Submitted: 07.03.2024
Accepted: 22.04.2024
Early publication date: 26.06.2024

Endokrynologia Polska
DOI: 10.5603/ep.99689
ISSN 0423–104X, e-ISSN 2299–8306
Volume/Tom 75; Number/Numer 3/2024

Metabolic-associated fatty liver disease and the role of hormones in its aetiopathogenesis

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Abstract

Metabolic-associated fatty liver disease (MAFLD) is a newly coined term that links the presence of liver steatosis (characterised by the accumulation of lipids in at least 5% of liver cells) with a condition of overall systemic metabolic dysfunction. MAFLD impacts 24–36% of the global population. As per the official guidelines, a diagnosis of MAFLD can be made when hepatosteatosis is accompanied by type 2 diabetes mellitus, overweight, obesity, or at least 2 other specific metabolic abnormalities (increased waist circumference, hypertension, dyslipidaemia, prediabetes, elevated C-reactive protein level, or increased homeostasis model assessment of insulin resistance: HOMA-IR). MAFLD is a heterogeneous illness associated with multiple diseases that impact various organs, particularly endocrine organs. Endocrinopathies can significantly influence the progression and severity of MAFLD. This paper provides a brief overview of the existing research on the connection between liver steatosis and the functioning of endocrine organs. The authors also propose dividing endocrine diseases into those having a possible, strong, and clear relationship with hepatosteatosis (for the purpose of preliminary recommendations regarding the need for monitoring the possible progression of MAFLD in these groups of patients). **(Endokrynol Pol 2024; 75 (3): 237–252)**

Key words: *metabolic-associated fatty liver disease; liver; obesity; diabetes; MAFLD; NAFLD*

Introduction

Metabolic-associated fatty liver disease (MAFLD) is a novel diagnostic concept developed in 2020 by Eslam et al. to highlight the significance of metabolic disorders such as overweight, obesity, and type 2 diabetes as the primary factors contributing to fatty liver disease [1]. MAFLD is an inflammatory liver disease that affects around 24–36% of the global population. It involves the accumulation of lipids, primarily triglycerides, in at least 5% of liver cells — the development of the disease is influenced by various factors such as genetics, environment, and lifestyle [2]. MAFLD is diagnosed when fatty liver disease is present along with type 2 diabetes, overweight, or obesity (determined by body mass index thresholds specific to the population), or at least 2 other metabolic abnormalities [such as increased waist circumference, arterial hypertension, hypertriglyceridaemia, low high-density lipoprotein (HDL) cholesterol levels, prediabetes, elevated C-reactive protein levels, or increased homeostasis model assessment of insulin resistance (HOMA-IR)] — specific diagnostic criteria for MAFLD are outlined in Figure 1.

MAFLD has replaced the term non-alcoholic fatty liver disease (NAFLD); however, it is important to note the distinct criteria for diagnosing each condition (NAFLD is diagnosed in patients with confirmed fatty liver disease where excessive alcohol consumption and other causes of hepatosteatosis, like viral hepatitis or autoimmune diseases, are not present). This approach appears to be correct for various reasons, as emphasised in expert research: NAFLD is indirectly linked to metabolic features crucial for the advancement of fatty liver disease; the development of new treatment methods is hindered by the absence of NAFLD criteria based on these metabolic factors and additionally; patients not meeting NAFLD criteria may face stigma due to the term "non-alcoholic" [3, 4]. In simple words, MAFLD, given the significant link between fatty liver disease and insulin resistance, is important, because almost all diabetic individuals and 60% of patients with metabolic syndrome display signs of steatohepatitis on liver biopsies, indicating that MAFLD could be an early consequence of diabetes, obesity, and their cohabitation — known as diabesity [5, 6]. Insulin resistance stimulates lipogenesis in the liver and impairs lipolysis in both the liver and adipose tissue — this leads to an increased movement of free fatty acids into the liver and disrupts the function of adipose tissue by influencing the secretion of adipokines and cytokines. An important problem of fatty liver disease is the development of chronic inflammation, liver fibrosis,

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cirrhosis, and hepatocellular carcinoma — MAFLD concept is more effective than NAFLD in identifying patients with severe hepatic fibrosis [7].

MAFLD is a heterogeneous illness, associated with a wide range of multiple organ diseases, including endocrinopathies, and there is increasing evidence suggesting they might significantly influence the progression and severity of the disease. This short review discusses the existing research about the relationship between MAFLD (and slightly broader hepatosteatosis) and the function of particular endocrine organs.

Hepatosteatosis in relation to hypothalamus and pituitary gland function

Current literature on hepatic steatosis in hypothalamus and pituitary gland illnesses discusses mainly the impact of growth hormone (GH) and prolactin (PRL) secretion abnormalities, with some consideration given to vasopressin as well.

GH is released by the anterior pituitary in a pulsatile manner and stimulates the production of insulin-like growth factor 1 (IGF-1). The GH–IGF-1 axis is controlled by a specific intracellular signalling pathway that includes Janus kinase 2 (JAK-2) and signal transducer and activator of transcription 5 (STAT-5) — this pathway regulates target genes, resulting in enhanced systemic insulin resistance, lipolysis in visceral adipose tissue, and senescence of hepatic stellate cells, which reduces hepatofibrosis [8, 9]. Therefore, patients with GH deficiency (regardless of its cause) usually present an android type of obesity, increased body fat (by about 10% through intrahepatic lipid accumulation), an atherogenic lipid profile, and signs of insulin resistance, which lead to the development of metabolic syndrome and hepatosteatosis linked with metabolic dysfunction (like MAFLD), which was confirmed in previous scientific reports [10–14]. It is worth emphasising that treating GH deficiency with recombinant human GH or using tesamorelin (an analogue of the GH-releasing hormone) has been shown to have a positive impact on the course of fatty liver disease, reducing hepatic and visceral fat deposits, limiting the degree of hepatofibrosis (by reduction in the levels fibrosis markers: hyaluronic acid and type IV collagen), and lowering the concentrations of transaminases, independent of its effects on body weight and composition [15–19]. The increased level of pro-inflammatory cytokines [like tumor necrosis factor alpha (TNF-α) or C-C motif chemokine ligand 3, associated with GH deficiency] is also reduced after GH replacement therapy [20]. Although it is proven that patients with metabolically determined hepatic steatosis and fibrosis show decreased levels of GH and IGF-1 [21], this is insufficient to suggest using recombinant GH as a treatment for MAFLD without concurrent GH deficiency. However, it is important to be vigilant and actively diagnose patients with GH deficiency, either using standard tools like abdominal ultrasound or more advanced methods like elastography liver examination to assess the severity of liver steatosis and fibrosis.

The connection between acromegaly (characterised by excessive GH secretion) and hepatic steatosis remains unclear. Higher levels of GH and IGF-1 are linked to increased lipolysis and a reduction in the volume of visceral and superficial adipose tissue (which is probably associated with enhanced ATP production in the liver [22]) — however, acromegaly also leads to insulin resistance, resulting in carbohydrate disorders: approximately 13–30% of patients develop diabetes mellitus, while 60–70% experience impaired glucose tolerance, the severity of these conditions is linked to the duration and intensity of acromegaly, the patient's age, and the concentrations of GH, IGF-1, and insulin-like growth factor-binding protein 3 (IGFBP-3) [23, 24]. Current research indicates that individuals with active acromegaly tend to have a reduced volume of liver fat, and successful biochemical management of acromegaly can lead to an increase in this lipid content [25–27]. Conversely, other studies have demonstrated that patients with acromegaly exhibit higher incidences of hepatosteatosis, which may improve with disease control [28]. This difference may be due to the unique body structure of acromegaly (acromegalic lipodystrophy, which affects the function of GH and IGF-1 receptors differently from the general population) — additionally, comorbidities and complications of acromegaly, like the above-mentioned carbohydrate metabolism disorders, could play a role [29]. Additional research is required to further our comprehension of this phenomenon.

PRL is a polypeptide hormone secreted by lactotroph cells in the anterior pituitary gland, primarily regulated by dopamine, thyroid-stimulating hormone (TSH), TSH-releasing hormone, and circulating oestrogens. PRL primarily acts in pregnancy and lactation but also influences food intake, glucolipid metabolism, and the development of liver steatosis, due to the fact that prolactin receptors are found in the liver, pancreas, and adipose tissue, where their activation inhibits fatty acid synthase in adipose tissue and reduces hepatic lipid content [9, 30, 31]. Hyperprolactinaemia is the predominant malfunction of the hypothalamic-pituitary axis (affecting 0.4% of the general adult population), more prevalent in women, (with a rate of 9–17% in women with reproductive disorders) [30] — it can lead to insulin resistance and carbohydrate metabolism disorders due to the structural resemblance between

PRL and GH, down-regulation of insulin receptors, and increased concentrations of free fatty acids. Additional problems include hypogonadism and the antidopaminergic impact of elevated PRL production, which contribute to overweight, obesity, and atherogenic dyslipidaemia [24]. Chronic hyperprolactinaemia can cause fatty liver disease by affecting the signalling pathways of de novo lipogenesis [32]. The case report of a 13-year-old patient who developed NAFLD due to prolactinoma-related obesity and all these diseases were successfully treated with long-acting dopamine agonist cabergoline (albeit a single one) also seems to confirm the influence of hyperprolactinaemia on the development of fatty liver disease [33]. Interestingly, the study by Zhu et al. did not establish a connection between elevated prolactin levels and liver fat accumulation in males, indicating a potential sex-specific issue that is not clearly understood [34]. Even more doubts are raised by the fact that we have data about how severe fatty liver disease may also be associated with low PRL levels [31]. In 2022, a Chinese study team confirmed that low PRL levels within the normal range were indicators of MAFLD — they also found that as PRL levels rose, the incidence of MAFLD decreased in both males and females [35]. Establishing a causal association between elevated PRL levels and MAFLD is challenging due to the correlation between PRL levels and body mass index (BMI), as well as the presence of other comorbidities that may have a greater impact on the development of steatosis.

Arginine vasopressin (AVP), also known as antidiuretic hormone (ADH), is a neurohormone produced from a pre-pro-hormone precursor in the supraoptic and paraventricular nuclei of the hypothalamus in reaction to elevated plasma osmolality and reduced blood volume. Due to the short half-life and poor stability of AVP in plasma samples, we use copeptin in clinical practice — a stable and physiologically inactive fragment of pro-vasopressin, released alongside AVP [36]. Recent investigations have shown that copeptin concentration is a reliable indicator of the severity of fatty liver disease, independent of body adiposity and other metabolic disorders, but only in cases of diabetes and obesity [37–40]. However, it has not been demonstrated in a non-animal model that AVP can impact the development of liver steatosis. Considering ADH's effect on hepatic fat metabolism, it appears plausible because it reduces plasma non-esterified fatty acids, stimulates hepatic lipogenesis (via the V1a receptor), and suppresses liver lipolysis [41–43]. We await additional study focused on diagnosing MAFLD in ADH-related conditions such as diabetes insipidus or syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Thyroid function and liver steatosis

Thyroid hormones elevate the basal metabolic rate, stimulate protein synthesis and catabolism (with catabolism being more prominent), and initiate hepatic lipogenesis and lipolysis in the liver and adipose tissue, which provide fatty acids for the production of ATP by influencing on cholesterol synthesis and clearance and its conversion into bile acids, regulation of the expression of the sterol regulatory element-binding protein-2 (SREBP-2), and stimulation of lipoprotein lipase catabolizing triglyceride-rich lipoproteins, reducing the risk of developing an atherosclerotic lipid profile. Thyroid hormone deficiency leads to weight gain, an atherogenic lipid profile, an elevated concentration of free fatty acids, reduced tissue glucose uptake, and increased oxidation, resulting in insulin resistance. Additionally, hypothyroidism leads to the secretion of counter-regulatory hormones such as cortisol, catecholamines, or glucagon. This phenomenon has also been noticed in subclinical hypothyroidism, where the peripheral hormone concentrations remain normal and only the TSH level is raised [24, 44, 45]. In the Rotterdam Study analysing the incidence of fatty liver disease in patients with hypothyroidism or hyperthyroidism, only patients with hypothyroidism were characterised by a statistically significantly higher odds ratio for this liver structure disorder [1.32; 95% confidence interval (CI): 1.08–1.62] — a similar relationship was also observed for the development of liver fibrosis (defined as liver stiffness in transient elastography examination greater than or equal to 8 kPa) — significant results were obtained only for subclinical hypothyroidism (2.14; 95% CI: 1.04–4.07) and clinical hypothyroidism (6.64; 95% CI: 1.04–23.98) [46]. Similar outcomes were achieved in further meta-analyses [47, 48].

Hypothyroidism per se may cause a modest elevation in serum alanine aminotransferase (ALT) and gamma-glutamyl transferase peptide (GGTP) concentrations, possibly resulting from hepatic steatosis. Potential causative factors include impaired triglyceride metabolism in the liver (by promoting hepatic lipogenesis due to increased SREBP-1c activity), reduced activity of glucose uptake receptors in pancreatic beta cells (leading to decreased insulin secretion, decreased lipolysis, and increased transport of free fatty acids to the liver) or elevated adipocytokines concentrations such as leptin, visfatin, IL-1, and TNF-α with decreased adiponectin (seen characteristically in hypothyroidism, diabetes, and obesity and contributing to hepatic inflammation via an increase in oxygen free radicals) [49–51]. The frequency of fatty liver disease appears to be inversely proportional to the concentration of fT_4, and this relationship follows a dose-dependent

pattern [52]. We also must not forget about the complications of fatty liver disease – in addition to the previously mentioned effects of free radicals, Sinha et al. proposed that a possible reason for hepatitis in the course of MAFLD (MASH: metabolic-associated steatohepatitis) with the coexistence of hypothyroidism could be the impaired expression of intrahepatic deiodinase, leading to reduced levels of T_3 in the liver [53]. Several studies conducted by scientists from China and Korea have shown a direct and independent positive link between NAFLD/MAFLD and AITD — Chen et al. suggested that the main link in this relationship could be the induction of inflammation by adipokines (such as IL-6 or leptin) and the activation of receptors that can identify pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) through Toll-like receptors and other receptors found on thyrocytes; however, the authors emphasised the necessity for additional research on this topic [54–56]. This is particularly important when we take into account the results of the study by Zhang et al., who found that antibodies against thyroglobulin are potentially a protective factor for the development of MAFLD, especially in women [57]. It seems justified to conclude that in patients with hypothyroidism, particularly caused by autoimmunity, it is important to check for the development of MAFLD and ensure correct therapy aimed at maintaining the euthyroid state.

Research on the prevalence of fatty liver disease in hyperthyroidism is conclusive – individuals with this condition have reduced intrahepatic fat volume and a decreased occurrence of hepatosteatosis [46, 58]. Although this relationship seems to be different from the one we are looking for, one study found that hepatosteatosis is linked to a higher occurrence of lymph node metastasis and the $BRAF^{V600E}$ mutation in papillary thyroid carcinoma in females [59]. There is currently no evidence or justification to consider this thyroid-related illnesses as pathophysiologically linked to the development of MAFLD.

MAFLD and calcium-phosphate metabolism

The current research on the connection between fatty liver illness related to metabolism and calcium-phosphate metabolism disorders mostly focuses on vitamin D.

Vitamin D is a multifunctional hormone that plays a role far beyond regulating calcium and phosphorus homeostasis and bone health; its impact extends to various organs due to the widespread presence of vitamin D receptors. Numerous studies have confirmed its involvement in altering inflammatory processes, among which we include MAFLD. The National Health and Nutrition Examination Survey (NHANES III) data analysis revealed an inverse correlation between patients' serum vitamin D levels and the severity of NAFLD [60]. A meta-analysis including 8 randomised controlled trials confirmed that vitamin D supplementation has a protective effect against insulin resistance and reduces serum ALT levels in patients with fatty liver disease [61]. A multivariable analysis conducted by scientists from Korea showed that by maintaining a serum 25(OH)D level ≥ 30 ng/mL, it is possible to reduce the risk of developing NAFLD by 21% [62]. Dal et al.'s study revealed that a decrease of 1 ng/dL in 25(OH)D levels is associated with a 3.7% increase in the risk of fatty liver disease [63]. Vitamin D in its active form modulates the immune system, causing anti-inflammatory, antifibrogenic, and antiproliferative effects in the liver [by inhibiting the expression in the liver of such mediators as platelet-derived growth factor, transforming growth factor β (TGF-β) collagen, α-smooth muscle actin, or tissue inhibitors of metalloproteinase-1], as well as acting on oxidative stress markers in adipose tissue [64–67]. Evidence also shows that a vitamin D-deficient diet enhances toll-like receptor activation, which leads to insulin resistance and impacts lipid metabolism in the liver, ultimately promoting steatosis [68]. The existence of liver-specific deletions of vitamin D receptor (VDR) and hepatocyte nuclear factor 4 alpha (HNF4α) genes can also lead to insulin resistance — vitamin D supplementation can counteract this impact by interacting with HNF4α and activating VDR [69]. Vitamin D treatment in human promonocytic cells has been found to control the transcription of the insulin receptor (IR) gene, resulting in heightened phosphatidylinositol 3-kinase (PI3K) activity and improved insulin-induced glucose oxidation and cellular transport — when PI3K interacts with the pleckstrin homology domain, leading to the phosphorylation of phosphoinositide-dependent protein kinase and increased insulin sensitivity. Deleting p110β in adipocytes (the catalytic site of PI3K) in an in vivo investigation resulted in adipose tissue insulin resistance, obesity, and hepatosteatosis, but this has not been confirmed in human studies on NAFLD or MAFLD [70–72]. Liver steatosis can result in hepatofibrosis — in an animal study conducted by Wahsh et al., the administration of a VDR agonist (calcipotriol) was found to impact fibrogenic pathways and mitigate liver fibrosis by decreasing the levels of hepatic collagen-1-alpha-1, tissue inhibitor of metalloproteinase (TIMP), and TGF-β1 protein, as well as the activity of the TGF-β-SMAD pathway, which is a significant fibrogenic mechanism in the liver [73].

Some studies did not establish a clear connection between vitamin D levels and did not find any positive impact of vitamin D supplementation on

the progression of fatty liver disease — differences in research findings can stem from multiple factors, but primarily from the diversity of the groups examined [74–76]. An interesting observation came from Patel et al., who showed that individuals with fatty liver disease exhibit a lighter skin tone, which is essential in the skin's photochemical synthesis of vitamin D [74]. Genetic variations may also have a significant impact — VDR polymorphisms (especially those very common in the general population like rs4588 and rs7041) may strongly impact the response to vitamin D treatment, affecting serum 25(OH)D levels and metabolic parameters [such as insulin resistance, glycated haemoglobin (HbA_{1c}), and lipid profile] [77–79].

Considering all the information provided, the potential connection between vitamin D and the formation of liver steatosis is plausible but needs more investigation. Although liver steatosis may not directly necessitate it, it is crucial to acknowledge that diabetes and obesity, which are part of the MAFLD diagnosis criteria and are also conditions associated with an increased risk of vitamin D insufficiency, require evaluation of 25(OH) D levels in the blood serum and administration of appropriate vitamin D doses in cases of deficiency [80].

Adrenal hormones and hepatosteatosis

Glucocorticosteroids (GCS) are synthesised in the zona fasciculata of the adrenal glands in response to ACTH secreted by the pituitary gland. Cortisol, the most significant hormone from GCS group, controls several processes to maintain metabolic balance and facilitate adjustment to stressful conditions — elevated GCS levels have been linked to the development of all aspects of metabolic syndrome, including obesity, hyperglycaemia, hypertension, dyslipidaemia, as well as liver steatosis. Hypercortisolaemia results in increased lipolysis of adipose tissue and catabolism of muscle proteins, which serve as materials for glucose generation in the liver, subsequently delivering glucose to the brain. Increased lipolysis in adipose tissue results in higher levels of glycerol and free fatty acids entering the bloodstream, which are subsequently taken up by the liver, causing elevated triglyceride production and hepatosteatosis. It is also worth remembering that GCS increases the production of triglycerides by regulating gene transcription, which turns carbohydrates into fatty acids through de novo lipogenesis [81, 82]. Although not all studies confirm this, the incidence of liver steatosis in disease linked with hypercortisolaemia (like Cushing's syndrome) is estimated to be more frequent than in the general population and ranges from 26% to 56% [83–85]; on the other hand, NAFLD/MAFLD patients exhibited subclinical hypercortisolaemia, elevated urine cortisol levels, and decreased cortisol suppression in response to dexamethasone [86, 87]. Steroidogenic enzymes are highly significant from a pathological perspective. GCS is synthesised by the action of 11β-hydroxysteroid-dehydrogenase-1 and -2 (11β-HSD1 and 11β-HSD2), which interconvert cortisone and cortisol — both of these enzymes are highly expressed in the liver, and abnormalities in their function may also play a role in liver structural disorders [9]. This is confirmed by studies based on animal models — transgenic mice with overexpressing 11β-HSD1 in adipocytes had higher GCS levels and rapidly exhibited metabolic syndrome symptoms (such as liver steatosis); conversely, mice with knockout 11β-HSD1 had lower GCS levels, decreased triglycerides, and enhanced hepatic insulin sensitivity, regardless of exogenous GCS administration [88–90]. It has been theorised that selective inhibition of 11β-HSD1 may be an effective therapy for fatty liver disease — Hoffmann-La Roche developed an experimental oral drug (RO5093151) that showed effectiveness and safety in reducing liver fat in patients with NAFLD during a phase 1b clinical trial, in which the average fat content decreased from 16.7% to 14.3% after 12 weeks of use; however, the current status of this treatment approach is unknown [91]. Other important enzymes in glucosteroidogenesis include 5α- and 5β-reductase, which enhance GCS clearance and restrict their availability in tissues (for example, by converting cortisol into inactive forms like tetrahydrometabolites or 5α-tetrahydrocortisol through alpha-ring metabolism) [82]. Once again, evidence for the importance of the action of these enzymes is provided by animal models — 5α-reductase knockout mice on a high-fat diet or rats treated with finasteride to inhibit 5α-reductase showed increased progression of hepatic steatosis [92, 93]. An increase in hepatic cortisol clearance by 5α-reductases is believed to be a protective mechanism that helps maintain the liver's metabolic function by reducing exposure to cortisol and preventing harmful effects caused by glucocorticoids, such as hepatic lipogenesis and gluconeogenesis with increased glucose output, which worsen hepatic and peripheral insulin resistance. Interestingly, however, in human studies, hepatic glucocorticosteroid regulation changes as steatosis progresses to steatohepatitis. In simple steatosis, 5α-reductase levels rise and 11β-HSD1 levels drop, resulting in decreased hepatic cortisol levels — however, in hepatitis, 5α-reductase levels decrease and 11β-HSD1 levels increase (particularly in CD68-positive macrophages in liver, indicating potential involvement of 11β-HSD1 in the response to chronic inflammation), leading to elevated hepatic cortisol levels [9, 94]. Considering the majority of research findings and the clear association between high levels of cortisol and the develop-

ment of features of metabolic syndrome, it is highly likely that there is a strong connection between excessive GCS secretion and MAFLD, which practicing physicians should be aware of.

Mineralocorticosteroids (MCS) are hormones synthesised by the outermost region of the adrenal cortex, known as the zona glomerulosa. The primary representative of MCS is aldosterone, whose synthesis and secretion are controlled by the renin-angiotensin-aldosterone system (RAAS). MCS is essential for regulating adequate levels of sodium and potassium, as well as the proper volume of extracellular fluids. RAAS may also play a role in the development of insulin resistance, hepatosteatosis, and hepatofibrosis, possibly due to the influence of aldosterone and angiotensin II, which, through the nucleotide-binding oligomerisation domain-like receptor family pyrin domain-containing 3 inflammatory vesicle-associated pathways, can stimulate hepatic stellate cells, promoting their differentiation into myofibroblasts and the accumulation of collagen and protein in the extracellular matrix; another possible mechanism for RAAS-dependent insulin resistance involves enhancing the degradation of the insulin receptor substrates IRS-1 and IRS-2 through a process mediated by reactive oxygen species and boosting the mRNA expression of enzymes involved in glycogen synthesis [82, 95–99]. Several human studies have shown a connection between aldosterone and fatty liver disease. The Jackson Hearth Study demonstrated that each doubling of aldosterone was correlated with a 1.08 Hounsfield unit reduction in computed tomography scan, which was equivalent to a significant link with liver steatosis [100]. The study by Hu et al. revealed that the risk of fatty liver disease rose 1.04- and 1.24-fold for every 1 ng/dL and 5 ng/dL rise in plasma aldosterone concentration; moreover, they observed a substantial increase in the risk of developing new-onset NAFLD when aldosterone levels were ≥ 13 ng/dL [97]. Zhejiang University researchers also discovered a greater occurrence of hepatic steatosis in primary hyperaldosteronism; however, they also observed that individuals with hypokalaemia had a much worse metabolic status compared to patients with normokalaemia, confirming findings from Italian scientists a decade earlier [101, 102]. The effects were also noticed in patients who apply RAAS blocking medications, such as for the treatment of hormone-independent arterial hypertension — the use of eplerenone, finerenone, spironolactone, losartan, or telmisartan (which suppresses the activity of RAAS) had a beneficial effect on hepatic steatosis, inflammation, and fibrosis in several studies [103–108]. Telmisartan is noteworthy for its dual action of blocking the angiotensin II receptor and acting as a selective PPAR modulator, which leads to therapeutic advantages by modulating PPAR in lipid and glucose metabolism without the adverse effects seen with traditional PPAR activators, such as fluid retention, weight gain, or swelling [109]. A randomised controlled trial involving 23 patients with MAFLD showed that those treated with spironolactone and vitamin E experienced improvements in steatosis and insulin resistance compared to those treated with vitamin E alone [110]. A territory-wide cohort research from China demonstrated that treatment with angiotensin-converting enzyme inhibitors is linked to a reduced risk of liver-related events in patients with NAFLD, defined as a composite endpoint of liver cancer and cirrhosis complications. Research findings and our understanding of pathophysiology suggest that aldosterone, particularly primary hyperaldosteronism, significantly influences the onset and advancement of hepatic steatosis and its associated consequences; however, we must also consider the additional effects of disorders that are associated with or caused by elevated levels of aldosterone.

Androgens are also significant hormones that the adrenal cortex secretes in the context of MAFLD. Dehydroepiandrosterone (DHEA) and its sulphated form, DHEAS, are the primary adrenal androgens studied in relation to the development of MAFLD. DHEA and DHEAS play crucial roles in oxidative stress, insulin sensitivity, lipid metabolism, and collagen formation — the beneficial effect of DHEA and DHEAS on the features of metabolic syndromes such as diabetes, obesity, atherosclerosis, and others, may also have consequences for the development of MAFLD [9, 111]. DHEA has been shown to protect against fatty liver disease by enhancing insulin sensitivity (through the activation of peroxisome proliferator-activated receptor alpha), protecting hepatocytes from damage caused by oxidative stress (by reducing malondialdehyde levels, enhancing superoxide dismutase activity, and increasing glutathione levels) and inflammation (due to the limitation of the activity of tumour necrosis factor alpha, IL-1, IL-6, and IL-10) — additionally, DHEA inhibits the production of procollagen type 1, a precursor to collagen associated with hepatofibrosis development [112–115]. Moreover, DHEA suppresses the activity of 11β-HSD1 in adipose tissue, leading to decreased cortisol production locally, which has a protective effect against the development of metabolic syndrome symptoms, as discussed in the section on GCS [9, 116, 117]. Importantly, however, human studies in this aspect are contradictory; some indicate a significant link between low levels of DHEA and DHEAS and fatty liver disease, particularly in its severe stages like steatohepatitis, hepatofibrosis, and cirrhosis [118–122] — conversely, other studies suggest that elevated levels of androgens are connected to hepatosteatosis [123–125]. A meta-analysis by Zhang

et al. revealed that DHEA levels were linked to hepatosteatosis in the basic model, but this association disappeared after adjusting for cardiometabolic risk factors — for women, there was no connection found between DHEA or DHEAS and NAFLD in any of the models [126]. Therefore, the possibility that the effect of DHEA and DHEAS concentrations on liver steatosis and fibrosis, despite the highly probable pathophysiological premises mentioned above, overlaps with the effect of other metabolic disorders of cardiovascular importance becomes justified. The authors of the meta-analysis noted that the limited number of studies in this field may lead to more definitive results in the future.

When examining the involvement of adrenal glands in hepatosteatosis development, it is important to also take into account the potential influence of catecholamines produced by both the chromaffin cells of the adrenal medulla and the postganglionic fibres of the sympathetic nervous system. MAFLD becomes more common as individuals age, marked by a rise in β-adrenergic receptor activity and resulting lipid accumulation in liver cells. Research using a mouse model demonstrated that the extended use of the β2-agonist formoterol leads to an increase in hepatic lipid content. Patients with metabolic syndrome show elevated liver triglycerides and lipid droplet contents due to heightened sympathetic activity from catecholamines, which is also associated with upregulated expression of genes related to fatty acid uptake (CD36) and de novo lipogenesis (DGAT1 and DGAT2) [127–132]. Sigala et al. demonstrated that human primary hepatic stellate cells rely on catecholamines for their survival and fibrogenic effects — they observed heightened regulation of the fibrogenic α/β-adrenergic receptor and neuropeptide Y receptors in patients with MAFLD, MASH, and cirrhosis, indicating the potential use of adrenoreceptor and neuropeptide Y antagonists in treating patients with MAFLD [133]. Adori et al. propose that persistent overstimulation of the sympathetic nervous system is a crucial element in the deterioration of liver tissue leading to hepatofibrosis. However, additional research is needed in this field. At this point, it seems justified to consider the influence of catecholamines on the development of MAFLD and MASH as potentially probable [134].

Liver steatosis, oestrogens, and androgens in women

Oestrogens in women play a protective role against hepatic fat accumulation and fibrosis by promoting lipolysis and reducing lipogenesis, mostly via boosting the phosphorylation of acetyl coenzyme-A carboxylase through a pathway mediated by oestrogen receptor α, which in turn reduces the production of reactive oxygen species and acts against inflammatory reactions [135–137]. Menopause is a physiological state of oestrogen deficiency in which, along with the duration of the deficiency of these sex hormones, the risk of development and progression of MAFLD increases significantly — it is advisable to consider both menopausal status and the age of the last menstrual period when evaluating the risk of hepatofibrosis in women with MAFLD [138–140]. Oestrogen deficiency after oophorectomy results in higher liver fat accumulation and the development of insulin resistance - oestrogen therapy, like in menopause, can help restore the correct phenotype and decrease intrahepatic triglyceride levels [141–145]. On the other hand, in a comprehensive study of women with MAFLD features, the use of contraceptives in pre-menopausal women and hormone replacement therapy in post-menopausal women was associated with a higher risk of severe lobular inflammation, regardless of age, body mass index, and insulin resistance; however, further analysis revealed that the risk of severe lobular inflammation was specifically linked to progesterone, not oestrogen [146]. Female patients with breast cancer undergoing tamoxifen and toremifene treatment (selective oestrogen receptor modulators: SERM, which act antiestrogenically) exhibited a greater incidence of excessive intraabdominal fat accumulation and MAFLD, independently of body mass index [147–150]. Fortunately, although these medicines have many severe negative effects, the progression of MAFLD to MASH and cirrhosis is rarely seen [148, 151, 152].

Elevated androgen levels in women can lead to an increased risk of hepatosteatosis by negatively impacting lipid metabolism, insulin sensitivity, and the expansion of visceral fat tissue. Androgens can lead to hepatosteatosis by prolonging the half-life of low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) through inhibiting LDL-receptor expression — compared to PCOS women with normal androgen levels, those with elevated androgens exhibited higher levels of LDL, triglycerides, and values for the HOMA-IR [153, 154]. Testosterone (specifically in women) also can enhance the expression of genes that influence de novo lipogenesis in human liver cells. It has also been noticed that hyperandrogenism in women negatively impacts angiogenesis in ovarian tissue, perhaps exacerbating preexisting polycystic ovary syndrome (PCOS) [155] — interestingly, Kumarendran et al. discovered that serum testosterone levels > 3.0 nmol/L were associated with a higher risk of NAFLD in women with PCOS [156]. We mention PCOS because this is an androgen-dependent disease that is considered the most common cause of anovulatory infertility and a risk factor for cardiometabolic

complications — women with this condition experience various symptoms, including additional metabolic (dyslipidaemia, hypertension, obesity, hyperinsulinaemia, and insulin resistance) and psychological issues. In their 2023 meta-analysis, Yao et al. definitively showed that women with PCOS had a 2.6–3.0 times greater likelihood of acquiring liver steatosis linked to metabolic dysfunctions [157].

Hyperandrogenaemia (with PCOS as the main representative, in its classic or ovulatory phenotype) and hypogonadism in women are closely linked to an increased risk of developing MAFLD, primarily because of concomitant insulin resistance features. It is justified to actively monitor these individuals using abdominal ultrasound to confirm or exclude hepatosteatosis and to pay particular attention to serum liver enzymes in laboratory data.

Liver steatosis and sex hormones in males

Regarding men, the impact of sex hormones on liver health appears to be inversely related compared to women, according to obviously another gender-specific definition of hypogonadism – men with low levels of androgens and high levels of oestrogens displayed signs of fatty liver disease. Research using an animal model showed that knockout of the 5α-reductase type 1 receptor and the androgen receptor combined with a high-fat diet leads to the development of hepatosteatosis and carbohydrate metabolism disorders, and accelerates body weight gain — male mice exhibited reduced testicular volume, decreased testosterone levels, and compromised reproductive function [93, 158, 159]. Testosterone deficiency can contribute to insulin resistance and triglyceride accumulation in the liver; this effect can be reversed by reducing hepatic lipogenesis, increasing the oxidation of fatty acids and their export from the liver, suppressing inflammatory processes within the liver, and influencing the expression of genes involved in glucolipid metabolism through epigenetic mechanisms [160–164]. Treating orchidectomised rats with dihydrotestosterone reduced lipid accumulation and cholesterol synthesis in the liver by upregulating carnitine palmitotyltransferase1 expression and 3-hydroxy-3-methyl-glutarylCoA reductase phosphorylation through an androgen receptor-mediated pathway [135]. Analysing available human studies, it was observed that a study by Barbonetti et al. revealed a correlation between total and free testosterone levels and the likelihood of having MAFLD — the risk increased by 3% for every 1 pg/mL fall in free testosterone concentration [165]. A study involving more than 380,000 individuals with proven prostate cancer found that older men on antiandrogen therapy were at a higher risk of being diagnosed with various liver illnesses such as hepatosteatosis, hepatofibrosis, and cirrhosis [125]. Patients diagnosed with hypogonadism, who received hormonal treatment with testosterone undecanoate for one year, experienced a notable decrease in visceral fat volume and saw improvements in inflammatory marker levels [166]. Obviously, we must remember about the bidirectional relationship between metabolic syndrome and androgens because decreased testosterone and its byproducts may be intimately linked and secondary to obesity or glucose-lipid disorders, and not necessarily the other way around — for example, imbalanced leptin levels associated with obesity lead to elevated oestrogen levels, which subsequently enhance aromatase activity, which in turn reciprocally suppresses testosterone levels and the hypothalamic-pituitary-gonadal axis (in such a situation, the targeted first-line treatment should be focused on obesity, not hypogonadism) [167–169]. One such possibility is, in addition to changing the lifestyle of an obese patient, implementing treatment with GLP-1 analogues (for example, semaglutide in a dose appropriate to the clinical situation), in which the possibility of improving androgen levels while maintaining high safety of therapy has been confirmed [170].

The interpenetration of the features of the metabolic syndrome and hypogonadism in men should not prompt a revision of the guidelines for androgen replacement treatment in males based merely on the detection of MAFLD. It is not recommended that screening tests be performed for hypogonadism in men in the case of a recent diagnosis of MAFLD without other accompanying clinical symptoms (like fatigue, decreased libido, depressed mood [9]); however, in patients already diagnosed with hypogonadism, regardless of its cause, it is appropriate to perform ultrasound assessment of the liver and laboratory tests of liver enzymes to confirm or rule out the diagnosis of MAFLD.

Diagnosis, monitoring, and treatment of MAFLD

The diagnosis of MAFLD is based on the presence of hepatosteatosis, as previously discussed and illustrated in Figure 1. An abdominal ultrasound is the most accessible diagnostic for assessing liver health (a typical image of hepatosteatosis is bright liver echotexture and blurring of the hepatic vasculature), although it has low sensitivity when steatosis affects < 25–30% of hepatocytes [171]. A more sensitive metric is the controlled attenuation parameter (CAP) performed during transient elastography, which allows the assessment of steatosis even when lipid droplets are present within 5% of the liver tissue — the drawback of this technology

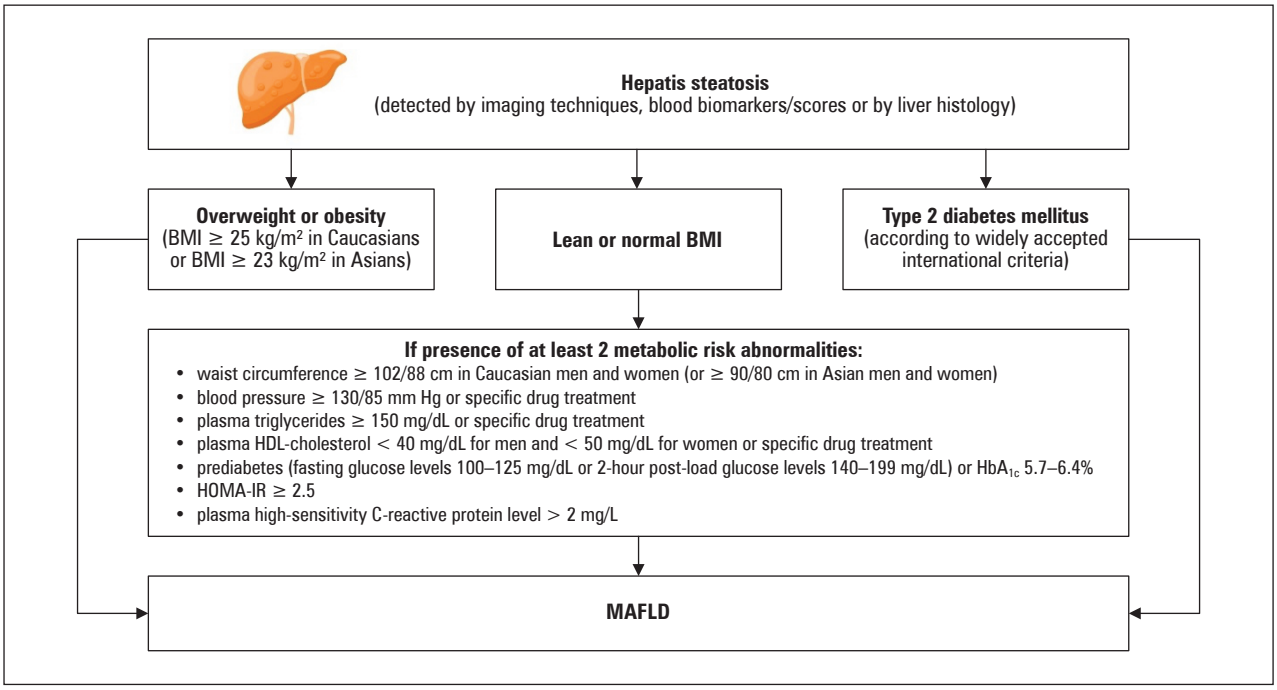

Figure 1. *Diagnostic criteria for metabolic-associated fatty liver disease (MAFLD). BMI — body mass index; HDL — high-density lipoprotein; HbA1c — glycated haemoglobin; HOMA-IR — homeostasis model assessment of insulin resistance;*

is its restricted availability [172]. If elastography is unavailable, ultrasonography is the preferred imaging tool for screening for fatty liver due to its low cost, safety, and accessibility in clinical and population settings. It is challenging to determine the speed at which fatty liver disease can develop due to the intricate nature of our metabolism, making it a multifactorial process that occurs gradually over time. Song et al. demonstrated in an animal model that expression of genes involved in de novo lipogenesis and the subsequent development of hepatosteatosis lasted from 22 to 38 weeks [173]. While not directly applicable to a human model, this suggestion remains important in indicating the frequency of monitoring liver steatosis progression and related repercussions. MAFLD encompasses of progressive stages of liver disease, beginning with simple steatosis and progressing through MASH, fibrosis, cirrhosis, and hepatocellular carcinoma. Danish researchers determined that the median time for fatty liver rearrangement in MASH and hepatofibrosis (and possible further stages) is 25 months, but according to long-term follow-up studies, progression usually takes 8 to 13 years [174–177]. The gold standard for diagnosing hepatofibrosis is a core needle biopsy of the liver, which is invasive. Due to the common occurrence of MAFLD, non-invasive indicators are typically utilised for screening liver fibrosis. Table 1 displays the most frequently used non-invasive hepatofibrosis markers in clinical practice [178–185]. As to the guidelines of the American Association for the Study of Liver Diseases (AASLD), it is recommended that all patients with hepatic steatosis or suspected MAFLD undergo primary risk assessment (in the opinion of the AASLD, the preferred method for this evaluation is FIB-4) — it is suggested to reassess the liver fibrosis risk every 1–2 years [181, 186]. The authors of this manuscript have analysed available guidelines and information and have formulated their own recommendations regarding the monitoring of liver steatosis and fibrosis development in endocrine disorders (categorised into diseases with a possible, strong, and clearly related relationship with the development of MAFLD), which are presented in Table 2. While additional confirmation is necessary, we believe that these findings offer a solid foundation for easily integrating suitable habits into routine clinical practice.

Treatment of MAFLD is a complex issue. Besides offering therapy for the cause, it is imperative to uphold a nutritious and balanced diet as well as engage in regular physical activity, because these factors greatly contribute to improving cardiometabolic health. An effective nutritional intervention can be seen in the implementation of the Mediterranean diet, which improves metabolic state due to its influence on insulin resistance [187–190]. On the other hand, some scientific groups state that there is insufficient evidence to endorse any particular dietary intervention, as long as the meals are properly balanced in terms of micro- and macronutrients [191]. There is evidence indicating

Table 1. *The most frequently used non-invasive hepatofibrosis markers in clinical practice*

Non-invasive serum test	Formula or components of test
APRI [178]	100 × (AST [U/L]/upper limit of normal AST)/platelet count [10^9/L]
BARD [179]	Weighted sum of: BMI ≥ 28 = 1 point; AST/ALT ≥ 0.8 = 2 points; presence of diabetes = 1 point
FIB-4 [181]	(age [years] × AST [U/L])/(platelet count [10^9/L [× $ALT^{1/2}$)
NFS [182]	−1.675 + 0.037 × age [years] + 0.094 × BMI [kg/m^2] + 1.13 × IFG/diabetes [yes = 1, no = 0] + 0.99 × AST/ALT ratio − 0.013 × platelet [×10^9/L] − 0.66 × albumin [g/dL]
Fibrometer NAFLD [184]	0.4184 glucose [mmol/L] + 0.0701 AST [U/L] + 0.0008 ferritin [ug/L] − 0.0102 platelet [10^9/L] 0.0260 ALT [U/L] + 0.0459 body weight [kg] + 0.0842 age [years] + 11.6226
ELF [183]	Age, hyaluronic acid, amino-terminal propeptide of type III collagen, tissue inhibitor of metalloproteinase 1
LFRI [185]	Age, hyaluronic acid, amino-terminal propeptide of type III collagen, collagen type IV, laminin

AST — aspartate transaminase; BMI — body mass index; ALT — alanine aminotransferase; IFG — impaired fasting glucose

Table 2. *Authors' recommendations about monitoring liver steatosis and fibrosis development in the course of endocrine disorders*

Endocrine disorders possibly related to the etiopathogenesis of liver steatosis	Acromegaly Hyper- and hypoprolactinemia Pheochromocytoma/paraganglioma Vitamin D deficiency	The authors suggest periodic ultrasound abdominal examinations (or transient elastography) and assessing the risk of hepatofibrosis (with the use of non-invasive markers) during the care of patients with endocrine disorders possible related to the aetiopathogenesis of liver steatosis, especially: • after diagnosis; • when any signs of metabolic syndrome are present.
Endocrine disorders with a potentially strong relationship with the etiopathogenesis of liver steatosis	GH deficiency Hypothyroidism Hypercortisolaemia Primary hyperaldosteronism Hypogonadism PCOS	The authors suggest periodic ultrasound abdominal examinations (or transient elastography) and assessing the risk of hepatofibrosis (with the use of non-invasive markers) during the care of patients with endocrine disorders with a potentially strong relationship with the etiopathogenesis of liver steatosis, especially: • after diagnosis; • when any signs of metabolic syndrome are present; • at least once every 2 years, if no troubling symptoms are present.
Endocrine disorders clearly related to the etiopathogenesis of liver steatosis	Overweight and obesity Type 2 diabetes mellitus and prediabetes states	The authors suggest periodic ultrasound abdominal examinations (or transient elastography) and assessing the risk of hepatofibrosis (with the use of non-invasive markers) during the care of patients with endocrine disorders clearly related to the etiopathogenesis of liver steatosis (constituting the criteria for MAFLD diagnosis), especially: • after diagnosis • at least once every year, if no troubling symptoms or any other signs of metabolic syndrome are present.

GH — growth hormone; PCOS — polycystic ovary syndrome; MAFLD — metabolic-associated fatty liver disease

that nutritional intervention may have greater effects in patients with specific genetic polymorphisms (especially PNPLA3-rs738409) [192, 193]. Physical activity is an equally important element of MAFLD therapy — it is recommended to engage in regular exercise at a moderate intensity, at least 5 times a week, for a total of 150 minutes per week, or increase their activity level by more than 60 minutes per week compared to the previous week - this is important in order to prevent the development of liver steatosis and its associated complications related to the fibrosis process [186, 194–196]. In terms of pharmacotherapy, currently no drugs have been officially approved for the treatment of MAFLD or MASH. However, based on the understanding of the underlying mechanisms of these disorders, the literature often suggests co-treatment options such as vitamin E, pioglitazone, GLP-1 analogues (liraglutide, semaglutide), SGLT-2 inhibitors, or dual GLP-1/GIP agonists (tirzepatide) [186]. Additional observations and study findings are unquestionably required, especially in groups of patients with the above-mentioned endocrine diseases.

Conclusions

Given the high incidence of fatty liver disease in the population of patients with endocrine disorders, it is imperative to comprehend its aetiology to offer improved management for these patients. This concise overview emphasises the strong possible connections

between hormones and MAFLD, specifically focusing on growth hormone deficiency, hypothyroidism, hypercortisolaemia, primary hyperaldosteronism, and hypogonadism. The authors also proposed simple recommendations for monitoring individuals with particular endocrine disorders to detect the potential development of hepatosteatosis and hepatofibrosis. MAFLD is a complex metabolic disease, and although its pathogenesis and pathophysiology still raise doubts and generate questions, it is important to keep this condition in mind during routine clinical practice, particularly in the field of endocrinology.

Author contributions

Both authors of the paper were equally involved in its preparation, including the literature review.

Funding

The article was funded by the Department of Endocrinology and Diabetology (Nicolaus Copernicus University, Collegium Medicum) using statutory funding.

Acknowledgments

None.

Conflict of interest

All authors certify that they have no affiliations with or involvement in any organisation or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript

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