# Lipid Effects of Endocrine Medications

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**Abstract**

Various alterations of lipid homeostasis have a significant role in the pathophysiology of the artherosclerotic process. The effects of usual lipid-lowering agents such as statins, fibrates, or niacin are well known, but other endocrine therapeutic agents could also affect the blood levels of various lipoproteins and, in turn, influence atheroma formation. In this review, we attempt to summarize the effect of several hormonal and non-hormonal endocrine agents on lipid metabolism, including insulin, thyroid hormone, sex hormones, glucocorticoids, growth hormone, and several anti-diabetic agents.

**Keywords:** lipids; cardiovascular; cholesterol; LDL; HDL; insulin; growth hormone; thyroid hormone; testosterone; estrogen

## Introduction

Many endocrine therapeutic agents (hormonal and non-hormonal) can affect lipid metabolism (Table 1). Several hormones play important roles in maintaining lipid homeostasis and ultimately can influence the atherosclerotic process. Other non-hormonal endocrine therapeutic agents exert stimulatory or inhibitory effects on key effectors of lipid metabolic pathways and thereby influence lipid levels. This article focuses on the effect of endocrine medications other than conventional anti-hyperlipidemic agents on lipid parameters.

## Hormones and Their Analogues

### Insulin

Insulin is a 51-amino acid peptide hormone, secreted by the pancreatic beta cells, which exerts its action by binding to specific transmembrane receptors on target cells. The activation of the insulin receptor is propagated via subsequent phosphorylation of signaling molecules, resulting in insulin's metabolic effects. Insulin plays a fundamental role in lipid homeostasis by driving most cells to preferentially oxidize carbohydrates instead of fatty acids for energy. It further influences lipid levels by 1) stimulating adipose tissue lipoprotein lipase, resulting in the clearance of chylomicrons and very low-density lipoprotein (VLDL) particles from the circulation with attendant delivery of fatty acids to the adipose tissue; 2) promoting triglyceride synthesis in adipocytes; 3) decreasing lipoprotein lipase activity in the skeletal muscle [1], thereby preventing lipid accumulation in this tissue; and 4) reducing lipolysis by inhibiting hormone-sensitive lipase in adipocytes. The net effect of insulin action on lipid metabolism results in a

reduction of circulating triglycerides and triglyceride-rich lipoprotein level. Hypertriglyceridemia is one of the most common lipid abnormalities seen in poorly controlled diabetic patients and this is frequently associated with low plasma high-density lipoprotein (HDL) level and an increase in apolipoprotein B (apoB)-containing (atherogenic) lipoproteins. Additionally, insulin resistance in type 2 diabetes has been associated with an increased number of VLDL, intermediate-density lipoprotein (IDL), and low-density lipoprotein (LDL) particles, with larger VLDL size and smaller LDL and HDL particles [2, 3]. Acute increases in insulin have also been known to increase expression of the LDL receptor and promote LDL clearance from the plasma [4].

Thyroid hormones

Alterations in thyroid function (both clinical and subclinical) can produce a significant effect on lipid homeostasis. The beneficial effect of thyroid hormone treatment on cholesterol levels has been known since the 1930s [5]. Hypothyroidism has been associated with a decrease in the number and activity of the LDL receptors on cell membranes [6] and with a decreased activity of adipose tissue lipoprotein lipase [7]. The clinical consequences are increased levels of total and LDL cholesterol and triglycerides, and these changes are improved by thyroid hormone replacement therapy [8]. Levothyroxine treatment has been also shown to reduce non-HDL cholesterol, apoB, and lipoprotein(a) (Lp (a)) levels, as well as carotid artery intima-media thickness in patients with hypothyroidism [9]. Thyroid hormones bind to specific thyroid receptors (TR), alpha and beta, which are encoded by separate genes and have different tissue distributions [10]. TR-beta1 is the predominant isoform expressed in the liver, and its

activation by thyroid hormone analogs has been shown in mice to stimulate reverse cholesterol transport. This is achieved by increasing the expression of the hepatic HDL receptor SR-BI, which increases cholesterol re-uptake in the liver by stimulating the activity of cholesterol 7 alpha-hydroxylase, which produces more bile acids from cholesterol, and by increasing the fecal excretion of bile acids [11]. Recently, the thyroid hormone analogue eprotirome has been shown to have a beneficial effect on lipid profile of patients with hypercholesterolemia who were already receiving statin therapy. Eprotirome (Karo Bio, Huddinge, Sweden) is a tri-iodothyronine hormone analogue containing two bromides, with a higher affinity for the TR-beta isoform, and has only minimal uptake in non-hepatic tissues. In a 12-week randomized, placebo-controlled trial, eprotirome significantly reduced the levels of serum LDL cholesterol, apoB, triglycerides, and Lp(a) lipoprotein [12•].

Estrogens and progestins

Oral estrogen replacement therapy in women has been associated with beneficial effects on lipid profile. For example, in a study of 58 postmenopausal women with hypercholesterolemia, combined estrogen and progestin therapy resulted in a mean decrease of 14% in the total cholesterol level, 24% reduction of the LDL level, and a 7% mean increase of the HDL cholesterol. There was also a significant reduction of the mean Lp(a) levels by 27%, but mean triglyceride level increased by 29% with hormone therapy [13]. Data from several large, randomized, placebo-controlled studies such as Women's Health Initiative (WHI) and Heart and Estrogen/progestin Replacement Study (HERS) also demonstrated significant reductions in the LDL cholesterol and increases in the HDL

and triglyceride levels [14, 15]. Other studies have confirmed similar reductions in the lipoprotein Lp(a) levels of about 20% [16]. However, in both the WHI and HERS trials, the favorable changes in the lipoprotein metabolism induced by estrogens did not offer any protective cardiovascular effect. Moreover, treatment with synthetic progestins appeared to further worsen cardiovascular outcome. For example, in the combined estrogen-progestin arm of WHI, the hazard ratio for coronary heart disease was increased to 1.24 (95% CI, 1.0–1.5), with most of the excess risk occurring in older women [14, 15]. The addition of progestins might reduce the beneficial effects of estrogens by decreasing HDL cholesterol level, with synthetic agents like medroxiprogesterone and levonorgestrel being worse than natural progesterone [17]. Transdermal estrogens do not produce significant lipid changes likely due to a lack of the "first pass" effect on the liver, and they might also be less thrombogenic. Nonetheless, transdermal estrogens have also been associated with a non-significant increase in the cardiovascular event rate in postmenopausal women with known cardiovascular disease [18].

Androgens

The relationship among testosterone levels, testosterone replacement therapy, and the lipid profile is complex. Several prospective and retrospective studies [19, 20] have shown an association between low testosterone levels and adverse lipid profiles, including elevated total cholesterol and triglyceride levels. Other recent publications have reported that low total testosterone concentrations are also associated with low HDL levels [21]. The effect of testosterone replacement therapy on lipid profile in men is similarly complex and even conflicting. For example, Zitzmann et al. [22] reported that

hypogonadal men treated with 1000 mg of testosterone undecanoate every 10 to 14 weeks had a significant decrease in LDL cholesterol and also an increase in HDL levels compared with the pre-treatment values. However, other studies, while confirming a positive effect of testosterone replacement on LDL levels, showed no changes in HDL cholesterol [23] or even significant reductions [24]. The Testosterone in Older Men with Mobility Limitations (TOM) trial enrolled a total of 209 men (mean age, 74 years) and was terminated early because of a significantly higher rate of adverse cardiovascular events in the testosterone arm than in the placebo group. Compared with the placebo group, testosterone therapy was associated with a reduction in LDL and HDL cholesterol and no change in the triglyceride level [25•]. In a recent meta-analysis of 51 studies, testosterone treatment was associated with a significant but very small reduction in HDL cholesterol (weighted mean difference, -0.49 mg/dL; 95%, CI, -0.85 to -0.13) with no significant effect on mortality or cardiovascular outcomes [26••].

Growth hormone

Patients with growth hormone deficiency (GHD) tend to have unfavorable changes in body composition and lipid metabolism compared with normal individuals [27, 28]. In a study of 64 men with GHD, total cholesterol, LDL cholesterol, and apo-B levels were significantly higher compared with age- and sex-matched controls and inversely related with insulin-like growth factor-I levels [29]. The effect of GH replacement therapy on serum lipids in patients with GHD is controversial, with some studies reporting improvements in total and LDL cholesterol [28, 30] whereas others showed no change [31•]. For example, in a placebo-controlled study of women with GHD, low-dose GH

replacement resulted in decreased body fat and visceral adipose tissue, increased HDL cholesterol, and decreased total cholesterol, high-sensitivity C-reactive protein (hsCRP), and tissue plasminogen activator levels compared with placebo [30]. In contrast, a randomized, placebo-controlled trial by Miller et al. [31•] in GH-deficient patients being treated for acromegaly showed a positive effect of GH replacement on the total body fat mass, visceral adiposity, and hsCRP but did not produce any significant changes of other cholesterol and cardiovascular risk markers. However, despite the weak and controversial effect on the cholesterol profile, other studies showed a decrease in carotid arterial intima-media thickness in GHD patients receiving replacement therapy [32, 33]. This suggests that other anti-atherogenic factors are positively influenced by the GH therapy, but so far there are no randomized controlled studies to show a reduction in the cardiovascular events or mortality with GH replacement therapy.

Glucocorticoids

The fact that pharmacologic doses of corticosteroid agents can affect plasma lipid levels has been known for decades, and the overall effect depends on the route of administration, dose, and duration of treatment. Several small prospective studies reported elevations of total and HDL cholesterol levels, a neutral effect on LDL cholesterol, and variable response of the triglyceride levels with oral agents, but no significant changes of plasma lipids were seen with the inhaled preparations [34]. Short-term use of low-to-moderate doses of oral prednisone has been associated with a 20% increase in total cholesterol, a 34% increase in HDL cholesterol, and no significant change in the triglyceride and LDL levels [35]. Similar changes were reported in a large

observational study using data from over 15,000 participants in The Third National Health and Nutrition Examination Survey [36]. Glucocorticoid use was associated with a higher HDL cholesterol level and a lower ratio of total cholesterol to HDL cholesterol among individuals ages 60 years or older (multivariate difference 9.0 mg/dL [95% CI, 3.9–14.1] and -0.6 mg/dL [95% CI, -0.9 to -0.3], respectively) but not among those younger than age 60 years (multivariate difference -1.5 mg/dL [95% CI, -5.4 to 2.5] and 0.1 mg/dL [95% CI, -0.3 to 0.5], respectively) [36]. Long-term oral glucocorticoid use, as with Cushing's disease, has been associated with an increase in cardiovascular risk as demonstrated by several large retrospective studies. One report showed a significant association between ever use of oral glucocorticoids and any cardiovascular or cerebrovascular outcome (adjusted odds ratio [OR] = 1.25; 95% CI, 1.21–1.29). The association was stronger for current use of oral glucocorticoids than for recent or past use, with highest OR seen in the group with the highest average daily dose. The increase in the risk of ischemic heart disease alone was somewhat lower with current use (OR = 1.20; 95% CI, 1.11–1.29) [37].

Glucagon-like peptide-1 analogues

Glucagon-like peptide-1 (GLP-1) is an incretin that is a transcriptional product of the proglucagon gene. It is most commonly produced by the intestinal L cell in response to the presence of nutrients. GLP-1 stimulates insulin production and inhibits glucagon release and may also improve insulin sensitivity by increasing the expression of glucokinase and GLUT2 [38]. It may also inhibit B-cell apoptosis and stimulate B-cell proliferation, although this has only been demonstrated in rodent models [39]. The half-

life of GLP-1 is less than 2 minutes as it is degraded rapidly by dipeptidyl peptidase-4 (DPP-4) [40].

GLP receptor agonists such as exenatide (Byetta; Amylin pharmaceuticals, Eli Lilly, Indianapolis, IN) and liraglutide (Victoza; Novo Nordisk, Bagsvaerd, Denmark) bind GLP receptors to induce the effects of GLP-1 but are resistant to degradation by DPP-4 due to reduced homology to the endogenous hormone. Exenatide has been shown to improve fasting and post-prandial lipid profiles. Initial studies demonstrated improvement in triglyceride and HDL levels [41]. A large longitudinal prospective trial demonstrated reduction in fasting LDL by 6%, reduction in triglycerides by 12%, and increase in HDL by 24% in patients with type 2 diabetes [42•]. These improvements persisted at 3 years and may be related to exanetide-associated weight loss and improved glycemic control. Reduction in abdominal adiposity as measured by waist circumference was also associated with improved lipid profile. A subsequent placebo-controlled crossover study demonstrated that the improvements in lipid profile could also be found acutely in the post-prandial state in patients with glucose intolerance or recent diagnosis of type 2 diabetes [43••]. Patients given exanetide versus placebo prior to a high calorie, fat-enriched meal, were found to have lower concentrations of triglycerides, apoB-48 and apoC-III, and remnant lipoprotein (RLP) up to 8 hours post-prandially. Previous studies have demonstrated that higher post-prandial triglyceride concentrations predict cardiovascular risk, and that this relationship is independent of other traditional cardiovascular risk factors [44]. This is likely related to the notion that post-prandial triglycerides are carried on a number of potentially pro-atherogenic lipoprotein particles.

RLPs are a product of lipoprotein lipase–mediated removal of triglycerides from chylomicrons or VLDL. Increased RLPs are associated with progression atherosclerosis [45]. ApoC-III inhibits lipoprotein lipase activity and interferes with receptor-mediated uptake of triglyceride-rich lipoproteins. Elevated levels of apoC-III in VLDL and LDL particles were shown to predict cardiovascular risk in humans [46]. Non-esterified fatty acids (NEFA) have been associated with increased inflammation and local production of reactive oxidation species and have also been associated with increased cardiovascular risk [47]. In the same study evaluating the post-prandial effects of exenatide, there was no significant decline in NEFA in the early post-prandial period (0-4 hours) with exenatide versus placebo, but exenatide appeared to reduce NEFA levels in the late post-prandial period (6–8 hours), and the difference was significant ($P < 0.0001$). This prolonged reduction in NEFA may demonstrate a drug time–related effect with exenatide compared to placebo [43]. These findings demonstrated improvement in lipid profile independent of glucose tolerance status or weight loss associated with exenatide. This may be related to delayed gastric emptying along with other mechanisms that are yet to be clearly identified.

**Non-hormonal endocrine agents**

Thiazolidinediones

Thiazolidinediones are activators of the peroxisome proliferator–activated receptors. This action helps to improve insulin sensitivity. In addition, various studies have found antioxidant, anti-inflammatory, and anti-proliferative properties of this class of drugs [48]. When administered as monotherapy, pioglitazone has been shown to decrease

triglycerides and increase HDL significantly when compared with glibenclamide or metformin [49]. Although LDL and total cholesterol levels increase modestly with pioglitazone, the total cholesterol to HDL ratio has been shown to decrease.

The Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) was a large prospective trial that demonstrated 16% risk reduction in principal secondary endpoint (all-cause mortality, myocardial infarction, and stroke) in comparison with placebo. This study showed a similar effect on lipids as other studies, by reducing triglyceride and raising HDL and LDL [50]. The Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone (CHICAGO) study evaluated mean carotid-intima thickness (CIMT) and progression of CIMT over 72 weeks with pioglitazone treatment in comparison with glimepiride. At week 72, mean CIMT was less with pioglitazone versus glimepiride (−0.001 mm vs +0.012 mm). Pioglitazone also slowed progression of maximum CIMT compared with glimepiride (0.002 mm vs 0.026 mm). These findings were independent of other factors such as statin use or diabetes control and may indicate improved artherosclerotic outcome from pioglitazone use [51]. Davidson et al. [52] found that when adjusting for other cardiovascular risk factors, pioglitazone's effect on CIMT at 72 weeks could be attributed to improvement in HDL cholesterol.

It is important to note, however, that the beneficial effect on lipid profile does not extend to the entire drug class. A direct comparison study of pioglitazone and rosiglitazone showed that triglyceride levels were reduced with pioglitazone but increased with rosiglitazone. Additionally, the increase in HDL cholesterol was greater

and the increase in LDL cholesterol was less for pioglitazone compared with rosiglitazone, respectively. LDL particle concentration was reduced with pioglitazone and increased with rosiglitazone. LDL particle size increased more with pioglitazone [53].

Dipeptidyl peptidase-4 inhibitors

Dipeptidyl peptidase-4 (DPP-4) inhibitors reduce the breakdown of endogenous GLP-1 in the body. Studies evaluating lipid changes in DPP-4 inhibitors are limited. The addition of sitagliptin (Januvia; Merck & Co., Whitehouse Station, NJ) to metformin to help improve glycemic control in uncontrolled diabetic patients showed a small but statistically significant decrease in total cholesterol (2.8%), triglycerides (16.9%), and non-HDL cholesterol (4.8%) when compared with placebo. There was a small but statistically significant increase in HDL (2%) but no difference in LDL between the sitagliptin and placebo group [54]. Another placebo-controlled study showed that treatment with vildagliptin (Galvus, Novartis) for 4 weeks improves postprandial plasma triglyceride and apoB-48–containing triglyceride-rich lipoprotein particle metabolism after a fat-rich meal [55]. There is no known mechanism for changes in lipid metabolism produced by this class of agents beyond improvement in glucose control.

Metformin

Metformin is a biguanide and a commonly used agent for diabetes management. Metformin improves blood sugars by inhibiting hepatic gluconeogenesis by activation of AMP-activated protein kinase (AMPK), which increases production of proteins that

inhibit transcription of hepatic gluconeogenesis genes. A meta-analysis of 31 studies published in 2004 assessed metformin's effect on cardiovascular risk factors. Small but significant reductions in LDL (6.5%) and total cholesterol (4.6%) were also demonstrated independently of blood glucose control. A significant reduction in triglycerides was seen, but the difference was not significant when controlling for level of blood glucose control, and metformin did not significantly affect HDL cholesterol levels [56]. Metformin therapy was associated with a significant risk reductions of myocardial infarction (33%; $P = 0.005$) and death from any cause (27%; $P = 0.002$) in 10 years of post-trial follow-up of patients originally enrolled in the United Kingdom Prospective Diabetes Study [57].

**Conclusions**

A number of hormonal and non-hormonal endocrine therapeutic agents impact lipoprotein metabolism, and the resultant alterations in circulating lipid levels may significantly influence the atherosclerotic process. Although the magnitude and direction of the impact of endocrine medications on lipid parameters are variable, some such agents can produce important negative effects on lipid parameters that clinicians should consider for long-term therapy. Other endocrine agents produce changes that are consistently beneficial (growth hormone, thyroxine, pioglitazone) and have been associated with a decrease in the carotid arterial intima-media thickness. However, there are currently no large, randomized prospective trials evaluating the effect of hormonal replacement therapy for hormonal deficiency states (thyroid, growth hormone, testosterone, estrogen) demonstrating a reduction in the cardiovascular events or mortality.

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