



Unveiling the role of aldosterone in metabolic dysfunction–associated steatotic liver disease

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Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD) is an increasing global health challenge closely linked to obesity and the metabolic syndrome. This review explores the role of aldosterone as a central contributor to metabolic dysfunction, highlighting its association with adipose tissue dysfunction and systemic insulin resistance which can further influence MASLD development and progression. While aldosterone-related organ damage has been extensively studied in other contexts such as kidney disease, its involvement in MASLD has received less attention. Beyond classical renin-angiotensin-aldosterone system activation, aldosterone secretion can be directly stimulated by leptin and other adipogenic factors, creating a pathogenic link between obesity and metabolic impairment. Aldosterone amplifies chronic inflammation, oxidative stress and insulin resistance, primarily through mineralocorticoid receptor (MR)-dependent mechanisms. These involve both genomic actions regulating pro-inflammatory genes and rapid non-genomic signalling. Additionally, aldosterone MR-independent effects, can further contribute to oxidative stress and inflammatory responses. Significantly, the MR is expressed in liver cells, including hepatocytes, liver sinusoidal endothelial cells, Kupffer cells, and hepatic stellate cells. This expression can allow for direct aldosterone-mediated effect on hepatic inflammation, oxidative stress, and fibrosis, which can occur alongside or independently of systemic metabolic pathways. Such direct mechanisms may explain associations found in clinical studies correlating high aldosterone levels -even with low renin- with the prevalence and progression of MASLD. Recognizing aldosterone as a pleiotropic hormone that integrates metabolic and hepatic disease offers new insights into the cardio-kidney-metabolic syndrome and underscores the potential for targeted therapies.

Keywords Aldosterone · Metabolic dysfunction-associated steatotic liver disease · Liver fibrosis · Metabolic syndrome · Renin-angiotensin system

1 Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is currently the most common chronic liver disease globally, affecting over one third of the adult population. MASLD prevalence and burden of disease is increasing

along with the increase in the prevalence of obesity, type 2 diabetes and metabolic syndrome [1].

Hepatic consequences of MASLD are associated with its progress to steatohepatitis, fibrosis, advanced fibrosis, cirrhosis and/or liver cancer. However, MASLD is also closely associated with extrahepatic complications, where cardiovascular events are the leading cause of death in this population [2].

Adipose tissue dysfunction and insulin resistance are key drivers in MASLD, which can lead to increased flux of free fatty acids to the liver, accumulation of toxic lipid species and lipotoxicity. Lipotoxicity induces endoplasmic reticulum stress, mitochondrial dysfunction and oxidative stress, ultimately triggering hepatocyte apoptosis and inflammation [3]. Genes involved in lipid metabolism (e.g. variants in PNPLA3, TM6SF2) can modulate susceptibility and disease severity, interacting with environmental factors such

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as diet, endocrine chemical disruptors and physical activity [4]. These processes form the basis of metabolic syndrome, which includes glycemic alterations, low HDL-cholesterol, hypertriglyceridemia, obesity and/or hypertension; and for MASLD diagnosis at least one of these criteria has to accompany the evidence of liver steatosis [4].

Among the pathogenic mechanisms related to MASLD, the activation of the renin-angiotensin-aldosterone system (RAAS) has been hypothesised to have a role either as a driver and consequence of MASLD, with evidence mainly supported through animal models (mice) and human clinical data predominantly observational [5]. The RAAS cascade starts in the liver, where angiotensinogen is produced, which has been found to be upregulated in cirrhosis and associated with the activation of hepatic stellate cells promoting fibrogenesis [6]. In addition, adipocytes can also secrete adipokines and angiotensinogen, both of which contribute to sympathetic nervous system and RAAS activation [7, 8]. Angiotensinogen regulation varies across sites, where different gene transcription factors are present in liver and adipocytes [9]. Renin cleaves angiotensinogen to form angiotensin I, and is released in response to decreased renal perfusion, reduced sodium delivery, or sympathetic activation. Importantly, renin operates below substrate saturation at physiological levels, making angiotensinogen a key limiting driver of RAAS activity. Angiotensin I is then converted by angiotensin converting enzyme (ACE) into angiotensin II, which stimulates aldosterone synthesis in the adrenal cortex [9, 10]. These mechanisms create a synergistic-amplifying loop where metabolic dysfunction and lipid accumulation activate intrahepatic RAAS, angiotensin II promotes further lipid accumulation, oxidative stress and inflammation, worsening steatohepatitis and fibrosis, ultimately perpetuating metabolic dysfunction and RAAS activation [11, 12]. Additionally, these alterations can also lead to the development of endothelial dysfunction, vascular stiffness and hypertension, especially through aldosterone, the final metabolite of the cascade [12–14].

Aldosterone is a mineralocorticoid hormone produced in the zona glomerulosa of the adrenal cortex from cholesterol -which is converted to intermediary metabolites and finally aldosterone through the aldosterone synthase enzyme (CYP11B2)-. The main function of aldosterone is to regulate salt, water balance, and blood pressure. Its secretion is stimulated through the RAAS activation -as already mentioned-, elevated serum potassium and adrenocorticotrophic hormone [15]. Aldosterone acts mainly via the mineralocorticoid receptor (MR) which is the primary receptor for aldosterone effects, although MR-independent pathways have also been described. The MR, encoded by the NR3C2 gene, is a member of the nuclear receptor superfamily of ligand-dependent transcription factors. Its activation is not exclusively

dependent on aldosterone, as cortisol binds the MR with comparable affinity. The enzyme 11 β -hydroxysteroid dehydrogenase (HSD) regulates the activation of cortisol, as 11 β -HSD1 catalyses the conversion of inactive cortisone to active cortisol, and 11 β -HSD2 mediates the reverse reaction, thereby limiting cortisol availability. Tissues with low 11 β -HSD2 expression, such as the liver, increased cortisol production mediated by 11 β -HSD1 can be present so that MR activation could be substantially influenced by cortisol rather than aldosterone. This tissue-specific balance has important implications for interpreting the complexity of MR activation, as endogenous cortisol may confound or modulate the apparent contribution of aldosterone to MR-dependent pathways [16].

When aldosterone binds the MR it can act through a classical genomic pathway translocating to the nucleus where regulates the expression of multiple genes involved in ion transport in the renal tubular epithelium, including the epithelial sodium channel (ENaC) and the Na⁺/K⁺-ATPase, thereby promoting sodium and water reabsorption and potassium excretion. This pathway predominates under physiological conditions providing sustained responses for maintaining sodium/volume homeostasis. Simultaneously, when aldosterone binds MR, there are other rapid non-genomic effects that are produced to give immediate response to blood pressure regulation (e.g., rapid vasoconstriction and phosphorylation of existing ENaC, among others). Finally, a MR-independent non-genomic pathway is relevant specially in pathological conditions which include aldosterone excess and will be further discussed.

Elevated aldosterone may occur in the setting of high renin -secondary aldosteronism- or low renin -primary aldosteronism (PA)-, the latter typically due to aldosterone-producing adenomas or hyperplasia and sometimes accompanied by cortisol co-secretion which can enhance organ damage in PA. Clinical consequences of PA include hypertension (often drug-resistant), decreased plasma renin activity and hypokalemia. Regardless of blood pressure, PA has been associated with increased cardiovascular and renal morbidity [17]. Management of PA involves treatment with mineralocorticoid receptor antagonists (e.g., spironolactone, eplerenone), and sometimes adrenalectomy when unilateral disease is confirmed. Additionally, novel aldosterone synthase inhibitors have shown promising results in PA management in phase 3 clinical trials [18].

From a clinical perspective, aldosterone excess beyond PA drives myocardial remodelling, vascular fibrosis, endothelial dysfunction, and inflammation [19]. These alterations may result in myocardial fibrosis with impaired diastolic function, vascular stiffening, increased stroke risk, and renal damage marked by hyperfiltration and glomerulosclerosis leading to chronic kidney disease. MASLD and renal disease

are hallmark manifestations of the cardio-kidney-metabolic syndrome, arising from adipose tissue dysfunction and a cascade of insulin resistance, chronic inflammation, and neurohormonal activation [20]. Within this interconnected metabolic framework, aldosterone excess has emerged as a potential contributor to metabolic dysregulation.

The association between aldosterone excess and metabolic syndrome has been studied previously having positive associations in clinical cross-sectional studies [21, 22]. However, whether the associations are causal, or mediated through other confounding factors (e.g.: renin-dependent aldosteronism, co-secretion of cortisol) remains to be elucidated [22].

Finally, the association between aldosterone and liver disease, and more specifically with MASLD has been less investigated. Preclinical and translational studies indicate that pharmacological inhibition of RAAS may attenuate liver fibrosis and inflammation through its effects on hepatic stellate cells and vascular function [23]. Hepatic stellate cells are key mediators of fibrosis through its activation into collagen-producing myofibroblasts and evidence has shown in animal models that RAAS and angiotensin-II inhibitors reduce its activation suppressing pro-fibrotic signalling pathways [24–26]. Further research is needed to confirm these findings in clinical populations with MASLD.

The present review aims to provide a comprehensive updated overview on the potential influence of aldosterone in MASLD, by analysing current evidence of its association with each metabolic syndrome component and MASLD. Ultimately, we aim to provide potential mechanistic insights of the evidence on sex differences. We believe that this review will help detect gaps of knowledge and pave the way for identifying novel pathogenic mechanisms and potential treatment targets in MASLD.

2 Aldosterone and metabolic syndrome components

Aldosterone is a pleiotropic hormone with a systemic role beyond blood pressure regulation. The MRs are present in several tissues such as endothelial cells, adipocytes, immune cells, muscle, pancreatic β -cells, and hepatic cells, among others. The activation of MRs through aldosterone binding in different tissues has been associated with endothelial dysfunction, oxidative stress, inflammation and fibrosis, leading to vascular ageing and organ damage.

Aldosterone binds to the cytoplasmic MR where it has a genomic action by translocating to the nucleus and regulating gene transcription. In the nucleus, aldosterone-MR complex acts as a ligand-activated transcription factor, binding to specific DNA sequences known as MR response

elements in the promoter regions of target genes. Classical genes expressed include ENaC-Na/K ATPase which regulates sodium and water balance, but other pro-inflammatory and pro-fibrotic genes can be activated and contribute to inflammation, vascular and metabolic dysfunction. These include Plasminogen Activator Inhibitor-1 (PAI-1), Transforming Growth Factor- β (TGF- β), Endothelin-1 (ET-1) and Connective Tissue Growth Factor (CTGF), among others [27]. On the other hand, aldosterone can act through non-genomic pathways with rapid cellular effects not requiring gene transcription or protein synthesis. These effects can be mediated by MR-dependent (mainly) and MR-independent mechanisms. MR-dependent non-genomic mechanisms include the activation of kinase signalling cascades, increased intracellular calcium and phosphorylation of MR itself [19]. MR-independent pathways involve other molecules such as the G-protein coupled estrogen receptor (GPER), Caveolin-1 and striatin scaffolding proteins, which can lead to reactive oxygen species production and inflammation [28]. However, it should be taken into account that there's a substantial cross-talk between all these mechanistic pathways, and all of them are relevant in contributing to cardio-kidney-metabolic diseases [19].

Additionally, beyond RAAS activation, aldosterone secretion and consequent MR activation can be enhanced by mediators produced by other tissues, such as leptin derived from adipose tissue, as discussed below [29, 30]. All this together, can contribute to insulin resistance, dyslipidemia and adipose tissue dysfunction - core components of the metabolic syndrome. In parallel, aldosterone-mediated endothelial dysfunction and activation of the RAAS accelerates cardiovascular remodelling and impair renal function, thereby linking metabolic dysregulation with the cardio-kidney metabolic syndrome, where elevated aldosterone levels and MR overactivation are increasingly recognized unifying mechanisms [19].

Below we discuss evidence on the association between aldosterone excess and each component of the metabolic syndrome.

2.1 Aldosterone and adipose tissue dysfunction

The link between dysfunctional adipose tissue and activation of the RAAS was described more than 10 years ago as evidenced in the studies referenced throughout this manuscript [31]. Adipocytes have a well-known classic endocrine role through the secretion of adipokines including leptin which regulates appetite and energy expenditure, and adiponectin which enhances insulin sensitivity and exerts anti-inflammatory effects, but also angiotensinogen can be partially secreted and modulated in human adipose tissue. Evidence in human and mouse adipocytes showed the

presence of aldosterone synthase and the ability to secrete aldosterone, which regulates adipocyte differentiation and vascular function in an autocrine and paracrine manner, respectively [32]. There's also evidence of stimulation of aldosterone independent of RAAS activation, by adipogenic factors, specially leptin [29, 33, 34]. Leptin has been shown to induce aldosterone synthase expression, resulting in aldosterone excess, which has been proposed as a mechanistic link between obesity and hypertension [33, 35]. Non-esterified fatty acids (palmitic acid and linoleic acid), which are in excess in obesity and metabolic syndrome, have also demonstrated to induce the expression of aldosterone synthase subsequently increasing aldosterone levels [36].

On the other hand, weight loss in the context of obesity has been found to be associated with a decrease in plasma aldosterone levels, which reinforces the potential role of aldosterone in adiposity [37–40].

Obesity phenotyping has evolved in the last decade beyond the use of body mass index (BMI) for assessing the cardiometabolic risk, which does not reflect adipose tissue distribution. Adipose tissue can be divided into subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT), the later playing the main pathogenic role in metabolic diseases. VAT can be further classified between periorgan fat (e.g., perirenal, epicardial) which exerts harmful effects via mechanical compression and local pro-inflammatory signalling, and intraorgan fat (e.g., hepatic steatosis, intramyocardial fat) which mainly drivers lipotoxicity and cellular dysfunction. In clinical practice, VAT is commonly estimated using waist circumference.

Clinical studies on the association between PA and VAT have reported that increased abdominal visceral-to-subcutaneous fat ratio interacts with increased plasma aldosterone con cardiac function [41]. Regarding specific VAT depots, main evidence has been published around perirenal adipose tissue. A recent study from Shen H et al. with prospective data from the UK Biobank, demonstrated an association between increased perirenal adipose tissue, idiopathic hyperaldosteronism and low-renin hypertension, where suggested mechanisms explaining the association included the compression of renal parenchyma and vasculature, as well as paracrine effects through adipokine secretion [42]. Consistently, a study in individuals with PA reported that perirenal adipose tissue accumulation was associated with higher aldosterone levels as well as renal and metabolic disturbances (increased fasting glucose, uric acid, C reactive protein, triglycerides, among others) [43]. In the experimental part of this study, mice treated with MR antagonists exhibited reduced markers of macrophage infiltration and fibrosis in perirenal adipose tissue, suggesting that perirenal fat accumulation may contribute to the mechanisms linking MR activation to cardiometabolic and renal dysfunction in PA [43].

Beyond perirenal fat infiltration, also periadrenal adipose tissue in aldosterone-producing adenomas have been shown to exert endocrine and paracrine effects that may influence the pathophysiology and outcomes of PA [44]. However, data on the association between aldosterone excess and adipose tissue depots at other specific anatomical locations remains limited. Excess aldosterone has been described to disrupt autophagy in perivascular adipose tissue, ultimately driving to inflammation, oxidative stress, vascular impairment and metabolic dysfunction [45, 46].

Taken together, these findings suggest that adipose tissue is involved in aldosterone production and modulation through mechanisms that extend beyond classical RAAS activation.

2.2 Aldosterone, insulin resistance and diabetes

Elevated aldosterone levels, due to PA or activation of the RAAS, have been found associated with development of type 2 diabetes through oxidative stress, inflammation and dysregulation of adipokines, contributing to insulin resistance [47].

Aldosterone excess, acting via the MR, activates kinases such as Src which phosphorylate insulin receptor substrate-1 (IRS-1) at specific serine residues. This aberrant phosphorylation marks IRS-1 for ubiquitination and proteasomal degradation, reducing IRS-1 protein levels in different cells such as adipocytes, vascular smooth muscle, skeletal muscle and myocytes [48]. The loss of IRS-1 disrupts downstream insulin signalling, decreasing Akt phosphorylation and glucose uptake, leading to insulin resistance. This process can be further amplified by aldosterone-induced ROS production [49].

Additionally, vesicle trafficking and membrane fusion of glucose transporter 4 (GLUT4) are disrupted. MR-aldosterone overactivation also decreases GLUT4 gene expression at the nuclear level. Therefore, a reduction of GLUT4 availability at the membrane is observed, decreasing glucose uptake and contributing to systemic insulin resistance [48, 50]. Another mechanism of hyperglycemia has been described through the action of aldosterone at the glucocorticoid receptor level, by increasing the expression of hepatic glucose-6-phosphate dehydrogenase (G6PD), promoting gluconeogenesis and elevating blood glucose levels in mice model receiving aldosterone [51]. This evidence on metabolic consequences mediated by aldosterone through other receptors is especially relevant since this effect can escape from treatment with MR blockers. Finally, the pro-inflammatory and profibrotic effects of aldosterone can also act in the pancreas, directly producing β -cell dysfunction with decreased insulin production [52, 53]. This dysfunction can be mediated through MR-dependent mechanisms

and MR-independent reactive species generation in the pancreatic β -cells [54]. All these mechanisms can explain the association between excess aldosterone, insulin resistance, hyperglycemia and type 2 diabetes.

Regarding clinical evidence, several studies have reported a reduced incidence of type 2 diabetes following treatment with either MR antagonists or adrenalectomy in the setting of PA [55, 56]. Elevated aldosterone levels, even within a normal range, have been associated with the development of insulin resistance in non-diabetic individuals over a 10-year follow-up [57].

On the other hand, from the type 2 diabetes perspective, MR antagonists have demonstrated beneficial effects by improving insulin sensitivity and attenuating kidney disease, underscoring the central role of aldosterone, MR activation and RAAS signalling in metabolic and renal regulation [58]. Supporting this, RAAS activation has been linked with incident type 2 diabetes in adults from the Jackson Heart Study, with adiposity potentially mediating this association, particularly in individuals with prediabetes [59]. Also, aldosterone excess has been found to be prevalent in the setting of type 2 diabetes -even with low renin levels- [60], and associated with diabetic kidney disease development, highlighting the pathological impact of aldosterone in this context [61].

Overall, these findings show that aldosterone can be a key mechanistic driver linking metabolic dysfunction through insulin resistance and type 2 diabetes via MR-dependent and independent pathways including impaired insulin signalling, reduced GLUT4-mediated glucose uptake, pancreatic β -cell dysfunction, oxidative stress and inflammation.

2.3 Aldosterone and dyslipidemia

The association between aldosterone excess and/or PA remains underexplored, with few studies focusing on this relationship. A study including general population found that higher levels of aldosterone were associated with increased serum concentrations of LDL-C, non-HDL-C and decreased HDL-C, and no associations were found with renin and aldosterone-to-renin ratio [62]. Regarding PA, a recent metanalysis has shown that bilateral PA when compared to unilateral PA has worse lipid and metabolic profile with higher values of LDL-C, total cholesterol, fasting blood glucose, glycated hemoglobin A1c and homeostasis model assessment-insulin resistance (HOMA-IR), with no relevant differences in HDL-C, suggesting that the higher secretion of aldosterone in bilateral PA, is associated with worse lipid profile [63]. Potential mechanisms linking aldosterone with lipid profile disturbances have been studied. In particular, Caveolin-1, which is a scaffolding protein that form caveolae-specialized lipid raft microdomains in the

plasma membrane that regulates signals, demonstrated in both in vivo and in vitro models that when its expression is decreased, it activates the effect of aldosterone-MR signalling on lipid pathways [64].

2.4 Aldosterone and hypertension

Aldosterone is a key regulator of blood pressure, through sodium retention and volume expansion, and its excess is a well-known cause of hypertension [65]. Mechanisms linking this association are mainly genomic (ENaC and Na/K ATPase expression) but also related with vascular damage. Excess aldosterone in vascular smooth muscle has been shown to downregulate the IRS-1/AKT signalling pathway, which under normal conditions promotes nitric oxide synthesis. Its downregulation leads to vasoconstriction, increased vascular remodelling and arterial stiffness, ultimately contributing to the development of hypertension. Other mechanisms linking aldosterone with hypertension involve MR and ENaC activation in the brain that mediate central aldosterone-induced sympathetic hyperactivity in hypertension [66].

The most common cause of secondary hypertension is PA, which is associated with cardiovascular and renal complications, as well as metabolic disturbances such as insulin resistance and adipose tissue dysfunction [67, 68]. On the other hand, excess aldosterone in primary hypertension has also been linked with worse clinical outcomes. A recent study on individuals with primary hypertension found that aldosterone was an independent factor associated with kidney damage, after adjustment for blood pressure treatment, sex, ethnicity, age, renin levels and many other potential confounding factors [69]. Mechanisms linking hypertension-mediated organ damage associated with MR activation also include non-classical pathways (independent of the sodium-retaining effects) which mediate oxidative stress, inflammation and fibrosis (Fig. 1).

3 Crosstalk between aldosterone and MASLD

3.1 Potential mechanistic pathways linking aldosterone and MASLD

The association between aldosterone and MASLD is supported by the evidence linking aldosterone to each component of the metabolic syndrome as discussed in the previous section. These mechanisms can contribute to MASLD in an indirect pathway and have been established in previous clinical and animal models (Fig. 1). However, beyond these indirect pathways, excess aldosterone may also exert

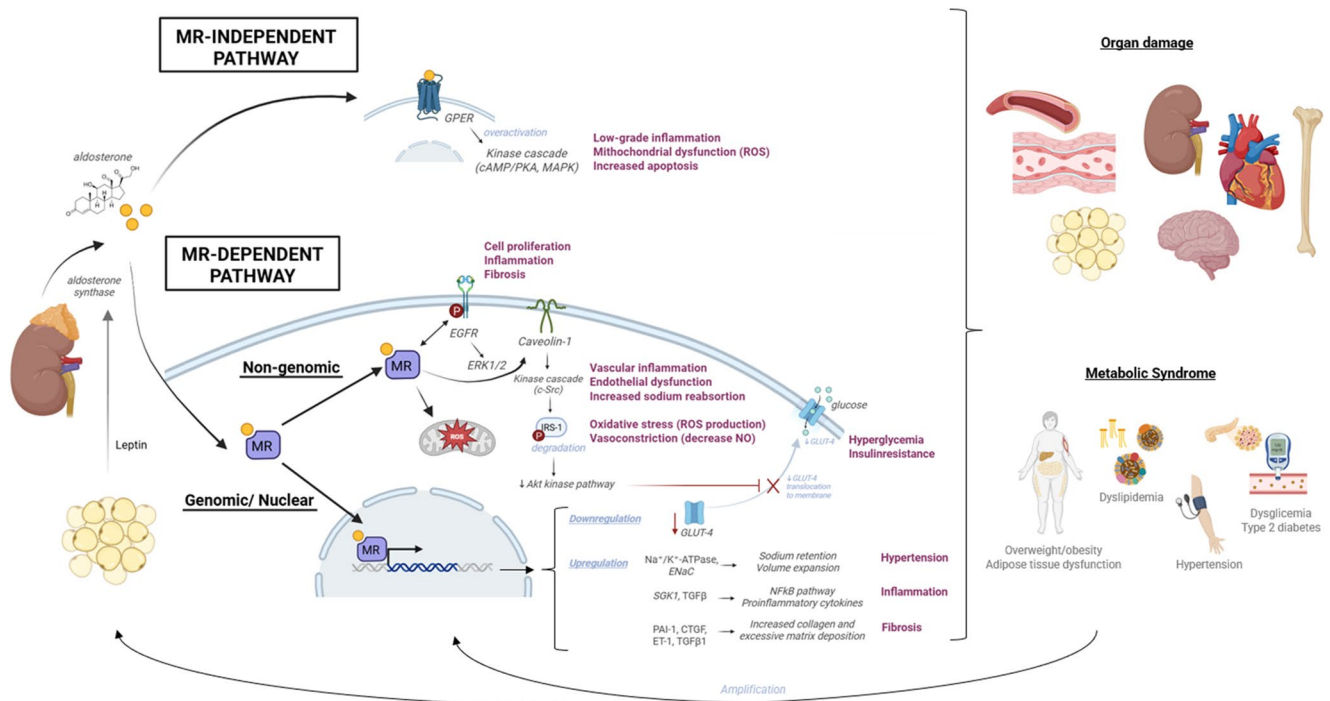


Fig. 1 Pathophysiological mechanisms in which aldosterone contributes to metabolic dysfunction and indirectly to MASLD. Aldosterone can be stimulated by the renin–angiotensin system or by other factors, including leptin. Leptin, an adipokine secreted by adipose tissue, induces aldosterone synthase expression, resulting in aldosterone excess. Aldosterone excess can act independently through a MR-independent pathway by overactivating GPER, resulting in mitochondrial dysfunction, production of reactive oxygen species, and inflammation. The main mechanism by which aldosterone acts is through binding to the MR in the cytosol of cells expressing MR. Once aldosterone binds to MR, it can act through a rapid non-genomic pathway, producing mitochondrial dysfunction and ROS formation, and stimulating transmembrane receptor EGFR and transmembrane scaffolding protein Caveolin-1, among others. This can further activate a kinase cascade involving c-Src, leading to endothelial dysfunction, particularly in vascular smooth muscle cells. Additionally, it can induce phosphorylation and degradation of IRS-1, which leads to reduced GLUT-4 translocation to the membrane, resulting in hyperglycemia and insulin resistance. On the other hand, the aldosterone–MR complex can act through a genomic (nuclear) pathway by regulating gene expression. Downregulation of GLUT-4 expression contributes to hyperglycemia

and insulin resistance. Upregulation of sodium transporters at the renal level represents one of the classical mechanisms of sodium retention, volume expansion, and hypertension development. Genes regulating inflammatory pathways can be upregulated, leading to inflammation, and specific genes such as PAI-1, CTGF, and ET-1 can directly promote fibrosis. Taken together, these mechanisms can damage different cells and organs, most notably the kidney, heart, and blood vessels. Other consequences of these aldosterone-induced metabolic disturbances include contribution to components of the metabolic syndrome and further amplification of adipose tissue dysfunction, potentially leading to increased leptin and aldosterone synthesis. *Abbreviations*, ATPase, adenosine triphosphatase; cAMP, cyclic adenosine monophosphate; c-Src, cellular Src kinase; CTGF, connective tissue growth factor; EGFR, epidermal growth factor receptor; ENaC, epithelial sodium channel; ERK1/2, extracellular signal-regulated kinase 1/2; ET-1, endothelin-1; GLUT-4, glucose transporter type 4; GPER, G protein–coupled estrogen receptor; IRS-1, insulin receptor substrate-1; K⁺, potassium; MAPK, mitogen-activated protein kinase; MR, mineralocorticoid receptor; Na⁺, sodium; PAI-1, plasminogen activator inhibitor-1; PKA, protein kinase A; SGK1, serum- and glucocorticoid-inducible kinase 1; TGF-β, transforming growth factor beta

a direct role in MASLD via its effects on inflammation, oxidative stress and fibrosis, through the proposed mechanisms discussed below (Fig. 2). The MR has been found to be expressed in different hepatic cells including the hepatocytes, liver sinusoidal endothelial cells (LSEC), Kupffer cells and hepatic stellate cells [70]. Nevertheless, information on the mechanistic pathways between aldosterone and MASLD specific for every liver cell type is scarce.

In the natural course of MASLD, early stages such as steatosis and steatohepatitis can be linked to aldosterone via inflammatory pathways and metabolic dysregulation. Progression to fibrosis is often amplified by other determinants

in addition to metabolic syndrome and adipose tissue dysfunction, which include diet, alcohol intake, endocrine chemical disruptors and genetic predisposition [1]. However, the mechanisms by which aldosterone may influence fibrotic progression in MASLD have not been elucidated.

In hepatocytes from rats, increased MR activation is associated with dysregulation of glucose and lipid metabolism, leading to increased apoptosis and a proinflammatory environment [71, 72]. These disturbances can impair hepatocellular lipid metabolism, affecting the primary mechanisms underlying hepatic steatosis, the earliest stage of MASLD. In hepatic steatosis, hepatocytes accumulate lipid droplets,

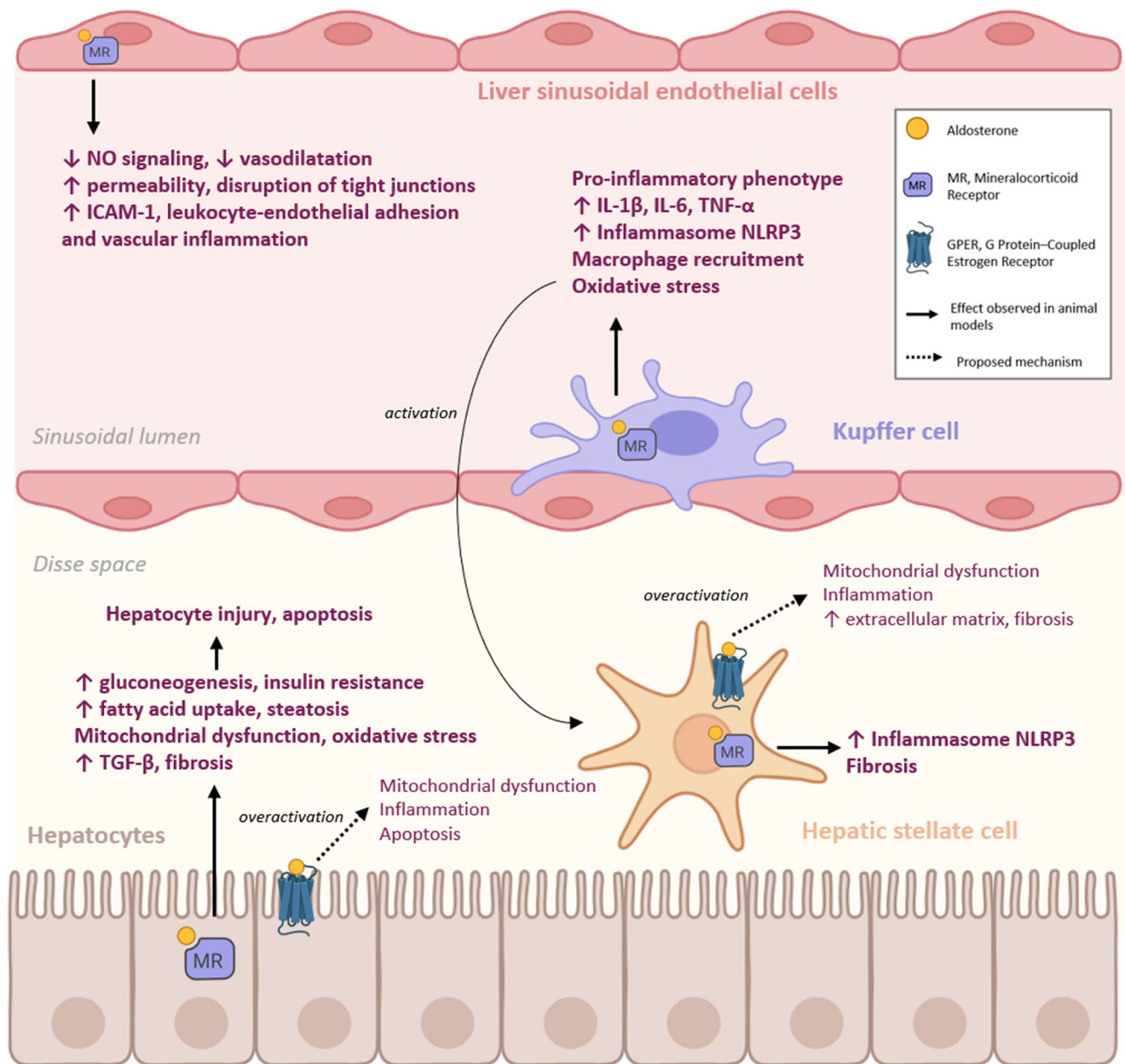


Fig. 2 Proposed direct mechanisms of aldosterone on liver cells. MR activation, through cortisol or aldosterone activation, can drive cell-specific pathological responses in the liver that promote MASLD development and progression. In hepatocytes, MR activation disrupts glucose and lipid metabolism, leading to lipid accumulation, oxidative stress, inflammation, and apoptosis. In liver sinusoidal endothelial cells, MR activation induces endothelial dysfunction, capillarization, increased permeability, leukocyte adhesion, and pro-fibrotic signaling. In Kupffer cells, MR activation promotes a pro-inflammatory phenotype with cytokine release, oxidative stress, and immune cell recruitment, further amplifying inflammation and indirectly activating hepatic stellate cells. In hepatic stellate cells, MR signalling contributes

to activation into collagen-producing myofibroblast-like cells, driving fibrosis, although MR-independent effects of aldosterone could be also implicated. Additionally, aldosterone can act through MR-independent pathways, particularly via GPER, which is expressed in hepatocytes and stellate cells and may contribute to liver injury, although its pathological role remains incompletely defined. *Abbreviations*, ICAM-1, intercellular adhesion molecule-1; GPER, G protein-coupled estrogen receptor; MR, mineralocorticoid receptor; TNF- α , tumour necrosis factor alpha; IL, interleukin; NLRP3, NOD-like receptor pyrin domain-containing inflammasome; LSEC, liver sinusoidal endothelial cells; NO, nitric oxide

which in excess lead to lipotoxicity, thereby amplifying oxidative stress and inflammation, and ultimately triggering hepatocyte injury and apoptosis [73].

In response to the metabolic stress from the hepatocytes, LSEC undergo capillarization and lose their anti-inflammatory and anti-fibrotic properties, which include prevention of Kupffer cell activation, immune cell recruitment, production of vasodilators and maintenance of hepatic stellate cell quiescence, among others. This leads to further hepatocyte dysfunction, and secretion of pro-fibrotic mediators (e.g., TGF- β) from LSEC [74, 75]. In this regard, TGF- β is one of the proteins whose expression is upregulated by excess of aldosterone via its genomic action, suggesting that a cross-talk between aldosterone excess and LSEC may contribute to the development of liver fibrosis. Activation of the MR in LSEC can lead to endothelial dysfunction through nitric oxide signalling dysregulation, increased permeability and leukocyte adhesion through upregulation of intracellular adhesion molecule-1 (ICAM-1), contributing to inflammation and fibrosis [76, 77].

Injured hepatocytes and LSEC can activate Kupffer cells and hepatic stellate cells, which are key mediators in liver fibrosis. Kupffer cells are the resident macrophages of the liver, which release proinflammatory cytokines, amplifying hepatic inflammation and further inducing the activation of hepatic stellate cells [74]. Activation of the MR in Kupffer cells can lead to CD8 T-cell activation, a polarization towards a pro-inflammatory phenotype, cytokine production (IL-1 β , IL-6, TNF- α), oxidative stress, macrophage recruitment and indirect stellate cell activation through inflammatory mediators [78, 79].

Activated hepatic stellate cells can differentiate into myofibroblast-like cells, producing collagen and extracellular matrix, leading to hepatic fibrosis and architectural distortion. Regarding MR expression in the hepatic stellate cells, contradictory results have been found in rats, with some studies detecting mRNA [80, 81]. However, one study did not find evidence of MR mRNA but observed an increase of extracellular matrix proteins after aldosterone administration [82], suggesting additional MR-independent mechanisms of aldosterone harm in the liver [83]. Aldosterone, through MR activation in Kupffer cells and hepatic stellate cells, promotes NLRP3 inflammasome expression and assembly that further activates hepatic stellate cells and drives fibrosis in mice, which has been found to be a key driver of fibrosis in preclinical models [24, 84].

Besides MR activation, aldosterone can act through MR-independent mechanisms in the liver that could explain the mentioned findings and the associations found in the studies below, especially since MR in the liver can be also activated by cortisol due to low 11 β -HSD2 local expression. The main described MR-independent mechanism in animal models is

through GPER activation, which also has been found to be expressed in liver cells from animal models -mainly hepatocytes and stellate cells- [85–87]. Studies of GPER on liver have been focused mainly on its physiological protective estrogen-activation, and information on harmful consequences of its overactivation in the liver through aldosterone excess is lacking. More information is needed on MR-independent mechanisms of aldosterone, especially in MASLD.

3.2 Clinical and experimental studies on aldosterone and MASLD

Most of the available evidence derives from animal models or human individuals with PA (Table 1). Regarding PA, a cross-sectional study including 120 individuals showed that plasma aldosterone levels were associated with the presence of MASLD in PA [88], whereas another cross-sectional single centre study on 91 patients showed that liver steatosis was increased at PA diagnosis, and improved after medical or surgical treatment [89]. Improvements on liver steatosis after PA treatment could be due to broader metabolic disturbances related to aldosterone. A third study comparing 222 individuals with and 222 without PA showed that MASLD was more common in PA, where hypokalemic PA individuals had the worse metabolic status (more severe dyslipidemia, insulin resistance and increased serum uric acid levels) [90]. These studies are mainly cross sectional, limiting the assessment of causality, and mainly include individuals with PA in whom additional confounding factors such as the severity of the metabolic diseases and mild autonomous cortisol co-secretion could be present.

A broader genetic-association study including 125,357 individuals from the UK biobank, showed through a Mendelian randomisation analysis that increased polygenic risk scores for renin-independent aldosteronism (a broader category which may include individuals with PA) were associated with increased risk of MASLD and MASLD-related cirrhosis [91]. By using genetic proxies for aldosterone dysregulation, Mendelian randomisation reduces confounding and provides support for a causal and mechanistic role of aldosterone in MASLD development and progression.

Besides PA, a cohort study including 3,713 hypertensive individuals over a 10 year period, showed that increased aldosterone plasma concentrations were associated with new-onset MASLD, suggesting a causal link [92]. Another study including 2,507 individuals from the Jackson Heart Study cohort found that aldosterone levels were significantly correlated with increased hepatic steatosis measured through with liver attenuation in computed tomography, an association that only remained in women after fully-adjusted

Table 1 Main studies on aldosterone and MASLD

First Author, year	Type of research	Type of study, sample size, or type of intervention	Main results
Aldosterone and MASLD associations			
Tizianel I, 2025(89)	Observational, clinical data	Cross-sectional study including 149 individuals. Among them 41 with PA (20 unilateral, 21 bilateral), 50 with non-functioning adenomas, 48 MACS and 10 adrenal CS.	Prevalence of MASLD assessed by liver/spleen ratio* was higher in PA compared to non-functioning adenomas (49% vs. 14%, $p < 0.001$) and MACS (49% vs. 25%, $p < 0.05$) and similar to adrenal CS (49% vs. 45%, $p = 0.61$).
Zeng Q, 2025(91)	Observational, clinical data	Mendelian randomisation study of 125,357 participants from the UK Biobank.	Renin-independent-aldosteronism assessed through polygenic risk scores was genetically associated with higher risks of MASLD (OR 1.28, 95% CI 1.09–1.49) and cirrhosis (OR 1.49, 95% CI 1.03–2.16).
Hu J, 2023(92)	Observational, clinical data	Cohort study of 3,713 hypertensive individuals over a 10-year retrospective period.	There was a non-linear positive J-shaped relationship between plasma aldosterone and new-onset MASLD. In particular plasma aldosterone increased risk of MASLD with a HR for highest tertile 3 of 1.71 (95% CI 1.47–1.98), and an inflection point in plasma aldosterone at 13ng/dL for the non-linear association.
Chen Y, 2021(90)	Observational, clinical data	Case-control study including 444 individuals (222 with PA and 222 without).	The prevalence of MASLD was higher in PA patients than in non-PA patients (35.1% vs. 29.7%), although the patterns of obesity, dyslipidemia and insulin resistance were similar. Within PA, hypokalemic PA had a more MASLD prevalence (44% vs. 27%, $p < 0.05$) and worse metabolic status than normokalemic PA patients, including higher BMI (25.4 vs. 24.1, $p < 0.05$).
Kumar A, 2022(93)	Observational, clinical data	Cross-sectional community-based study of 2,507 African Americans from the Jackson Heart Study who were not under ACEi, ARB, or MR antagonists.	Liver fat through CT scan liver attenuation as measured and each doubling of aldosterone was associated with 1.08 HU decrease (95% CI 1.47 – -0.69, $p < 0.001$), which was significant only in women after full multivariate adjustment by decreasing 0.94 HU (95% CI – 1.35 – -0.52, $p < 0.001$).
Fallo F, 2010(88)	Observational, clinical data	Case-control study matched by sex, age and BMI including 120 individuals (40 PA, 40 with low-renin essential hypertension and 40 normotensive).	MASLD was a frequent finding in PA (57.5%), where PA with hypokalemia were more insulin resistant compared with normokalemia (HOMA index 5.1 vs. 4.3, $p < 0.01$) and had higher prevalence of MASLD 72.7% vs. 38.8%, $p < 0.05$).
Mineralocorticoid receptor antagonism/deficiency			
Gamliel-Lazarovich A, 2013(94)	Experimental, preclinical animal models	Mice in high-fat diet, treated with adrenalectomy or eplerenone	Neither adrenalectomy nor eplerenone affected fatty liver formation or body weight. In cultured hepatocytes, triglyceride loading induced by high glucose, oleic acid or very low-density lipoprotein was not affected by aldosterone, spironolactone or eplerenone.
Muñoz-Durango N, 2020(79)	Experimental, preclinical animal models	Mice with methionine-choline deficient diet-induced MASH with deletion in MR from myeloid cells vs. controls.	Mice with MRs deletion exhibited reduced hepatic inflammation and lower hepatic triglyceride content; as well as costimulatory molecule CD86 by dendritic cells and the CD25 activation marker in CD8+T cells which were significantly reduced. Loss of MR in myeloid cells reduces lipid accumulation in the liver, in part through modulating the adaptive immune response, which is pivotal for the development of steatosis.

*Liver/spleen ratio refers to the ratio of hepatic attenuation to splenic attenuation measured in CT scan with Hounsfield units. Low values indicate hepatic steatosis

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CD, cluster of differentiation; CI, Confidence Interval; CS, Cushing Syndrome; CT, Computed Tomography; HOMA, homeostasis model assessment; HU, Hounsfield Units; HR, Hazard Ratio; PA, primary aldosteronism; MACS, mild autonomous cortisol secretion; MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis; MR, mineralocorticoid receptor; OR, Odds Ratio; PA, primary aldosteronism; UK, United Kingdom

multivariable models, despite being a cross-sectional study which limits causal inference [93].

Animal models have shown that in mice, aldosterone levels could be involved in diet-induced insulin resistance and glucose disturbances [79]. However, one study by Gamliel-Lazarovich A, et al. found no association in the development of fatty liver disease [94]. Regarding

this study, consideration should be taken since the authors compared mice treated with eplerenone with mice who underwent bilateral adrenalectomy and required saline solution for survival, so this could affect the interpretation of the results. Additionally, differences in animal models exist across studies, with mice being exposed to different diets and interventions (Table 1).

3.3 Evidence on RAAS and MR blockade in MASLD

Understanding the role of aldosterone in MASLD is relevant not only for advancing knowledge of disease pathophysiology, but also for identifying potential therapeutic targets. MR antagonists have demonstrated beneficial effects on cardiac function and renal disease, including within the cardio-kidney-metabolic syndrome, primarily through attenuation of MR-mediated inflammation, oxidative stress, fibrosis, and sodium retention, as well as improvement of insulin sensitivity. In line with this, prior evidence on RAAS blockade using ACEi and ARB indicates that individuals with MASLD receiving ACEi/ARB therapy exhibit a reduced risk of MASLD progression, adverse liver outcomes and cardiovascular events [25, 95–98]. However, these results could be a reflection of RAAS modulation rather than specific to aldosterone blockade.

MR antagonists have a direct effect on aldosterone levels but also could influence other molecules that bind to MR such as cortisol and its related-consequences. Importantly, the drug effects do not suppress aldosterone itself, allowing persistently elevated hormone levels to potentially exert MR-independent effects leading to oxidative stress and a proinflammatory environment. Current available MR antagonists include spironolactone, eplerenone and finerenone. When starting treatment with MR antagonists, patients should be monitored for hyperkalemia -especially in the setting of declining renal function-, with dose adjustments as appropriate. Spironolactone is commonly used in cirrhosis with ascites, although careful electrolyte monitoring is required to prevent neurological complications.

Spironolactone and eplerenone are steroidal MR antagonists, where spironolactone is less selective and binds to androgen and progesterone receptors, resulting in an increased hormonal side effects such as gynecomastia. Eplerenone is selective for the MR and has less adverse effects. Finerenone is a nonsteroidal MR antagonist, with high specificity for the MR, not interacting with other steroid receptors and having less side effects. In contrast to steroidal MR antagonists, finerenone shows less distribution to renal epithelial tissues, as its structure limits penetration across epithelial barriers, decreasing the risk of hyperkalemia.

Spironolactone, the most used MR blocker, has shown in a cohort study of 7,241 hypertensive individuals to have a benefit by reducing the risk of MASLD development [99]. Additionally, an interventional study combining spironolactone with vitamin E showed that in MASLD the combination offered an improvement on insulin resistance parameters when compared to vitamin E alone [100]. Finerenone, a relevant MR antagonist aimed at improving diabetic kidney disease, showed in a subgroup analysis of the FIDELITY

study, relevant improvement of kidney outcomes, as well as cardiovascular benefits on individuals with increased liver fibrosis risk assessed through FIB-4 index [101]. Information on other non-invasive liver tests, and their changes after treatment with MR antagonists is lacking. On the other hand, a single open-label proof-of-concept study with eplerenone on individuals with human immunodeficiency virus infection and hepatic steatosis showed an early increase of liver fat, although there was no control group [102]. Notable heterogeneity exists across the mentioned studies in terms of study population characteristics, liver disease measurements and outcomes, warranting careful interpretation. However, current MASLD guidelines do not incorporate this recommendation for the treatment due to the lack of RCT specifically designed for this purpose.

3.4 Sex-differences in the association between aldosterone and MASLD

Aldosterone and renin levels tend to be increased in men when compared to premenopausal women. Reference values for renin and aldosterone can differ also by ethnicity, where in Caucasian population range values for women have been described (renin 6.1-62.7 mIU/L, aldosterone <138-1179 pmol/L) and men (renin 6.1-62.7 mIU/L, aldosterone <138-1179 pmol/L) [103]. Despite women exhibit lower values, they present increased adrenal responsiveness, resulting in an enhanced aldosterone response to acute stimulation, which can manifest as greater salt sensitivity in blood pressure regulation [104]. Special attention should be placed since aldosterone and renin levels can fluctuate across the menstrual cycle in premenopausal women, with the luteal phase increasing levels of both hormones when comparing to the follicular phase, which can be due to increased levels of progesterone that antagonise the MR [105, 106].

Estrogens can modulate the MR pathway, inhibiting aldosterone synthesis via the estrogen receptor- β , resulting in lower aldosterone levels and blood pressure in premenopausal women. After the menopause, when estradiol levels decline, the estrogen-mediated inhibition is lost, and GPER receptors are activated stimulating aldosterone biosynthesis and a positive feedback loop, ultimately increasing blood pressure [107].

The impact of aldosterone in different tissues can present differences by sex, where there is evidence that the impact of aldosterone on cardiac remodelling is more pronounced in women independent of menopausal status [108]. Regarding adipose tissue dysfunction, leptin secretion triggers aldosterone synthase expression and increased plasma aldosterone, especially in female animal models. Additionally, in female animals, aldosterone blockade with

spironolactone restores blood pressure [35]. Male animals, however, exhibit enhanced sympathetic responses to leptin when compared to female [35, 109]. Body fat distribution is also associated with aldosterone sex-related differences, where evidence in humans has demonstrated that aldosterone in men has a stronger association with ectopic cardiac adiposity, whilst in women the association is stronger with total body fat [110]. It is particularly relevant when assessing menopausal status, as estrogens exert a protective effect by reducing VAT; an effect that disappears after menopause leading to increased cardiometabolic risk.

Regarding whether there may be a different response by sex to treatment with MR antagonists, a post-hoc subgroup analysis of the FIDELIO trial with finerenone, showed no differences in the risk in cardiovascular and kidney outcomes after stratifying by sex and menopausal status, including evaluation of interaction [111]. However, a more pronounced reduction in heart failure hospitalisations were observed in men [111].

There are also sex differences in MASLD, where premenopausal women benefit from the protective effects of estrogens on hepatic lipid metabolism, inflammation and fibrogenesis, when compared to men in which androgens impact negatively presenting increased prevalence and severity of MASLD. After menopause, estrogen deficiency increases the susceptibility of MASLD and accelerates fibrosis progression [112–114]. The interplay between sex hormones and genetic variants (e.g., PNPLA3, TM6SF2) are key in MASLD development and disease progression [112].

Given the known sex differences in aldosterone, leptin-induced aldosterone excess, and MASLD, we may think that the protective effect of estrogens over MASLD in premenopausal women could be associated with lower aldosterone levels when compared to men. In postmenopausal women, body fat distribution and leptin-triggered aldosterone enhancement could influence the development and progression of MASLD. However, sex differences in aldosterone and MASLD remains a field for future research.

4 Future perspectives

4.1 New and future treatments on aldosterone and its potential impact on MASLD

Recent advances in aldosterone-targeting therapies include non-steroidal-MR antagonists and aldosterone synthase inhibitors. Among non-steroidal MR antagonists, finerenone is the most implemented agent, which acts as a

selective non-steroidal MR antagonist inducing changes in the receptor that reduce recruitment of transcriptional cofactors attenuating proinflammatory and profibrotic gene expression. Finerenone is approved for individuals with diabetic kidney disease and has demonstrated improvement in kidney and cardiovascular outcomes with a superior safety profile when compared to steroidal MR antagonists [115]. Esaxerenone is another non-steroidal MR antagonist, which is commercialised in some countries for PA, hypertension and diabetic kidney disease and has shown to reduce blood pressure and albuminuria, with a renoprotective effect that could be partly independent of blood pressure lowering [116]. Ocedurenone represents a newer non-steroidal-MR antagonist under development, which is highly selective to MR to minimise adverse effects, designed for advanced chronic kidney disease and resistant hypertension, showing favorable results in phase 2 clinical trials [117].

Aldosterone synthase inhibitors constitute an emerging drug class designed to directly inhibit aldosterone synthase, the enzyme involved in aldosterone biosynthesis, resulting in reduced aldosterone production and attenuation of its pathological effects. By selectively targeting aldosterone synthase instead of the MR, this emerging drug class improves pharmacological specificity and reduces the impact on other molecules that bind the MR such as cortisol. Additionally, it can benefit from decreasing the overactivation of MR-independent pathways which are not triggered with MR antagonists. This is especially relevant given the growing evidence of MR-independent pathways in which aldosterone excess could have a detrimental metabolic effect, such as the one mediated through GPER overactivation (Fig. 1).

Novel agents in the aldosterone synthase inhibitors category include baxdrostat, lorundrostat, dexfadrostat phosphate, and vicardostat, which have reported promising results in phase 2 and phase 3 trials regarding blood pressure reductions and kidney damage parameters [118–121]. Baxdrostat is the most advanced compound in this class, which has been primarily studied in patients with resistant or uncontrolled hypertension and is being explored in PA, showing dose-dependent reductions in aldosterone levels and blood pressure lowering along with low rates of hyperkalemia and good tolerability [18]. Other aldosterone synthase inhibitors including larundrostat, dexfadrostat and vicardostat are in earlier stages of development. These novel agents are under active investigation for broader indications and may soon redefine the therapeutic landscape for aldosterone-mediated diseases.

Future studies will be needed to clarify the potential impact of selective aldosterone-synthase inhibitors on the development and progression of MASLD.

4.2 The role of the RAAS in precision medicine for obesity and MASLD

While aldosterone can play a key independent role in metabolic dysfunction, it can also be the final effector of the RAAS cascade. Thus, understanding the RAAS system is essential for a holistic view of the hormonal, metabolic and inflammatory pathways involved in obesity and MASLD.

In the setting of adipose tissue dysfunction and MASLD, overactivation of the RAAS axis promotes hepatic steatosis, inflammation, insulin resistance and fibrosis, through the previously mentioned multiple mechanistic pathways. Obesity and adipose tissue dysfunction could be playing an important role as triggers of aldosterone excess in the context of MASLD, so the assessment of MASLD and RAAS should also focus on weight loss with consequent aldosterone reduction [37, 38].

Refining the assessment of the RAAS axis and its regulatory mechanisms in clinical practice could improve patient stratification and inform personalised treatment decisions, with the aim to improve metabolic dysfunction and prevent the development and progression of comorbid conditions such as MASLD. In particular, evaluating circulating RAAS components, including renin and aldosterone, in metabolically unhealthy individuals, may aid the identification of candidates for targeted pharmacological intervention, constituting a potential important step towards precision medicine. Future metabolomic profiling may help in identifying intermediate metabolites within the RAAS pathway that contribute to aldosterone and RAAS regulation, ultimately enabling risk stratification based on metabolomic signatures. Including additional evaluation on sex-related hormonal and menopausal status could help further identify patients at higher risk of metabolic and organ damage associated to MASLD and increased aldosterone/RAAS activation.

4.3 Clinical validation framework for assessing the link between aldosterone and MASLD

To enhance the translational relevance of the evidence summarised in the manuscript, we suggest to incorporate the following measures in the MASLD clinical assessment beyond the standard evaluation:

- A) Anthropometric measurements: waist circumference, waist-to-height ratio. If available: bioimpedance analysis, dual-energy X-ray absorptiometry, fat and muscle segmentation through computed tomography, functional muscle strength test (e.g., handgrip strength).
- B) Adipose tissue and metabolic dysfunction biomarkers: HDL-cholesterol, LDL-cholesterol, Triglycerides, TG/

HDL ratio, Triglyceride-Glucose index, leptin, adiponectin, leptin/adiponectin ratio,

- C) RAAS molecules: plasma aldosterone, renin (direct renin or plasma renin activity), aldosterone-renin-ratio.
- D) MASLD outcomes: Fibrosis-4 index, Liver Risk Score, Enhanced Liver Fibrosis test (ELF, when available), Hepamet fibrosis score, transient elastography including the controlled attenuation parameter for steatosis assessment and liver stiffness for fibrosis.

Based on this integrated assessment, patients could be stratified according to fibrosis risk, prioritizing more intensive evaluation and closer follow-up in those with higher-risk profiles. Stratification may also incorporate aldosterone levels and the aldosterone-to-renin ratio, although these should be interpreted with caution in patients receiving medications that affect RAAS. In addition, the degree of metabolic dysfunction -captured by lipid-derived ratios and adipokine profiles- should be considered to better reflect the systemic drivers of disease progression. Finally, anthropometric measures that more accurately represent body fat distribution, and particularly visceral adiposity, should be included given their mechanistic link with aldosterone dysregulation and MASLD severity.

4.4 Future research priorities in MASLD and aldosterone

Despite growing evidence linking aldosterone to metabolic dysfunction and MASLD, several important knowledge gaps and areas of ongoing debate remain.

The contribution of aldosterone to adipose tissue dysfunction requires further clarification, particularly regarding adipose tissue depots, body fat distribution, and cell-specific MR activity.

At the hepatic level, the cell-type-specific effects of aldosterone across hepatocytes, hepatic stellate cells, Kupffer cells, and LSEC warrant further investigation.

Potential modifiers, including ethnicity and cardiometabolic comorbidities, have been variably addressed across studies and represent important factors for the development of personalized medicine approaches. Confounding by glucocorticoid receptor activation, such as mild autonomous cortisol secretion, may also influence observed associations between aldosterone, insulin resistance, and adipose tissue dysfunction and deserves greater consideration.

Sex-specific differences influencing susceptibility and disease progression are increasingly recognized but remain incompletely characterized.

Clinical evidence is limited by relatively short follow-up and heterogeneous study designs, contributing to some

variability in findings and uncertainty regarding causality versus association.

Future research should build on existing evidence through large prospective studies and mechanistic investigations in humans, alongside the development of biomarkers of aldosterone exposure, MR activity, and downstream metabolic effects, to support a more integrated RAAS assessment in MASLD within the broader cardiorenometabolic disease framework.

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Declarations

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