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REVIEW ARTICLE

Endocrine aspects beyond insulin resistance in metabolic dysfunction associated steatotic liver disease

José R. Barrientos-Ávalos[1,2], Brenda E. Vidrio-Huerta[1], and Sonia I. Dávila-Casas[1]*

[1]Department of Medical Clinics, Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara; [2]Endocrinology Service, Hospital Civil de Guadalajara Fray Antonio Alcalde. Guadalajara, Jalisco. Mexico

Abstract

The description of endocrine systems involved in the pathophysiology of metabolic dysfunction-associated steatotic liver disease (MASLD) has been essential to achieve a holistic understanding of all mechanisms contributing to hepatic injury. In this review, we approach these mechanisms from a different perspective, analyzing how they exert deleterious effects to varying degrees. Growth hormone plays a protective role, as supported by evidence, and its deficiency states are associated with hepatic fat accumulation. Regarding thyroid hormones and their hepatic function, we describe their mechanisms and how they contribute to maintaining metabolic health; conversely, their deficiency is consistently linked to the development of MASLD. Glucocorticoids, particularly in the context of excessive exogenous administration, have been widely demonstrated to induce not only hepatic metabolic dysfunction but also systemic alterations across multiple axes. Given their relevance, we also address mineralocorticoids, which, although less studied, exhibit specific roles in metabolic regulation. Similarly, prolactin is discussed for its involvement in insulin resistance. Finally, we examine sex hormones, whose systemic reduction directly impacts fatty acid metabolism within hepatocytes.

Keywords: Metabolic dysfunction associated steatotic liver disease. MASLD. Thyroid hormones. Growth hormone. Glucocorticoids. Sex steroids.

Aspectos endocrinológicos más allá de la resistencia a la insulina en la enfermedad hepática esteatósica asociada a disfunción metabólica

Resumen

La descripción de los sistemas endocrinos que desempeñan un papel en la fisiopatología de la enfermedad hepática esteatósica asociada a disfunción metabólica (MASLD, Metabolic dysfunction-Associated Steatotic Liver Disease) ha sido importante para comprender de manera holística todos los sistemas que contribuyen al daño hepático. En esta revisión abordamos estos mecanismos desde una perspectiva diferente, analizando cómo ejercen efectos deletéreos en diferentes grados. La hormona del crecimiento desempeña un papel protector, como respalda la evidencia, y sus estados de deficiencia están asociados con la acumulación de grasa hepática. Respecto a las hormonas tiroideas y su función hepática, describimos sus mecanismos y cómo contribuyen a mantener una buena salud metabólica; por el contrario, su deficiencia está consistentemente relacionada con el desarrollo de MASLD. Se ha demostrado ampliamente que los glucocorticoides, en particular con una administración exógena excesiva, inducen no solo disfunción metabólica hepática, sino también alteraciones sistémicas

***Correspondence:**
Brenda E. Vidrio-Huerta
E-mail: dra.brenda.vidrio@gmail.com

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en diversos ejes. Dada su relevancia, también abordamos los mineralocorticoides, menos estudiados, que tienen funciones específicas en la regulación metabólica. También se analiza la prolactina por su participación en la resistencia a la insulina. Finalmente, examinamos las hormonas sexuales, cuya disminución sistémica impacta de forma directa en el metabolismo de los ácidos grasos en los hepatocitos.

Palabras clave: Enfermedad hepática esteatósica asociada a disfunción metabólica. MASLD. Hormonas tiroideas. Hormona de crecimiento. Glucocorticoides. Esteroides sexuales.

Introduction

Over time, since hepatic damage caused by overweight and obesity has been recognized, the rapid development of knowledge for possible therapeutics has acknowledged that insulin resistance is the most compelling factor for the development and progression of metabolic dysfunction-associated steatotic liver disease (MASLD). However, it is not the only one, as we will explain below, there are other endocrine axes that contribute at multiple stages of disease development and provide generally deleterious specific effects, which is why they have been the subject of study and certainly of therapeutic development to improve patient prognosis.

Growth hormone

Growth hormone (GH) is a polypeptide secreted by the somatotropic cells of the anterior pituitary gland, through stimuli such as α-adrenergics, ghrelin, thyroid hormones, deep sleep, fasting, stress, and hypoglycemia, among others[1]. GH exerts its actions through the activation of receptors located in various tissues, primarily hepatic tissue. Intracellular signal transmission through its cytokine receptors triggers a phosphorylation cascade through the JAK-STAT pathway. The activation of JAK2 tyrosine kinase promotes the phosphorylation of intracellular molecules, such as STAT1, 3, and 5; indispensable components for the production of insulin-like growth factor 1 (IGF-1).

The main metabolic actions of GH/IGF-1 with direct impact on hepatic tissue involve increased lipolysis (predominantly of visceral fat) and β-oxidation of fatty acids, causing their mobilization into circulation. Additionally, they suppress hepatic *de novo* lipogenesis. These effects, in sum, result in lower intrahepatic lipid accumulation[2]. Furthermore, the most recent evidence has demonstrated that activation of the GH/IGF-1 axis could induce senescence of hepatic stellate cells, control inflammation, and reduce hepatic fibrosis[3,4].

On the other hand, GH deficiency has been linked to increased hepatic fat accumulation and greater risk of MASLD. Various cross-sectional studies have demonstrated a higher prevalence of MASLD in adult patients with hypopituitarism and severe GH deficiency secondary to resections of tumors such as pituitary adenomas and craniopharyngiomas, compared to patients without such deficiency[5-7]. One of the most recent studies of postsurgical patients following transsphenoidal resection for pituitary tumor reported a prevalence of MASLD of 36.9% in those with central GH deficiency, compared to 21.1% in those without hormone deficiency ($p = 0.01$), being twice as high in patients with deficiency after adjustment for confounding variables[8]. In contrast, patients with acromegaly present lower hepatic steatosis despite having greater insulin resistance[9], which increases after surgical control of the disease[10], suggesting a potential protective effect of GH/IGF-1 on hepatic steatosis, probably due to increased adenosine triphosphate synthesis stimulated by GH[11].

Some other conditions in which the role of the GH/IGF-1 axis in the appearance and progression of MASLD has been demonstrated are those associated with relative GH deficiency. For their part, overweight and obesity are factors related to a state of relative GH deficiency[12], which, together with the already well-established insulin resistance, could be considered an additional predisposing factor for the progression of hepatic steatosis. Another condition in which relative GH deficiency has been associated with hepatic fat accumulation is human immunodeficiency virus (HIV) infection, especially in patients with lipodystrophy[13], and in whom, additionally, due to antiretroviral treatment, greater weight gain occurs with increased abdominal fat and visceral fat accumulation, all of which are factors associated with higher prevalence of MASLD[14].

Effect of GH dysregulation treatment on MASLD

There are various potential mechanisms of GH therapy for the reduction of steatosis and the progression of MASLD. The increase in resting energy expenditure

would prevent hepatic fat accumulation, which could be regulated by the conversion of thyroxine (T4) to triiodothyronine (T3) influenced by the effect of GH. The mobilization and utilization of substrates favored by GH would reduce their intrahepatic accumulation. Furthermore, its central effect on energy expenditure regulation and heat production would promote increased carbohydrate utilization and improve insulin sensitivity[15].

GH replacement at standard doses in patients with deficiency due to hypopituitarism has demonstrated improved hepatic function, as well as reduced steatosis and fibrosis, both in case reports[16,17] and in clinical trials[6,18]. However, the effect of GH replacement in patients with relative deficiency has been evaluated in a limited way. A randomized trial that included patients with obesity and MASLD assessed hepatic fat fraction after administration of recombinant GH for 24 weeks, and found a reduction of −3.3% of intrahepatic fat in the treated group ($p = 0.14$), achieving hepatic fat fraction < 5% in 5 of 9 patients, compared to 1 of 9 untreated patients ($p = 0.04$)[19]. Similarly, Dichtel et al.[20] demonstrated a reduction of −8.9% ($p = 0.009$) in hepatic steatosis in individuals with overweight or obesity and MASLD after administration of subcutaneous GH for 6 months.

On the other hand, the effect of GH in patients with HIV and MASLD has been tested through the administration of tesamorelin, an analog of growth hormone-releasing hormone. After 12 months of treatment, it was observed that 35% of patients treated with the drug showed hepatic fat fraction < 5%, compared to 4% of the control group, without negatively affecting fasting glucose levels or glycosylated hemoglobin[21]. Similar results have been replicated with the use of tesamorelin in populations with the same characteristics[22], and it has even been demonstrated that this drug reduces the expression of genes related to inflammation, tissue repair, and cell division, and increases the expression of genes related to oxidative phosphorylation[23].

Suggested changes to metabolic dysfunction-associated steatohepatitis (MASH) therapy based on GH dysregulation

Although GH therapy may have beneficial effects in reducing hepatic steatosis, there is no related evidence for the management of steatohepatitis, so it should only be considered as part of management in patients with established chronic GH deficiency and not as part of systematic MASH treatment. Additionally, it is suggested to investigate GH deficiency in patients presenting poor control or progression of MASH, as an aggravating factor, to initiate hormonal replacement if deficiency is confirmed[24].

Thyroid hormones

The functional interaction of the thyroid gland and liver constitutes a dynamic and complex metabolic axis. Thyroid hormones, primarily T3 and T4, regulate hepatic metabolism of carbohydrates, proteins, and lipids[25]. The liver modulates the systemic bioavailability of thyroid hormones through the synthesis of transport proteins (thyroxine-binding globulin, transthyretin, and albumin)[24] and peripheral conversion of T4 to T3 by type 1 deiodinase, which is most abundant in the liver, being an important pathway for maintaining adequate plasma and tissue levels of T3[26].

For their part, thyroid hormones regulate hepatic lipid homeostasis through β-oxidation of fatty acids by activating the thyroid hormone receptor β (TRβ), which is the predominantly expressed form in the liver; its activation also increases cholesterol uptake and catabolism, as well as selective autophagy to prevent lipotoxicity[26]. Autophagy is a lysosomal process of cellular degradation that can adopt specific forms: lipophagy (degradation of fat droplets), mitophagy (mitochondrial turnover), and aggrephagy (elimination of protein aggregates)[27]. Autophagy by thyroid hormones is carried out through genomic and non-genomic mechanisms, mediated by TRβ, and through the activation of transcription factors, such as estrogen-related receptor α (ESRRA), Forkhead box protein O1 (FoxO1), and transcription factor EB (TFEB)[25,27].

In hypothyroidism, atherogenic dyslipidemia can develop through mechanisms that include increased cholesterol absorption in the small intestine and liver by Niemann-Pick C1-like 1 protein, decreased expression of low-density lipoprotein cholesterol (LDL-C) receptors and increased circulating apoB lipoproteins, reduced plasma cholesteryl ester transfer proteins, and decreased reverse cholesterol transport and bile acid synthesis to reduce hepatic cholesterol clearance[28].

Hypothyroidism also generates mitochondrial dysfunction, oxidative stress, and reactive oxygen species production, with excessive accumulation of fatty acids in hepatocytes[26]. When this mitochondrial dysfunction causes progression to MASLD, hepatic type 1 deiodinase activity is decreased, producing lower local conversion of T4 to T3 and reduced TRβ signaling, exacerbating lipotoxicity and fibrosis, generating

"intrahepatic hypothyroidism" and thus creating a hepatic vicious circle between decreased hepatic thyroid hormone concentrations and MASLD[29,30].

In hyperthyroidism, contrary effects predominate due to increased general metabolic rate: increased lipid catabolism, stimulation of gluconeogenesis and glycogenolysis, and hepatic insulin resistance. Severe thyrotoxicosis can frequently cause alterations in liver function tests and induce hepatotoxicity through mitochondrial oxidative stress; however, these alterations usually resolve with treatment[31].

Effect of thyroid dysregulation treatment on MASLD

Evaluation of thyroid function in patients with MASLD is fundamental, and vice versa, because thyroid dysfunction can act as an etiopathogenic factor and modulator of disease progression.

Elevated thyroid-stimulating hormone, even with normal free T4 levels, is significantly associated with higher prevalence and severity of MASLD, and this relationship appears to be bidirectional[29,32].

There are some interventions aimed at correcting thyroid dysfunction that have shown improvement in MASLD. Treatment with levothyroxine reduces total cholesterol and LDL-C, and increases hepatic lipase activity, thereby improving the lipid profile and insulin sensitivity[29], and decreases intrahepatic fat accumulation[24].

Treatment with T3 reduces lipids and hepatic fat but causes tachycardia, bone loss, and muscle atrophy by activation, as it activates both TRα (expressed in the cardiovascular and musculoskeletal systems) and TRβ (expressed primarily in the liver) thyroid receptors[33,34].

Therapeutic implications of thyroid hormones in MASLD

Seeking the beneficial effects of T3 activity in the liver, without having other extrahepatic adverse effects, molecules that were selective TRβ1 agonists began to be studied, which has become an important target in the treatment of MASLD based on thyroid hormones[30,32].

Resmetirom is an oral agonist 28 times more selective for TRβ than for TRα[10]. It is the first and only drug approved by the Food and Drug Administration to treat MASH with hepatic fibrosis. In the MAESTRO-NASH trial, complete resolution of MASH without any worsening in fibrosis was observed in 25.9% of patients who received 80 mg of resmetirom and in 29.9% of those who received 100 mg of resmetirom, compared to 9.7% of patients in the placebo group. Additionally, improvement in fibrosis by at least one stage was also observed in 24.2% of patients who received 80 mg of resmetirom and in 25.9% of those who received 100 mg of resmetirom, compared to 14.3% in the placebo group. Likewise, improvement in lipid profile and insulin sensitivity was found[35].

The American Association of Diabetes recognizes the benefits of resmetirom in reducing hepatic fat, fibrosis progression, and LDL-C levels, which may help reduce cardiovascular risk[36].

The safety profile has been favorable, with mild adverse effects such as diarrhea and nausea; however, the need persists to confirm the durability of response beyond the first year of treatment, and to evaluate its efficacy in more advanced stages of fibrosis or compensated cirrhosis[37].

There are other thyromimetics under study, such as VK2809, which has demonstrated a reduction in hepatic fat between 53.8% and 59.7% in 12 weeks, being generally well tolerated[28]. TG 68 is a selective TRβ that reduces serum triglycerides by up to 30%, induces mitochondrial β-oxidation of fatty acids, and decreases hepatic fat without showing cardiotoxic effects in animals[33]. MB07811 is a prodrug with HepDirect technology that reduces triglycerides and improves insulin sensitivity in animal models. KB-141 has shown high metabolic potency without tachycardia in primates, and other compounds in preclinical stage, such as CS27109 and CS271011, present promising profiles and, in some cases, hepatic antineoplastic potential[37].

Glucocorticoids

The contribution of glucocorticoids in the development of metabolic complications has been extensively described, especially in diseases such as diabetes, hypertension, dyslipidemias, and cardiovascular diseases. Because MASLD is closely linked to these diseases, it is not surprising that glucocorticoids impact the development, progression, and outcome of MASLD. The molecular mechanisms that explain their role in the pathophysiology of MASLD are described below.

Activation of the glucocorticoid receptor (GR) in the hepatocyte represents a key pathogenic axis in MASLD progression. This process begins with cortisol secretion by the zona fasciculata of the adrenal cortex in response to adrenocorticotropic hormone released by the anterior pituitary gland. Although circulating cortisol has systemic effects, its most deleterious action in the

liver is intracellular, where the enzyme 11β-hydroxysteroid dehydrogenase type 1 converts inactive cortisone into active cortisol, amplifying its local effect[38].

Once inside the cell, cortisol binds to the cytoplasmic GR, inducing its translocation to the nucleus and binding to glucocorticoid response elements in DNA. This interaction regulates the transcription of key genes, such as phosphoenolpyruvate carboxykinase (*PEPCK*) and glucose-6-phosphatase (*G6Pase*), which increase hepatic gluconeogenesis, and lipogenic genes such as sterol regulatory element-binding protein 1c (*SREBP-1c*), fatty acid synthase (*FASN*), and acetyl-CoA carboxylase (*ACC*), which promote *de novo* fatty acid synthesis[38].

The combination of hyperglycemia and lipogenesis leads to progressive accumulation of triglycerides in hepatocytes, establishing the steatosis phenotype characteristic of MASLD.

Excess intracellular lipids, together with inhibition of mitochondrial β-oxidation induced by cortisol, generate an environment of oxidative stress marked by reactive oxygen species production. These species activate the endoplasmic reticulum stress response, which includes activation of proteins such as protein kinase RNA-like endoplasmic reticulum kinase (PERK), inositol-requiring enzyme 1 (IRE1), and activating transcription factor 6. Sustained activation of these pathways culminates in the expression of *CCAAT*/enhancer-binding protein homologous protein (CHOP), a proapoptotic factor that promotes programmed cell death of hepatocytes[39].

Hepatocyte death and release of reactive oxygen species and damage-associated molecular patterns activate the NLRP3 inflammasome, promoting the secretion of interleukin 1 beta (IL-1β), tumor necrosis factor alpha (TNF-α), and interleukin 6 (IL-6). These proinflammatory cytokines recruit monocytes and macrophages to the liver, intensifying local inflammation and marking the transition from MASLD to MASH[40].

Furthermore, in the metabolically altered environment of the liver in MASLD, hepatic macrophages (including Kupffer cells and monocyte-derived cells) play a central role in inflammation and progression toward fibrosis. The GR in hepatic macrophages not only regulates their immune response but also establishes a functional axis with hepatocytes, modulating key metabolic processes such as ketogenesis.

During fasting, the GR in macrophages regulates the secretion of signals that directly impact hepatocytes. This interaction occurs through coordination between the GR and peroxisome proliferator-activated receptor alpha (PPARα), which modulates the expression of hepatic genes involved in ketone body production. This GR-PPARα axis is essential for maintaining energy homeostasis under conditions of nutritional restriction.

However, in the context of MASLD, this regulation is altered. The GR in macrophages can modify their secretory profile, affecting hepatic ketogenesis and contributing to an inflammatory environment. This metabolic dysfunction favors the polarization of macrophages toward a proinflammatory phenotype, characterized by the secretion of cytokines such as TNF-α and IL-1β, which activate hepatic stellate cells and promote extracellular matrix production.

Additionally, the GR influences the expression of PPARα-regulated genes in hepatocytes, suggesting that its activation may alter hepatic lipid and energy homeostasis. In murine models, this interaction has proven relevant for hepatic disease progression, as dysregulation of the GR-PPARα axis may favor lipid accumulation, oxidative stress, and chronic inflammation, all key factors in the transition from MASLD to MASH and fibrosis[41].

Mineralocorticoids

The molecular mechanisms by which mineralocorticoid receptors mediate inflammation and fibrosis include various pathways of key molecules, among which the serum and glucocorticoid-regulated kinase 1 (SGK1) and transforming growth factor beta notably stand out, both with post-transcriptional effects, which are overexpressed in response to mineralocorticoid receptor activation, and the phosphatidylinositol 3-kinase-dependent pathway is activated. SGK1 acts by amplifying the inflammatory response through nuclear factor kappa B (NFκB) activity, a transcription factor known to very broadly regulate inflammation mediated by cytokines, including tissue growth factor, playing a central role in the development of fibrosis[42].

Prolactin

From a pathophysiological perspective, prolactin appears to influence insulin sensitivity and energy metabolism. Some studies have demonstrated that prolactin can improve pancreatic beta cell function, increase glucose uptake, and promote glucose utilization, contributing to better energy homeostasis. Furthermore, physiologically elevated prolactin levels have been shown to improve hepatic insulin sensitivity, possibly through indirect effects mediated by dopamine in the hypothalamus.

In adipose tissue, prolactin also exerts direct effects. It has been demonstrated to regulate adipocyte function by inhibiting key enzymes such as lipoprotein lipase and fatty acid synthase, reducing lipogenesis. This action is particularly relevant in MASLD, where adipose tissue dysfunction and abnormal body fat distribution are factors that contribute to insulin resistance and hepatic disease development. In fact, the study mentions that both human adipose and hepatic tissue express prolactin receptors, reinforcing its role as a metabolic modulator.

Another proposed mechanism is the CD36 pathway, a fatty acid transporter protein, and PRL/PRLR (prolactin receptor) signaling, which improves hepatic steatosis through CD36 suppression, suggesting that prolactin could limit excessive lipid uptake by hepatocytes, thus reducing lipotoxicity and hepatic inflammation[43,44].

In women with type 2 diabetes, the development of MASLD is not linear with prolactin levels. Zhu et al. revealed a J-shaped relationship between serum prolactin levels and MASLD risk in women with type 2 diabetes. In women with normal PRL levels, it was observed that as prolactin increased within the physiological range, the risk of MASLD and hepatic fibrosis decreased significantly. However, in women with hyperprolactinemia, the risk progressively increased with higher PRL levels. This relationship was not observed in men, which the authors suggest reflects sex-specific hormonal influence in the interaction between PRL and hepatic pathophysiology. They further propose that prolactin, acting as a metabolic hormone, may have protective effects at physiological levels, but adverse effects when in excess, possibly due to its impact on inflammation, insulin resistance, and hormonal regulation[45].

This J-shaped pattern indicates that both low and excessively high prolactin levels may be associated with increased MASLD risk, while intermediate values within the physiological range could be protective. In women with type 2 diabetes, prolactin showed significant correlations with inflammation markers, insulin resistance, and alterations in hepatic enzymes, reinforcing its role in hepatic disease progression. Furthermore, it was observed that prolactin relates to sex hormones such as testosterone, which could explain part of the sex difference in this association. Together, these findings suggest that prolactin could be a useful biomarker to assess MASLD risk in diabetic women[45].

Sex hormones

Sex steroids modulate specific gene networks that influence hepatic pathophysiology in a sex-differentiated manner. Estrogens, through their nuclear and non-nuclear receptors (ESR1, ESRRA, ESRRB, ESRRG), exert significant influence on gene expression in female adipose tissue. In particular, genes such as *SH3BP2*, involved in T cell receptor signaling and lysosomal function, and *C8B*, a complement pathway component, were identified as key regulators in female-specific networks. These genes have shown functional connections with loci previously associated with MASLD in genome-wide association studies, suggesting a causal role in disease progression. In contrast, testosterone and its androgen receptor have demonstrated a more pronounced influence on male hepatic tissue. The male regulatory network includes genes such as *CHCHD6*, related to mitochondrial function, and *CD36*, involved in fatty acid metabolism[46].

In the canonical estrogen pathway, especially 17β-estradiol, they exert their action primarily through the nuclear receptor ERβ, highly expressed in female hepatocytes. This receptor regulates the expression of genes involved in *de novo* lipogenesis, fatty acid oxidation, and lipid transport, thereby modulating hepatic triglyceride accumulation. In conditions of estrogen deficiency, such as menopause or ovariectomy, dysregulation of these processes is observed, with increased *de novo* lipogenesis (via SREBP-1c, FASN, SCD1) and decreased fatty acid oxidation, favoring hepatic steatosis development.

Furthermore, ERβ participates in amino acid homeostasis, especially branched-chain amino acids, which are essential for lipid synthesis during reproduction. Its activation by dietary amino acids allows the female liver to adapt its metabolism to the energy demands of the estrous cycle. Loss of hepatic ERβ in murine models (LERKO, liver-specific insulin receptor knock-out) prevents this adaptation, exacerbating lipid accumulation and altering the lipoprotein profile.

Regarding inflammation, ERβ inhibits the JNK and NF-κB pathways, reducing the expression of proinflammatory cytokines such as TNF-α, IL-1β, and IL-6. Its absence favors macrophage polarization toward proinflammatory phenotypes, intensifying hepatic damage and progression toward NASH and fibrosis.

Regarding androgen action in women, excess androgens, as occurs in polycystic ovary syndrome, promote *de novo* lipogenesis, reduce insulin sensitivity, and

favor hepatic lipid accumulation. In men, testosterone deficiency increases JNK, NF-κB, and endoplasmic reticulum stress protein (PERK, IRE1α, CHOP) activation, exacerbating hepatocellular apoptosis[47].

Conclusions

MASLD has well-described pathophysiological mechanisms, primarily the molecular pathways of insulin resistance. In this review, we highlight endocrine pathways beyond a single canonical pathway. By considering them, not only is knowledge of the disease with its different factors expanded but it also contributes to the development of potential treatments. Proof of this is resmetirom, whose mechanism of action is different from insulin resistance. In that sense, the GH pathway or interventions in adrenal and sex steroids may be potential therapeutic targets.

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Conflicts of interest

J.R. Barrientos-Ávalos has been a speaker for Eli Lilly and Silanes. The remaining authors declare that they have no conflicts of interest.

Ethical considerations

Protection of human subjects and animals. The authors declare that no experiments have been conducted on humans or animals for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that they did not use any type of generative artificial intelligence for the writing of this manuscript.

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