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Review Article

Effects of the Pituitary-targeted Gland Axes on Hepatic Lipid Homeostasis in Endocrine-associated Fatty Liver Disease-A Concept Worth Revisiting

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Abstract

Hepatic lipid homeostasis is not only essential for maintaining normal cellular and systemic metabolic function but is also closely related to the steatosis of the liver. The controversy over the nomenclature of non-alcoholic fatty liver disease (NAFLD) in the past three years has once again sparked in-depth discussions on the pathogenesis of this disease and its impact on systemic metabolism. Pituitary-targeted gland axes (PTGA), an important hormone-regulating system, are indispensable in lipid homeostasis. This review focuses on the roles of thyroid hormones, adrenal hormones, sex hormones, and their receptors in hepatic lipid homeostasis, and summarizes recent research on pituitary target gland axes-related drugs regulating hepatic lipid metabolism. It also calls on researchers and clinicians to recognize the concept of endocrine-associated fatty liver disease (EAFLD) and to re-examine human lipid metabolism from the macroscopic perspective of homeostatic balance.

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Keywords: Lipid homeostasis; Metabolism; Pituitary-target gland axes (PTGA); Endocrine-associated fatty liver disease (EAFLD).

Abbreviations: ACTH, adrenocorticotropic hormone; ARE, androgen response element; CAD, coronary heart disease; ChREBP, carbohydrate response element binding protein; DNL, de novo lipogenesis; DHT, dihydrotestosterone; EAFLD, endocrine associated fatty liver disease; ERs, estrogen receptors; FAO, fatty acid oxidation; FAS, fatty acid synthase; FFAs, free fatty acids; FGF21, fibroblast growth factor 21; FSH, follicle-stimulating hormone; GC, glucocorticoids; GH, growth hormone; GPER, G protein-coupled estrogen receptor; HDL, high-density lipoprotein; HFD, high fatty diet; HMGCR, HMG-CoA reductase; HPA, hypothalamic-pituitary-adrenal axis; HPG, hypothalamic-pituitary-gonadal axis; HPT, hypothalamic-pituitary-thyroid axis; LDL, low-density lipoprotein; LH, luteinizing hormone; MAFLD, metabolic dysfunction-associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PCOS, polycystic ovary syndrome; PPAR, peroxisome proliferator-activated receptor; PRL, prolactin; PTGA, pituitary-targeted gland axes; RAAS, renin-angiotensin-aldosterone system; RXR, retinoid X receptor; SIRT1, sirtuin 1; SREBP-1, sterol regulatory element binding protein-1; SR-1B, scavenger receptor class B member 1; TG, triglycerides; TH, thyroid hormone; TR, thyroid hormone receptor; TREs, thyroid hormone response elements; TRβ, thyroid hormone receptor beta; TSH, thyroid-stimulating hormone; TT, testosterone; T2, 3,5-diiodo-l-thyronine; T3, triiodothyronine; T4, tetraiodothyronine; UCP2, uncoupling protein 2; VLDL, very low-density lipoprotein; 11β-HSD 1, 11β -hydroxysteroid dehydrogenase type 1.

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Introduction

The definition of fatty liver has recently become highly controversial. The liver is an important organ for maintaining lipid homeostasis, and disorders in liver lipid metabolism lead to hepatic steatosis. In 1980, Ludwig *et al*. proposed the concept of non-alcoholic steatohepatitis (NASH) to emphasize the pathological diagnosis of steatohepatitis in individuals without excessive alcohol consumption or other definite liver damage factors. In 1986, Schaffner *et al*. expanded the disease spectrum of NASH to non-alcoholic fatty liver disease (NAFLD), which includes simple fatty liver. However, it was not until 1999 that clinicians began to pay attention to the hazards and diagnosis of NAFLD/NASH. With the prevalence of overweight/abdominal obesity, NAFLD has become the world's largest chronic liver disease, closely related to cirrhosis, hepatocellular carcinoma, and liver failure. Whereas NAFLD places too much emphasis on alcohol and obesity, Professor Jacob George of the University of Sydney and other 30 experts in the field of fatty liver disease from 22 countries (mainly in the Asia Pacific region) proposed to change the name of NAFLD to metabolism-related fatty liver disease (MAFLD) in 2020. Three years later, 53 experts from the American Society for the Study of Liver Disease (AASLD), the European Society for the Study of the Liver (EASL), and the Latin American Society for the Study of the Liver (ALEH) published "A multi-society Delphi consensus statement on new fatty liver disease nomenclature", recommending the renaming of NAFLD to metabolic dysfunction-associated steatotic liver disease (MASLD). The two proposals to rename NAFLD have sparked heated discussions and attracted widespread attention from many clinicians.

Intrahepatic lipids are free fatty acids (FFAs) mainly derived from the lipolysis of triglycerides (TG) in adipose tissue or de novo lipogenesis (DNL) from glucose and fructose. Lipid removal occurs mainly through mitochondrial fatty acid oxidation (FAO) or the production of very low-density lipoprotein (VLDL).[1] The homeostasis of the endocrine system is associated with lipid homeostasis and plays crucial roles in regulating glucose and lipid metabolism.

In addition to type 2 diabetes mellitus and metabolic syndrome, NAFLD is also strongly associated with polycystic ova-

ry syndrome, growth hormone deficiency, hypopituitarism, and hypogonadism. Lonardo *et al*. first proposed the concept of "endocrine NAFLD" in 2006,[2] emphasizing the influence of endocrine factors, especially sex hormones, on NAFLD. The crosstalk between NAFLD and different endocrine diseases has been emphasized.[3–5] Here, we summarize the current studies on the effect of pituitary-targeted gland axes (PTGA) on hepatic lipid homeostasis and focus mainly on the three targeted gland hormones—adrenal, thyroid, and sex hormones. By re-proposing the concept of EAFLD, we call for an in-depth discussion on the concepts and mechanisms of MAFLD and NAFLD and to understand liver steatosis from the perspective of endocrine regulation and lipid homeostasis.

PTGA and hepatic lipid homeostasis

The pituitary gland includes the adenohypophysis and the neurohypophysis. The former consists of the anterior and posterior pituitary lobes, which co-ordinate communication between different organs in mammals by releasing a wide range of hormones through the pituitary hilar system, including thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), adrenocorticotropic hormone (ACTH), prolactin (PRL), and growth hormone (GH). The hypothalamic-pituitary-targeted gland axis is a regulatory loop that controls the homeostasis of hormone secretion and mainly includes the hypothalamic-pituitary-thyroid axis (HPT), hypothalamic-pituitary-adrenal axis (HPA), and hypothalamic-pituitary-gonadal axis (HPG). Hormones secreted by target glands exert their effects after interacting with specific receptors on cells in the liver and other tissues to regulate human growth, reproduction, stress, and metabolism. The liver is also an important site for the synthesis and metabolism of hormones and is susceptible to the local microenvironment.

HPT axis and hepatic lipid homeostasis

Thyroid-stimulating hormone (TSH) and hepatic lipid homeostasis

TSH works by binding to its receptor (TSHR) on the surface of thyroid follicular cells, which stimulates the synthesis and release of the active thyroid hormone (TH) triiodothyronine (T3), and its precursor, the prohormone thyroxine (T4). TSH receptors are also expressed in hepatocytes, where sterol regulatory element-binding protein 1c (SREBP1c) serves as a key regulator of adipogenesis. TSHR signaling in the liver co-activates both SREBP1c and SREBP2.[6] On the one hand, TSH combined with TSHR activates liver SREBP-1c through the cAMP/PKA/PPARα pathway to induce hepatic steatosis; on the other hand, it inhibits bile acid synthesis through the SREBP2-hepatocyte nuclear factor 4α (HNF4α)-CYP7A1 signaling pathway.[7,8] In addition, TSH inhibits cholesterol synthesis by regulating the phosphorylation of HMG-CoA reductase (HMGCR) via AMPK.[7] The above findings support the idea that TSH regulates hepatic lipid homeostasis; however, it is difficult to determine whether the direct action of TSH is independent of thyroid hormones owing to their mutual influence.[9]

Controversy exists regarding the relationship between TSH levels and NAFLD. A study in a population with normal thyroid function found that patients with NAFLD had higher FT3 levels, lower FT4 levels, and no significant difference in TSH levels.[10] The opposite conclusion was reached in another meta-analysis: TSH levels are an important risk factor for the development of NAFLD, independent of thyroid hormones.[11] M1 macrophage polarization induces phosphoprotein 1 (SPP1) secretion, which downregulates TRβ in hepatocytes and exacerbates hepatic lipid deposition followed by a compensatory increase in serum TSH, which can further lead to SPP1 secretion. Thus, the positive feedback crosstalk between the thyroid and the liver may be linked to the presence of TRβ and TSH and plays an important role in maintaining and amplifying the pathological process of NAFLD.[12]

TH and hepatic lipid homeostasis

TH exists in two forms: triiodothyronine (T3), the active form of TH, and tetraiodothyronine (T4), a prohormone activated by deiodinase at the cellular and circulatory levels. Circulating T3 is produced by the thyroid (20%) and the liver (80%), and T4 is mainly formed by deiodination. T3 action is mediated by the TH receptor (TR), a nuclear receptor. TR has two major isomers, TRα and TRβ. TRα is the major receptor located in bones and the heart, whereas TRβ is the major receptor located in the liver and kidney. TRβ1 controls the metabolism of cholesterol and lipoprotein. TR forms heterodimers with another nuclear receptor, the retinoid X receptor (RXR), and binds to TH response elements (TREs) in the regulatory regions of target genes to regulate their transcription.[9,13]

Mason *et al*. first reported the association between thyroid disease and serum cholesterol in 1930 and proposed the important role of thyroid function in cholesterol metabolism.[14] In 1951, Scow *et al*. demonstrated the critical role of the thyroid in the development of "fat-related diseases" using a hypothyroidism mouse model.[15] The current view is that thyroid hormones regulate lipid metabolism mainly by stimulating the mobilization and degradation of lipids and de novo synthesis of fatty acids in the liver.

T3 regulates liver cholesterol metabolism mainly through regulatory gene expression and cell signaling pathways. Thyroid hormones fine-tune hepatic lipogenesis via modulation of both SREBP-1 and carbohydrate response element-binding protein (ChREBP) gene expression,[16] and these effects are likely to be mediated through the activation of TRβ in the liver and adipocytes.[17] Although similar to the effect of T3 on hepatic lipids, 3,5-diiodo-l-thyronine (T2), the metabolite of triiodothyronine (T3), acts by increasing hepatic nuclear sirtuin 1 (SIRT1) activity rather than TRβ, mainly targeting peroxisome proliferator-activated receptor (PPAR)-γ coactivator (PGC-1α) and SREBP-1c, resulting in the downregulation of lipogenic genes.[16,18] This evidence makes T2 a potential selective agent for the treatment of NAFLD under specific metabolic conditions.

Thyroid hormones also produce non-genomic effects that typically start at the plasma membrane and are mediated mainly by integrin αvβ3, a molecule that may lead to liver cancer by mediating a cellular pathway.[19] Whether this is related to the progression of liver cancer in NAFLD remains to be determined.

Fatty acid synthase (FAS) is a key enzyme in liver adipogenesis, responsible for the synthesis of long-chain saturated fatty acids. T3 regulates FAS transcription and increases FAS activity through non-genomic interactions that target TRE by activating the PI 3-kinase ERK1/2 MAPK-dependent pathway.[20]

The effects of TH on hepatic lipid homeostasis are summarized in Figure 1.

HPA axis and hepatic lipid homeostasis

ACTH and hepatic lipid homeostasis

ACTH receptors are widely expressed in the reproductive system, bone tissue, sympathetic ganglia, adipocytes, eryth-

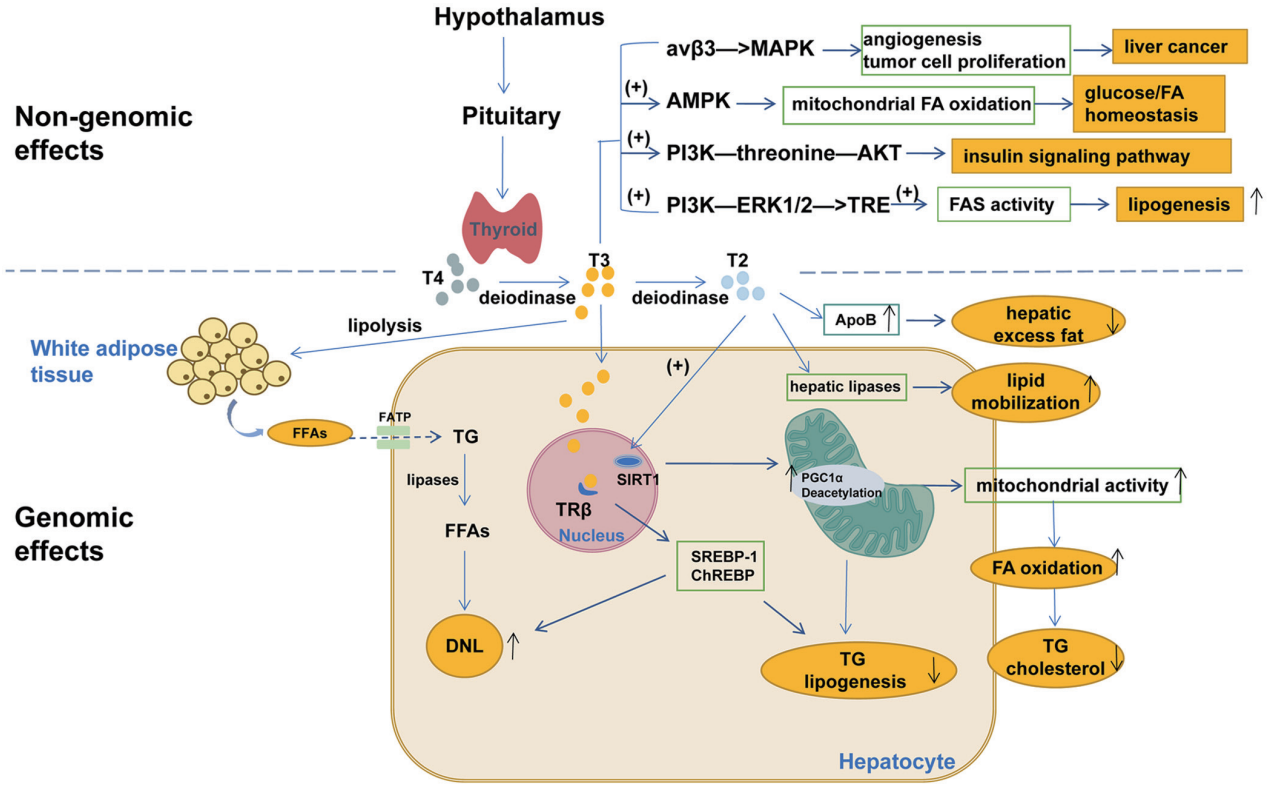

Fig. 1. Effects of thyroid hormone (TH) on hepatic lipid homeostasis. The thyroid gland mainly produces thyroxine (T4), and a portion of T4 undergoes deiodinase to form active T3. T3 can be further deiodinated and transformed into T2. Active T3 affects hepatic lipid metabolism through genomic and non-genomic effects. Non-genomic effects: T3 promotes mitochondrial fatty acid oxidation and affects fatty acid homeostasis through the AMPK pathway, and influences the insulin signaling pathway through PI3K/AKT; T3 increases FAS activity targeting TRE by activating the PI3-kinase ERK1/2 pathway. Moreover, T3 increases FAS activity through non-genomic interactions targeting TRE by integrin αvβ3, a possible molecule that leads to liver cancer. Genomic effects: T3 modulates the expression of SREBP-1 and ChREBP to reduce hepatic lipogenesis by activating TRβ. T2 increases mitochondrial activity and lowers cholesterol and TG by increasing SIRT1 activity and deacetylating PGC-1α subsequently. T2 also increases the expression of ApoB to reduce hepatic excess fat. Meanwhile, T2 also stimulates lipid mobilization by acting on hepatic lipases. ↑/↓ shows increasing or decreasing effects respectively. (+) shows activation effects. T4, thyroxine; T3, triiodothyronine; T2, 3,5,-l-diiodothyronine; TRβ, thyroid hormone receptor β; FA, fatty acid; TG, triglyceride; FAS, fatty acid synthase; TRE, thyroid hormone response elements; SIRT1, sirtuin 1.

rocytes, keratinocytes, and adrenal glands. In adipose tissue, ACTH stimulates lipolysis in mouse adipose tissue and adipocytes via MC2R-dependent cAMP/PKA activation.[21] The effects on hepatic lipid metabolism are more likely to be mediated through the HPA axis. Activation of the HPA axis pathway is closely related to insulin resistance (IR), glucose, and lipid metabolism disorders in type 2 diabetes mellitus (T2DM). Environmental pollution affects the HPA axis. Ambient PM2.5 exposure inhibits the HPA axis and demonstrates sex-associated differences in its effects on IR and disorders of hepatic lipid metabolism. Female mice are more susceptible than their male counterparts to ambient PM2.5 exposure-induced IR and hepatic lipid accumulation.[22] Moreover, alterations in HPA-axis activity and fatty acid (FA)-metabolism occur in (recurrent) major depressive disorder.[23] In conclusion, both emotional pressure and stress affect lipid metabolism by activating the HPA axis, and the underlying mechanism still needs to be further explored.

Glucocorticoids (GCs) and hepatic lipid homeostasis

Adrenal glands are composed of two embryonically, histologically, and functionally distinct units: the adrenal cortex and the medulla. The adrenal cortex secretes mineralocorticoids (e.g., aldosterone) that regulate sodium and potassium homeostasis, and GCs (e.g., cortisol) that regulate energy and immune homeostasis,[24] control inflammation, support reproduction[25] and regulate stress-related behaviors.[26]

Adrenal steroid genesis requires cholesterol as a substrate for the synthesis of steroid hormones and is controlled by two endocrine feedback circuits: the HPA that mainly regulates glucocorticoids and sex steroids, and the renin-angiotensin-aldosterone system (RAAS) that mainly regulates mineralocorticoids. Because aldosterone is mainly regulated by the RAAS system, it will not be discussed in this review; interested parties may read the relevant reviews.[3] Spironolactone, an aldosterone antagonist, improves IR in patients with NAFLD, has anti-inflammatory and antifibrotic effects on the liver, and therefore may be an effective therapeutic target for NAFLD. However, there are no large-scale clinical trials to further validate this hypothesis.[3,27,28]

GCs are produced by the adrenal gland under the control of pituitary ACTH secretion. They play a more important role in carbohydrate and lipid metabolism than mineralocorticoids and are synthesized and secreted from the zona fasciculate of the adrenal cortex. GCs have been implicated in the regulation of energy homeostasis (carbohydrate and lipid), reproduction, and growth as well as in the anti-inflammatory and immune responses.[29] Increased GC levels have been implicated in the pathogenesis of obesity, hyperglycemia, and NAFLD. The liver is the main site of glucocorticoid clearance, and 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) and liver 5α-reductase type 1 (SRD5A1) are

the main enzymes of glucocorticoid metabolism in the liver. 11β-HSD1 catalyzes the conversion of cortisone to cortisol. These enzyme-mediated metabolic transformations influence plasma and intracellular glucocorticoid levels, affecting their interaction with receptors[30,31] and regulating glucocorticoid-dependent target gene transcription.[32] The effects of GCs on lipid metabolism, fat accumulation, and NAFLD development are complex. Hepatic dysfunction may impair GC metabolism and alter the adrenal axis. The relationship between adrenal disorders and NAFLD is complex and bidirectional, whereas the underlying mechanisms remain unclear and speculative. Adrenal hypersecretion and insufficiency are both linked with altered hepatic function and the development of NAFLD.

High circulating GC levels are associated with an increased risk of visceral obesity, IR, diabetes, dyslipidemia, hypertension, hepatic steatosis, and coronary heart disease (CAD). Increased lipolysis of adipose tissue by GCs leads to enhanced release of FFA into circulation.[33] FFA are subsequently taken up by the liver, leading to increased triglyceride synthesis and hepatic steatosis. GCs also increase de novo synthesis of triglycerides (DNL) by inducing genes that convert carbohydrates to fatty acids, resulting in a specific distribution of adipose tissue throughout the body dominated by visceral fat. The correlation between GCs and lipid metabolism is well demonstrated in Cushing's syndrome.[34] A small study with 50 patients reported that approximately 20% of patients with Cushing's syndrome developed NAFLD. Targher *et al*. found that chronic HPA axis hyperactivity and subclinical hypercortisolism were present in patients with NAFLD.[35]

In peripheral tissues, such as adipose tissue, liver, kidney, and skeletal muscle, GCs can be regenerated from inactive 11-keto derivatives (cortisone) by 11β-HSD1 in humans.[36] The highest expression of 11β-HSD1 occurs in the liver, and liver 11β-HSD1 mRNA levels are both hormonally regulated and influenced by gender and diet.[37,38] Heterogeneity in human hepatic 11β-HSD1 activity may be associated with the development of IR and specific fatty liver and hypertension syndromes, while not significantly correlated with obesity. Therefore, 11β-HSD1 inhibitors are candidate treatment agents for dyslipidemia and metabolic syndrome. However, 11β-HSD1 has opposite effects in different histological stages of NAFLD, and inhibition of 11β-HSD1 may be beneficial in steatosis as it further reduces cortisol levels, whereas inhibition of 11β-HSD1 in NASH may exacerbate inflammatory responses. Therefore, the timing of drugs targeting 11β-HSD1 in NAFLD still needs to be further evaluated.

The effects of GCs on hepatic lipid homeostasis are shown in Figure 2.

HPG axis and hepatic lipid homeostasis

FSH, LH, and hepatic lipid homeostasis

FSH receptor (FSHR) is a glycosylated transmembrane protein belonging to the class of G protein-coupled receptors (GPCRs) that is expressed primarily in the gonads but also in human and mouse liver. The function of FSH is mediated primarily through FSHR, which regulates the function of ovarian granulosa cells and testicular supporting cells. The LH receptor (LHR), which is found primarily in the testis and ovary, binds to LH and stimulates androgen production. LHR gene expression levels in tissues are similar to those of FSHR.[21]

The anterior pituitary gland releases the gonadotropins, FSH, and LH, to regulate gonadal function. The classical view is that the mechanism underlying dyslipidemia in menopausal women is estrogen deficiency. However, it has been found that in addition to the gonads, other organs including bone, liver, and fat may be directly regulated by FSH. Epidemiological data suggest that serum FSH levels are positively correlated with serum total cholesterol levels. Blocking FSH reduces serum cholesterol by inhibiting hepatic cholesterol synthesis. In the underlying mechanism, FSH activates the Gi2α/β-arrestin-2/Akt pathway by binding to hepatic FSHR and preventing FoxO1 from inhibiting SREBP-2 gene transcription, which ultimately leads to the upregulation of SREBP-2 and results in increased cholesterol accumulation. This study suggests that inhibition of FSH signaling may be a novel therapeutic strategy for the treatment of menopausal hypercholesterolemia.[39] However, FSH in the pituitary gland also inhibits hepatic steatosis independently of the ovary through paracrine action on corticosteroids, suggesting that FSH plays a protective role in the liver. The explanation given here is similar to that of the pancreas: the structure and function of endocrine cells in the same gland affect the function of other endocrine cells.[40] In addition, the effects of FSH on hepatic lipid metabolism show gender dimorphism, and this study failed to detect FSHR in the pituitary gland of male mice, explaining why FSH does not regulate hepatic steatosis in male mice. In conclusion, FSH may affect lipid metabolism through paracrine effects outside the HPG axis, making it difficult to define the therapeutic value of FSH agonists or inhibitors for metabolic syndrome.

The concept of an "atypical pituitary hormone-target tissue axis" has been proposed because multiple types of pituitary hormone receptors are widely expressed in non-classical target organs, and each pituitary-derived hormone exhibits a wide range of biological effects in non-classical target organs.[21] Given the intricate metabolic pathways in the body, the role of endocrine hormones in different target organs deserves further exploration.

Sex hormones and hepatic lipid homeostasis

Estrogen, estrogen receptors (ER), and GPER

Sex hormones are steroid hormones, mainly including estrogen, progesterone, and testosterone. Genes regulated by sex hormones are expressed differently in various tissues, especially in the liver. The liver is a target organ for sex hormones: liver cells express the ERs ERα, also known as ESR1 or NR3A, ERβ, and GPER (G protein-coupled ER, also known as GPR 30) and the androgen receptor (AR) in both men and women. Sexual dimorphism of the liver has received more and more attention in recent years.

However, the expression levels of ER in the liver are not related to gender, but to age. ER levels are similar in male and female rats, with hepatic ER levels being highest in the perinatal period and beginning to decrease until puberty.[41] The expression levels of ER in the liver do not change after ovariectomy in rats. Interestingly, increasing evidence shows that estrogen also has indispensable metabolic functions in males. The aromatization of testosterone to E2 prevents the accumulation of intra-abdominal adiposity in males, and a clinical study showed that aromatase inhibition following decreased estrogen production leads to increased abdominal fat in men.[42]

The main isoform of ER in the liver is ERα in both males and females, and signaling of this pathway plays an important role in regulating adipogenesis in both males and females. The activity and expression of lipogenic genes, as well as the activity of certain enzymes in the liver are regulated by estrogen levels, and ERα signaling plays a major role in the metabolic protective effect of estrogen.[42]

Many aspects of metabolic balance, including glucose and

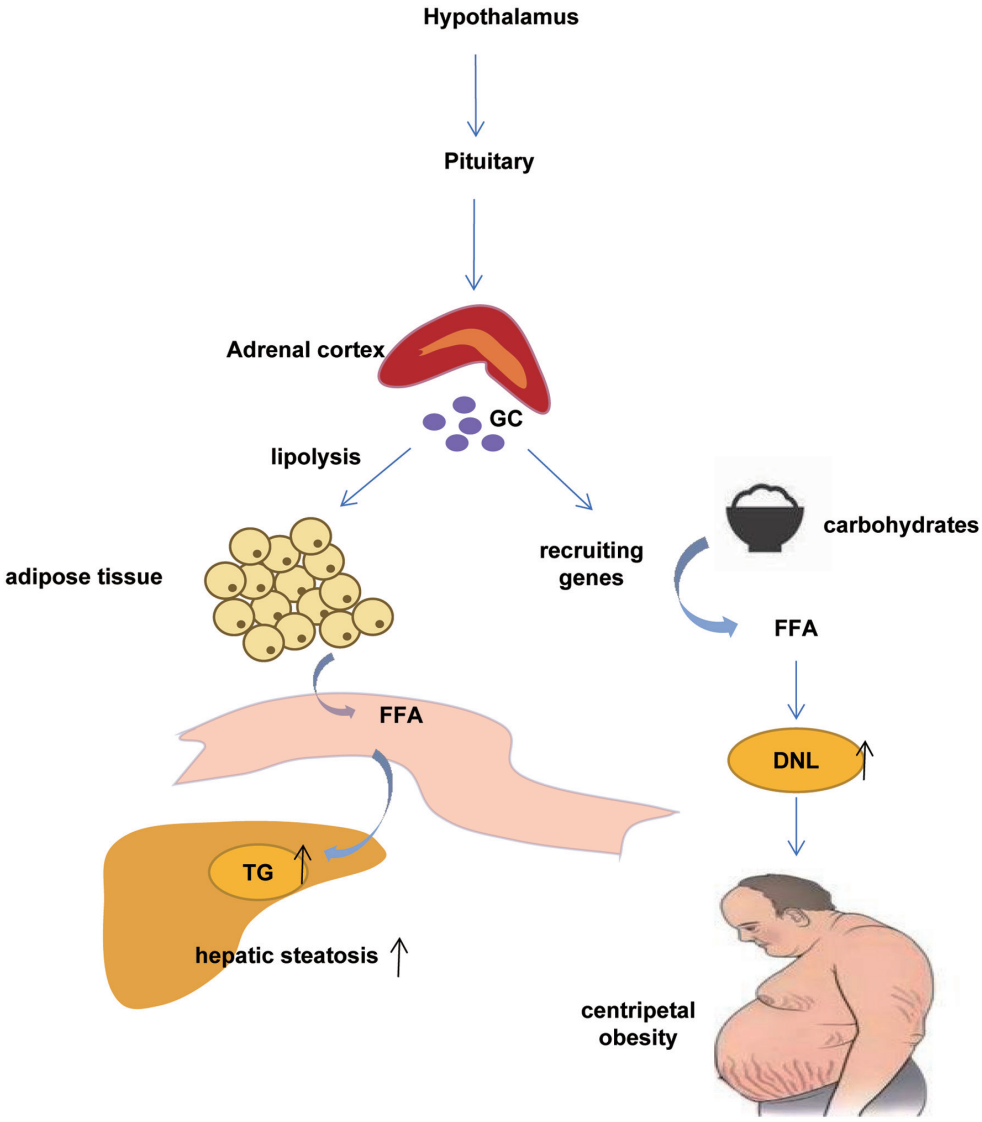

Fig. 2. Effects of glucocorticoids (GC) on hepatic lipid homeostasis. The adrenal cortex synthesizes and secretes glucocorticoids. On the one hand, GC increases lipolysis of adipose tissue, releasing free fatty acids into the circulation, which are subsequently taken up by hepatocytes, increasing TG and promoting hepatic steatosis. GC also increases de novo synthesis of triglycerides by recruiting genes that convert carbohydrates to fatty acids and leads to a specific distribution of adipose tissue throughout the body, centripetal obesity is the typical manifestation. ↑ shows increasing effects. DNL, de novo lipogenesis; FFA, fatty acid; TG, triglyceride.

lipids, are regulated differently in males and females. Estrogen makes women more resistant than men to diseases associated with metabolic disorders. The protective effect of estrogen is generally considered to be mainly achieved through the nuclear receptors ERα and ERβ and the membrane receptor G protein-coupled estrogen receptor 1 (GPER1).[43] The expression of SREBP-1C and lipid transporter genes, closely related to hepatic lipid metabolism, increases due to a decrease in ERα and liver-specific GPER gene expression, leading to hepatic steatosis. Chromatin immunoprecipitation revealed that dozens of lipid genes are transcriptionally regulated by ERα.[44] The expression levels of genes involved in cholesterol metabolism in the liver vary in an ERα-dependent manner with the four-day estrous cycle of mice.[44,45] Membrane-associated ERα, but not nuclear ERα, is associated with protection against hyperlipidemia by reducing the expression of liver lipid synthesis genes.[46] Interestingly, however, ERβ-deficient mice exhibit high body weight and low liver weight, which the authors propose may result from increased insulin sensitivity and reduced TG aggregation in the liver.[42,47] This suggests that ERβ may be related to liver fat deposition and diabetes. In addition, estradiol may also promote hepatic FAO by altering hepatic uncoupling protein 2 (UCP2) expression and increasing fibroblast growth factor 21 (FGF21) production by increasing hepatic oxygen consumption and ATP production.[48] Given that estrogen is transformed by the aromatization of testosterone, hepatic steatosis has been described in male mice with an aromatase gene deletion (Arko), but not in female mice, which can be normalized by estrogen treatment.[49]

GPER is also essential for liver lipid metabolism. GPER-deficient female mice fed a high-fat diet (HFD) exhibit hepatic steatosis, but not GPER-deficient males.[42] The sexual dimorphism of the effect of GPER on hepatic lipid metabolism

needs to be further explored. In the liver, both GPER and membrane-associated ERα are essential for lipid metabolism: the former may have a greater effect on lipid regulation in males,[45] whereas the latter has a greater effect on lipid regulation in females.[50] G-1, a GPER agonist, reduces TG accumulation and fatty acid synthesis in both human and rodent pancreatic β-cells,[42,51] but the impact of G-1 application on hepatic lipid metabolism still needs further study.

It is worth noting that estrogen regulation varies in different tissues. It plays essential roles in reducing peripheral low-density lipoprotein (LDL), increasing high-density lipoprotein (HDL), and promoting cholesterol secretion into bile. Estrogen-deficient animals may not have increased cholesterol synthesis but have reduced cholesterol catabolism, which is related to the decreased activity of 7α-hydroxylase.[52] GPER tends to regulate LDL rather than HDL metabolism.

Androgens and AR

Androgens, similar to estrogens, act on both nuclear and nonnuclear receptors. Their genomic effect is accomplished by activating nuclear receptors, which then bind to a specific DNA region, the androgen response element (ARE).[42,53] In addition to the classic ARE-mediated transcription, several non-genomic signaling pathways are activated by AR,[44] including the MAPK and PI3K/Akt pathways that interact with cytoplasmic signal transduction pathways. The specific role of membrane AR in hepatic metabolism is unknown.

Interestingly, the role of androgens in NAFLD is controversial. Several studies have shown that androgens promote NAFLD development and progression,[54] whereas the opposite finding that androgens protect against NAFLD is described by others.[55] The reason for such conflicting findings might be the various treatments or animal models utilized in different studies. Münzker *et al*. reported that a high testosterone (TT) to dihydrotestosterone (DHT) ratio (TT/DHT ratio) predicted the development and progression of NAFLD in patients with polycystic ovary syndrome (PCOS).[56] In contrast, the contribution of AR in hepatic steatosis is less controversial. Hepatic steatosis and IR are still present in hepatic AR knockout mice with HFD feeding. Increased lipid synthesis occurs after upregulating the expression of hepatic SREBP-1C, ACC, and PPARγ, whereas decreased FAO occurs after downregulating PPARα; however, such effects are evident in males but absent in females.[57] Therefore, hepatic AR plays a more prominent role in regulating liver lipid metabolism in males than in females. Testosterone is a member of the androgen family, either being converted to DHT binding to Ars or converted to E2 binding to ERs.

Hepatic scavenger receptor class B member 1 (SR-1B) plays a crucial role in regulating cholesterol uptake from circulating HDL. Androgens control hepatic cholesterol metabolism by affecting SR-1B and cholesterol 7α-hydroxylase, including promoting hepatic cholesterol uptake and inhibiting cholesterol clearance, which in turn increases cholesterol accumulation in the liver and thereby reduces serum cholesterol and LDL levels. Cholesterol 7α-hydroxylase, a key enzyme in the process of cholesterol clearance and bile formation, is reduced after DHT treatment.[57] SR-1B levels are increased in DHT-treated castrated obese mice compared with vector-treated castrated mice, and LDL secretion is decreased by DHT treatment.[42]

Androgens have different effects on males and females. Women with PCOS are at an increased risk for NAFLD owing to elevated levels of circulating androgens, which may be caused directly by a hepatotoxic effect or indirectly by obesity and IR.[58] It is manifested by elevated alanine aminotransferase levels. Normal females have lower levels of basal androgens compared with males, but elevated androgen levels in women increase lipid deposition in the liver. However, normal androgen levels and signal transduction prevent hepatic lipid accumulation in males, and androgen deficiency in men promotes fatty liver formation. The role of androgens in males and females needs further study.

In addition, the effect of androgens on cholesterol metabolism may vary with treatment duration. A clinical study showed that serum cholesterol levels increased after a single dose of testosterone by increasing the expression of HMGCR, although serum cholesterol levels in the subjects returned to baseline levels after some time.[59] The physiological mechanisms and effects of androgen-induced transcriptional upregulation of HMGCR have not been systematically elucidated and require further in-depth study.

The effects of sex hormones on hepatic lipid homeostasis are summarized in Figure 3. The roles of sex hormones and their receptors in lipid metabolism are complex, and some studies even contradict each other. It is difficult to obtain convincing conclusions by solely focusing on individual genes and proteins. A systematic biological approach to liver cholesterol metabolism homeostasis should be a future direction.

GH and hepatic lipid homeostasis

GH is a protein consisting of 191 amino acids secreted by the anterior pituitary gland in a pulsatile manner, mainly regulated by GH-releasing hormone (GHRH), which promotes the transcription of the GH gene, and growth inhibitor, which inhibits GH secretion.[60] The liver is a major target organ for GH, and this hormone along with its major mediator, insulin-like growth factor-1 (IGF-1), is under the control of the HPG axis, which is involved in metabolic functions in adults. GH can act either directly through the GH receptor or indirectly through its mediator, IGF-1. Both GH and IGF-1 have direct and indirect effects on liver structure and function.[61] The GH receptor is a cytokine receptor that signals through activation of the JAK2/STAT5 and MAPK/ERK pathways and is widely expressed in various tissues, including adipose tissue, kidney, bone, liver, brain, and pancreas.[62]

In adults, the main metabolic effects of GH are to increase lipolysis and protein synthesis, while decreasing insulin sensitivity and glucose uptake in the liver and muscle. GH induces TG uptake in the liver by increasing lipoprotein lipase (LPL) and hepatic lipase (HL) expression. In addition, GH induces hepatic TG storage by inhibiting intrahepatic lipolysis or lipid oxidation or promoting lipogenesis.[63]

GH deficiency, typically clinically associated with a high prevalence of NAFLD, can be reversed by growth hormone replacement therapy. This is supported by significant reductions in serum hepatic enzyme concentrations, improvements in histological changes in the livers of patients with NASH, and reduced levels of fibrosis markers.[64] Obese patients with NASH combined with advanced hepatic fibrosis have low serum GH levels, and normal GH levels essentially rule out advanced hepatic fibrosis.[65] Increased DNL occurs in hepatocyte-specific growth hormone receptor (GHR) knockout mice.[66] GH inhibits DNL, as well as the expression of peroxisome proliferator-activated receptor γ (PPAR-γ) and CD36 (a key regulator of free fatty acid uptake), and blocking the GH receptor or downstream signaling pathways (JAK2/STAT5) affects GH activation and ultimately leads to hepatic steatosis.[67]

Prolactin (PRL) and hepatic lipid homeostasis

PRL is a polypeptide hormone produced by anterior pitui-

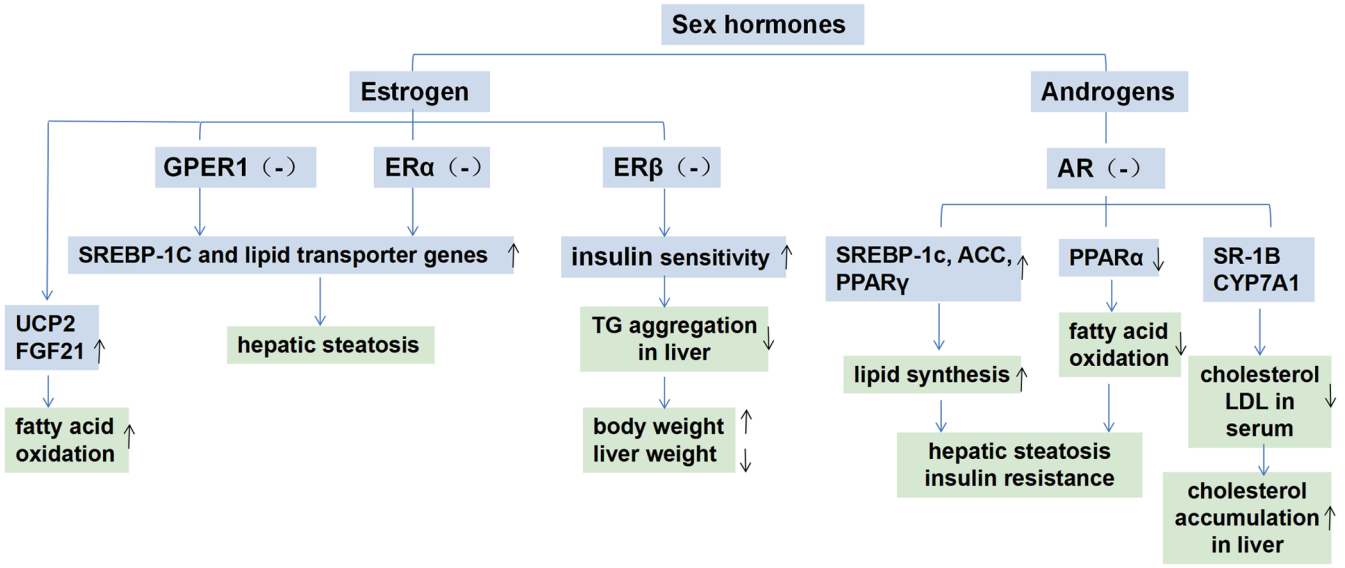

Fig. 3. Effects of sex hormones on hepatic lipid homeostasis. ↑/↓shows increasing or decreasing effects respectively. (–) shows receptor deficiency effects. TG, triglyceride; LDL, low-density lipoprotein; GPER, G protein-coupled estrogen receptor; ER, estrogen receptor; PPAR, peroxisome proliferator-activated receptor; FGF21, fibroblast growth factor 21; UCP2, uncoupling protein 2; SREBP-1, sterol regulatory element binding protein-1; SR-1B, scavenger receptor class B member 1.

tary PRL cells, and its action is mediated by the PRL receptor (PRLR). PRLR is a transmembrane protein expressed in most organs of mammals but mainly in the mammary glands and ovaries. Functional PRLR is present in hepatocytes.[68] PRL/PRLR levels are negatively correlated with NAFLD, i.e., patients with severe hepatic steatosis have lower PRL levels. PRL ameliorates hepatic steatosis and improves lipid accumulation via hepatic PRLR and fatty acid translocase (FAT)/CD36.[69] In addition, PRL reduces the expression of stearoyl coenzyme A desaturase 1 (SCD1), a rate-limiting enzyme in monounsaturated fatty acid biosynthesis, thereby reducing TG accumulation. Therefore, PRLR-modified PRL is a potential therapeutic target for NAFLD.[70]

Discussion

Homeostasis is a mechanism by which organisms control their internal environment to keep it relatively stable. Homeostasis corresponds to the health state of the human body. First, it is a variable state. Second, it changes within a certain range and is relatively constant. With the development of cybernetics and systems biology, homeostasis is not only limited to the stable state of the internal environment but also extends to many physiological processes that maintain coordination and stability in the organic body. It is also used for the stable state of different levels (cells, tissues, organs, systems, whole organisms, and social groups) and certain states that remain for certain periods.

Under the unhealthy condition of homeostasis deviation, many attempts have been made to study the role of thyroid, adrenal, and gonadal hormone analogs in regulating liver lipid metabolism, but no consensus has been reached. Pituitary target gland axis-related drugs that regulate hepatic lipid metabolism are summarized in Table 1.[9,13,71–115] The development of TH analogs was initially prompted by an attempt to exploit the effects of TH on lipid metabolism while avoiding unwanted cardiac effects.[71] Several clinical trials of TRβ agonists were conducted in patients with hypercholesterolemia, but these programs were terminated after reports of adverse effects in dogs with cartilage damage. In recent years, TRβ agonists have raised new interest in the treatment of NAFLD, and a couple of clinical trials have provided encouraging initial results.[72,73] 11β-HSD1 inhibitors may be promising candidates for further development owing to their therapeutic reduction in GC levels independent of the HPA axis.[74] Moreover, estrogen replacement therapy, phytoestrogens, and combination therapies may be effective options for the regulation of lipid metabolism homeostasis in postmenopausal women. GH ameliorates IR, inflammation, oxidative stress, and fibrosis, and patients with GH deficiency (GHD) should be screened for NAFLD. Exogenous GH treatment for secondary NAFLD appears feasible.

Lipid disorders are closely related to various metabolic and cardiovascular diseases. So far, the lipid-lowering drugs used in the clinic are all one-sided in lowering blood lipids, and few studies have combined the body's regulatory ability to modulate systemic lipid metabolism by playing a coordinated role in the homeostasis of the human neuro-endocrine-immune systems. Synthesis, absorption, and expulsion of cholesterol in the liver maintain the dynamic balance of circulating cholesterol, which constitutes the homeostasis of cholesterol metabolism in the liver. Recent studies are also progressively revealing the underlying mechanisms by which non-vesicular cholesterol flux contributes to hepatic and systemic lipid homeostasis.[116] The neuro-endocrine-immunomodulatory network plays an important role in the maintenance of lipid homeostasis in the liver. Recently, the gut-brain-liver axis has attracted extensive attention from researchers owing to its involvement in the intake of intestinal nutrients and its role as the first line of defense against metabolic disorders. As one of the neuroendocrine-immune regulatory networks in lipid metabolism, it has been extensively reviewed.[117–120]

Although various lipid-lowering medications are currently employed in clinical settings, the human body's lipid metabolism operates as a finely tuned, dynamic equilibrium. Rigorous regulation of these processes is essential for maintaining metabolic balance. Focusing solely on specific pathways or relying exclusively on reducing blood lipid levels to manage disease occurrence and progression is inevitably 'one-sided' and triggers a 'ripple effect.' Take statins, a representative

Table 1. Summary of PTGA-related drugs for regulating liver lipid metabolism

Hormone analogues/mimetics	Mechanism/Characteristics	Biological effects	Species	Clinical trials	Subjects	Refs
TRβ selective agonists						9,13, 71,75
MB07811 (VK2809)	Liver-targeted prodrugs. (10-fold TRβ selectivity than TRα)	Lower total cholesterol and LDL-cholesterol. (2) Lower triglyceride, liver fat content, and blood glucose.	Humans, monkeys, dogs, rabbits, rats, mice. Human, rats, mice.	Phase II ongoing	Primary hypercholesterolemia and NAFLD	76–79
MGL-3196 (resmetirom)	The selectivity and efficacy improved due to the cyanoazauracil substituent. (28-fold TRβ selectivity than TRα)	(1) Lower cholesterol, triglyceride, and hepatic fat. (2) Inhibit hepatic steatosis and fibrosis. (3) Heart protection.	Humans, mice.	Phase III ongoing	Biopsy-confirmed NASH (fibrosis stages 1–3) and the hepatic fat fraction of at least 10% at baseline	72,73, 80–83
GC-1 (sobetirome)	Stimulate reverse cholesterol transport, induce bile acid production, and biliary sterol secretion. (5-fold TRβ selectivity than TRα)	Lower total or LDL-cholesterol. (2) Lower triglyceride and adipose tissue.	Humans, monkeys, rats, mice. Rats, mice.	Ending in phase I	/	84–86
KB2115 (eprotirome)	Liver-targeted, induce net cholesterol excretion, and strongly stimulate bile acid synthesis. (TRβ selectivity not disclosed)	(1) Lower total cholesterol, LDL cholesterol, and triglycerides. (2) Increase fasting blood insulin, adverse effects on dogs' cartilage of withdrawal.	Humans, dogs.	Ending in phase III	Familial hypercholesterolemia	71,82, 87,88
Thyroid Hormone Metabolites (THM)						
T2	Endogenous THM, acts on the liver nuclear protein SIRT1(nuclear deacetylase), and stimulates hepatic mitochondrial fatty acid oxidation.	(1) Lower liver fat content and body weight. (2) Promote lipid mobilization and secretion as VLDL.	Humans, rats, tilapia.	/	/	89
Biogenic amine 3-iodothyronamine (T1AM)	Acts on G-protein-coupled trace amine receptor TAAR1 rather than TR.	(1) Increase lipid decomposition and oxidation. (2) No cardiac side effects.	Rats.	/	/	82
Selective inhibitor of 11β-HSD-1 enzyme						74
BMS-823778	(1) Inhibit the conversion of inactive cortisone to active cortisol. (2) Selectively lower the concentration of cortisol within the tissue without changing its plasma level during the stress response.[74]	Lower aortic cholesterol levels plaque size and atherosclerosis.	Humans, monkeys, mice.	Phase II ongoing	Primary hypercholesterolemia	90–92
MK-0736		Lower LDL-C, and body weight	Humans.	Ending in phase I	Peripheral arterial disease	93,94

(continued)

Table 1. *(continued)*

Hormone analogues/mimetics	Mechanism/Characteristics	Biological effects	Species	Clinical trials	Subjects	Refs
Compound 544	Competitive inhibitor for cortisone.	(1) Lower aortic total cholesterol, serum cholesterol, and triglycerides. (2) Lower fasting glucose, triglycerides, and free fatty acids improve glucose tolerance.	Humans, mice. Mice.	/	/	95
Sex hormone analogues/compounds						
Dehydroepiandrosterone (DHEA)	Precursor of sex steroid hormones, biotransformation into estrogen, up-regulates the expression of GPR30.	(1) Lower visceral and subcutaneous fat mass. (2) Elevate adipocytic adiponectin gene expression. (3) Lower hepatic steatosis, fibrosis, and inflammation in female mice.	Humans, rats, mice	/	/	96,97
Testosterone	Need to be further elucidated	(1) Lower total cholesterol and total body fat. (2) No change in LDL-C and body weight.	Humans	Not Applicable	People living with HIV/AIDS	98,99
L-arginine+ Estrogen	Stimulate synthesis and activity of the enzyme NO synthase.	Vasomotor, hemostatic and anti-inflammatory effects.	Humans	Phase II ongoing	Hypercholesterolemic postmenopausal women	100
Estrogens/ medroxyprogesterone/ progesterone/hormonal replacement therapy	Direct estrogen supplementation.	(1) HDL-C increased, LDL-C decreased significantly, no changes in TC levels. (2) Progestins alone or in combination with estrogens can induce insulin resistance. (3) No effect on plasma lipid or glucose. (4) Beneficial effect on hyperglycemia, and oxidative stress and ameliorates liver dysfunction.	Humans. Monkeys. Rats.	Phase III ongoing	Postmenopausal women, ages 45 to 64. One-third of the subjects had a hysterectomy.	101–104
G-1(Tespria)	Synthetic GPR30 agonist	(1) Lower body weight, body fat content, fasting cholesterol, glucose, insulin, and inflammatory markers. (2) Improve glucose and lipid homeostasis. (3) No feminizing effects on the uterus.	Mice	/	/	105,106
Selective estrogen receptor modulators (SERMs)						
Tamoxifen	ERα antagonist in breast, ERα agonist in bone.	Induce hepatic steatosis and hypercholesterolemia	Humans, rats, mice	Bioequivalency test	For breast cancer treatment and osteoporosis prevention	107–109
Raloxifene	ERα agonist	(1) Lower body weight, fat mass, and hyperleptinemia. (2) Lower total cholesterol and LDL-C	Rats. Humans	Bioequivalency test	For the treatment of postmenopausal osteoporosis	110,111
GSK232802A	nonsteroidal SERM, not act on the uterus	Lower body weight and reduce adiposity	Monkeys	/	/	112
Anastrozole/ Exemestane/etrozole	Aromatase inhibitors (AIs)	(1) Increase lean body mass with stable body fat mass. (2) Increase free serum T concentration and decrease sex hormone binding globulin	Humans	/	Adjuvant treatment of breast cancer (Long term assessment of metabolism is required)	107,113
Genistein	Phytoestrogens. Glucoside genistin in soybeans, ERβ selective ligand	Improve the utilization of glucose and lipids	Humans. Rats	Phase III	Treatment of NAFLD. Prevention and treatment of diabetes in animal models	114,115

class of lipid-lowering drugs. They act on the rate-limiting enzyme in cholesterol synthesis—3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR)—inhibiting cholesterol synthesis and effectively lowering blood lipid levels. However, a common drawback is the propensity to elevate transaminase levels because of liver damage. Clinical challenges such as drug-induced liver injury, resistance or rebound post-discontinuation, and disease progression despite normal blood cholesterol levels are prevalent.

Therefore, delving into a comprehensive exploration of the signaling molecules governing cholesterol metabolism in the future is poised to enhance our holistic understanding of lipid metabolism homeostasis. Unraveling the 'non-lipid-dependent effects' of lipid-lowering medications will not only foster judicious clinical drug administration but also illuminate pathways for the development of novel lipid-lowering therapeutics.

In the future, the methods of studying single serum indicators, proteins, or genes of lipid metabolism will be replaced by systems biology methods.[121] Based on animal homeostasis models in vivo and in vitro, using the data provided by "omics" (transcriptomics, proteomics, and functional omics) high-throughput detection technology, a more comprehensive assessment of homeostasis regulation regarding altered endocrine mechanisms involved in the different endocrine axes may be the way forward.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Study concept and design (JJ), creating tables and graphs (YL, MZ, SZ, LY, YY), drafting of the manuscript (YL, JJ), critical revision of the manuscript for important intellectual content (YL, JJ, SL), administrative, technical, or material support (MZ, JJ), and study supervision (JJ). All authors have made a significant contribution to this study and have approved the final manuscript.

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