies—such as cardiotoxicity and adverse skeletal effects mediated by THR- α (Mousa, Mahmoud et al. 2025). In March 2024, the FDA approved resmetirom for adults with moderate to advanced liver fibrosis secondary to MASH, provided there is no cirrhosis (Jamal, Elshaer et al. 2025, Liang, Gu et al. 2025). This regulatory decision was underpinned by data from the MAESTRO clinical program, which comprises multiple trials, designed to evaluate the safety and efficacy of resmetirom across various MASH patient subgroups (Liu, Zeng et al. 2025).

THR- β is a member of the nuclear hormone receptor superfamily and exerts its effects by binding to thyroid response elements (TREs) within DNA. Upon T3 binding, THR- β 1 promotes the transcription of genes involved in key hepatic processes, including cholesterol and lipid metabolism, mitochondrial biogenesis and function, hepatocyte proliferation, and carbohydrate metabolism.

Elevated thyroid hormone levels are known to augment mitochondrial oxygen consumption, stimulate mitochondrial biogenesis, and modulate the expression of proteins governing mitochondrial dynamics (fusion and fission) (Venediktova, Khmil et al. 2025).

Clinical investigations have demonstrated that Resmirirom can improve hepatic histological features, optimize lipid profiles, and induce MASH resolution, all without exacerbating hepatic fibrosis (Shakeel, Shaukat et al. 2025).

Directions for Future Research

The pathogenesis of MASLD is intricately layered, shaped by both genetic background and ethnic variation. Insulin resistance, lipotoxicity, oxidative stress, and persistent inflammation remain core elements within its multifaceted physiological landscape.

We propose that both ALD and MASLD originate from a fundamental disparity between oxygen supply and nutrient load to the liver. ALD's weaker association with metabolic syndrome reflects its simpler metabolic handling—ethanol is rapidly metabolized rather than stored. Conversely, carbohydrates, lipids, and proteins undergo a complex web of cytosolic metabolic pathways; the association with metabolic syndrome likely reflects the availability of alternative, non-oxidative metabolic routes. Current therapeutic approaches have targeted components of these metabolic networks, but results have been modest. Shifting the therapeutic emphasis toward rectifying the oxygen-nutrient imbalance may offer a more promising solution.

Managing the hepatic delivery of nutrients and ethanol remains a cornerstone of clinical care for this imbalance (Bhushan, Sohal et al. 2025; Kumar 2025). The introduction of novel anti-obesity medications is poised to enhance our capacity to address this supply-side challenge.

Thyromimetic agents promote the oxidation of surplus calories by selectively mimicking thyroid hormone activity within hepatic tissue, underpinning their therapeutic benefit.

Pharmacologic modulation of hepatic arterial flow presents another potential intervention for both alcoholic and non-alcoholic steatohepatitis. Obeticholic acid, for instance, is hypothesized to act via this mechanism (Lake-Bakaar, Robertson et al. 2022). There is also interest in exploring non-selective beta-blockers for their possible ability to induce hepatic arterial vasodilation.

Hyperbaric oxygen therapy (HBOT) increases the amount of oxygen delivered to the liver and therefore should be carefully examined as a potential strategy to address the mismatch between oxygen and nutrient supply. Notably, HBOT has been linked to episodes of hypoglycemia in diabetic patients receiving treatment for wound infections. This side effect may be due to increased glucose consumption under hyperoxic conditions (Laupland, Laupland et al. 2023).

Conflicts of Interest: The author declares no conflict of interest.

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