

MEDICATION INDUCED CHANGES IN LIPID AND LIPOPROTEINS

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ABSTRACT

Several medications and medication classes have been reported to affect the lipid profile. Risk factors include elevated lipid levels at baseline and high cardiovascular (CV) risk patients. This should be considered when evaluating patients with elevated levels of total cholesterol (TC), low-density lipoproteins cholesterol (LDL-C), non-high-density lipoprotein cholesterol (Non-HDL-C), triglycerides (TG) and reductions in high-density lipoprotein cholesterol (HDL-C). Cardiovascular medications, antipsychotics, anticonvulsants, hormones and certain immunosuppressives are just some of the more commonly known medications to have a negative impact on lipid levels. In some cases, this is a class effect and in others it might depend on dose and specific drug. However, how this translates to atherosclerotic cardiovascular disease (ASCVD) risk remains unknown, as there is insufficient evidence on the impact of these metabolic changes on overall risk of ASCVD. While for many of these medications, there is an abundance of literature and comprehensive reviews discussing the potential harmful effects of on lipoprotein metabolism there remains much debate about the actual long-term implications, if any, of these changes. A thorough risk-benefit analysis of each treatment associated with an adverse effect on the lipid profile should be done based on individual patient factors. In general, if negative changes in the lipid profile are observed during therapy, replacement with an equivalent alternative therapy can be recommended. If no equivalent therapy is available and treatment must be initiated, then monitoring of serum lipid levels is vital. The use of existing guidelines for the management of dyslipidemia in the general population can be referred to and in extreme cases when benefits do not outweigh the risks; the use of the suspected medication should be reassessed. For complete coverage of this area and all of Endocrinology, visit www.endotext.org.

INTRODUCTION

Secondary causes of dyslipidemia are important to identify as treatment of the underlying cause may alleviate the dyslipidemia and ultimately reduce the need for drug treatment or the need for combination pharmacotherapy.¹ Guidelines recommend that providers should evaluate for underlying conditions that could be causing dyslipidemias before initiating treatment in patients.² One such secondary cause of abnormally altered lipid or lipoprotein levels is medications used

for other indications.³ Serum lipid levels can be affected both positively and negatively by certain medications. Medications can affect lipid levels either directly or indirectly through effects on weight or glucose metabolism. This should be considered when evaluating patients with elevated levels of total cholesterol (TC), low-density lipoproteins cholesterol (LDL-C), non-high-density lipoprotein cholesterol (Non-HDL-C), triglycerides (TG) and reductions in high-density lipoprotein cholesterol (HDL-C).⁴

There have also been reports of various medications causing severe drug-induced hypertriglyceridemia that leads to acute pancreatitis.⁵⁻⁷ While there is a paucity of data describing the exact mechanism of drug-induced pancreatitis, it is known that severe hypertriglyceridemia (TG > 1000 mg/dl) can cause acute pancreatitis. Therefore, in the absence of other causes, medications should be evaluated in the presence of acute pancreatitis and severe hypertriglyceridemia.

Several medications and medication classes have been reported to affect the lipid profile (Table 1). In some cases, this is a class effect, and some instances agents belonging to the same class can have significantly different actions on lipid levels (e.g. beta blockers).⁸ This is a consideration to appreciate when selecting a specific agent for high-risk patients and concurrent medications known to induce lipid abnormalities should be evaluated for discontinuation or dosage reduction prior to initiating long-term lipid lowering agents. How this translates to atherosclerotic cardiovascular disease (ASCVD) risk remains unknown, as there is insufficient evidence on the impact of these metabolic changes on overall risk of ASCVD.

Table 1. Drugs That May Cause Dyslipidemias			
	LDL Cholesterol	Triglycerides	HDL Cholesterol
Cardiovascular /Endocrine			
Amiodarone	↑Variable	↔	↔
β-Blockers***	↔	↑10-40%	↓5-20%
Loop diuretics	↑5-10%	↑5-10%	↔
Thiazide diuretics (high dose)	↑5-10%	↑5-15%	↔
Sodium-glucose co-transporter 2 (SGLT2) inhibitors	↑3-8%	↔↓	↑Variable
Steroid Hormones/Anabolic Steroids			
Estrogen	↓7-20%	↑40%	↑5-20%
Select progestins	↑Variable	↓Variable	↓15-40%
Selective Estrogen Receptor Modulators	↓10-20%	↑0-30*	↔
Danazol	↑10-40%	↔	↓50%

Anabolic steroids	↑20%	↔	↓20-70%
Corticosteroids	↑Variable	↑Variable	↔
Antiviral Therapy			
Protease inhibitors	↑15-30%	↑15-200%	↔
Direct Acting Antivirals	↑12-27%	↔	↑14-20%
Immunosuppressants			
Cyclosporine and tacrolimus	↑0-50%	↑0-70%	↑0-90%
Corticosteroids	↑Variable	↑Variable	↔
Centrally Acting Medications			
First Generation antipsychotics	↔	↑22%	↓20%
Second Generation antipsychotics	↔	↑20-50%	↔
Anticonvulsants	↑Variable	↔	↑Variable
Other Medications			
Retinoids	↑15%	↑35-100%	↔**
Growth Hormone	↑10-25%	↔	↔↑7%
ABBREVIATIONS: LDL, low-density lipoprotein; HDL, high-density lipoprotein. *Raloxifene has not been shown to increase Triglyceride levels, while reported increases of up to 30% have been reported with use of tamoxifen**Data remains conflicting and some evidence shows a decrease, no effect, or increase***Varies based on individual drug			

ANTIHYPERTENSIVE DRUGS

There is an abundance of literature and comprehensive reviews discussing the potential harmful effects of antihypertensive drugs on lipoprotein metabolism and there remains much debate about the actual long term implications, if any, of these changes.⁹ The diuretics and β -adrenergic blockers have the most data to support their adverse effects on lipid levels.¹⁰⁻¹⁵

Diuretics

Thiazide and loop diuretics have been associated with increases in plasma cholesterol in studies of patients with hypertension. Recent recommendations from the American College of Cardiology/American Heart Association recommend thiazide diuretics as one of four specific medication classes to be considered as initial therapy for hypertension.¹⁶ In view of these recommendations and widespread use of diuretics, it is important to review the adverse metabolic effects. Use of high-dose thiazide diuretics (≥ 50 mg/day) may negatively affect lipoprotein levels, as seen in small studies, and some investigators have suggested that as a

result, diuretics could worsen coronary artery disease (CAD).¹² Total cholesterol levels can be increased by approximately 4% and LDL-C levels by approximately 10%.^{9,15,17} High density lipoprotein levels are not affected, while TG concentrations can also be elevated by 5-15%.⁹ Low dose hydrochlorothiazide (12.5 – 25 mg/day) has been shown not to effect plasma lipids in otherwise healthy men and women.¹² The dose appears to be a factor in resulting cholesterol levels¹⁸; however, there are conflicting data regarding whether the effects on lipid levels is primarily caused by higher doses.¹² Long term effects beyond one year remain undetermined as more recent studies showed that effects are short term and serum lipid levels return to initial levels.¹⁹ Additionally, thiazide diuretics have been shown to decrease the risk of cardiovascular (CV) events despite this effect on lipid levels.²⁰

Loop diuretics have similarly shown to increase LDL-C and TG with some studies showing changes of comparable magnitude and some showing effects that are less than thiazide diuretics.^{21,22} However, the effects appear to be acute and not expected at time intervals longer than the duration of action of furosemide (6 to 8 hours). One possibility is that hormones stimulated in response to decreased intravascular volume are responsible for some changes in lipid and lipoprotein levels.²² The effects of monotherapy with potassium-sparing diuretics on lipid levels is largely unknown, but the combination of a potassium-sparing diuretic and a thiazide show similar changes as monotherapy with a thiazide diuretic, suggesting no impact from potassium-sparing diuretics.

The mechanism of increased lipid levels caused by diuretics remains unclear. One theory is that a reduction in insulin sensitivity may cause an increase in hepatic production of cholesterol.^{17,23} The mechanism of an increase in TGs is not well understood. It has been recently suggested that they may modulate adipocyte differentiation leading to accumulation of plasma TGs in susceptible patients with a particular genetic polymorphism in the *NELL1* gene.²⁴ It is also thought that there are sex differences, as diuretics were shown to produce a greater short-term increase in TC and LDL-C in postmenopausal women than in men. Premenopausal women may have a protective effect from estrogens and have demonstrated no changes in lipid levels.¹⁵ Estrogens have been theorized to increase the number of hepatic LDL binding sites and stimulate the hepatic uptake of chylomicron remnants.¹⁷

β-Blockers

The metabolic adverse effects of β-blockers depend on dose and specific drug. While β-blocking agents have negligible effect on serum TC or LDL-C, they can increase TG levels from 10 to 40% and decrease HDL-C levels by approximately 5 to 20%.⁹ The evidence on duration of effect remains conflicting with studies citing effects to last less than 1 year¹⁹, and other studies reporting increased levels after several years of treatment.²⁴ The alterations in lipoprotein levels from β-blockers does not appear to be a class effect, and agents with intrinsic sympathomimetic activity (ISA), β1-selectivity, or vasodilatory effects (Table 2) are associated with a less pronounced effect.⁹ Non-selective β-blockers which cause peripheral vasoconstriction through peripheral β-adrenergic receptors seem to increase insulin resistance, leading to lowering of HDL-C, and increased TG.²⁵ Whereas, agents that are cardioselective and/or have alpha-1-

adrenoreceptor blocking activity do not appear to increase insulin resistance. Other potential mechanisms of β -blocker induced lipid changes are from β -blocker associated weight gain, a decreased lipid metabolism through a reduction in the muscle lipoprotein lipase enzyme, and endothelial dysfunction from peripheral vasoconstriction (Table 3).²⁶ The beneficial effects of carvedilol compared to metoprolol and atenolol on lipid parameters has been demonstrated in several small studies.^{13,25,27} Carvedilol has selective α -1-adrenoreceptor blocking activity, causing vasodilation and a reduction in insulin resistance. It remains unknown if these beneficial metabolic effects of carvedilol are seen with other beta-blockers with vasodilating properties, including nebivolol. Conversely, selective α -blocking agents (prazosin) have a beneficial effect on lipid profile and have been shown to increase HDL-C and decrease TG.^{28,29}

Table 2. Pharmacological Properties of β -Blockers

	Beta Selectivity	Intrinsic sympathomimetic (ISA) or α-blocking	Vasodilating Properties
More pronounced effect on lipid levels			
Atenolol	β 1 selective	-	-
Betaxolol	β 1 selective	-	-
Bisoprolol	β 1 selective	-	-
Metoprolol	β 1 selective	-	-
Nadolol	Nonselective	-	Vasoconstricting
Propranolol	Nonselective	-	Vasoconstricting
Timolol	Nonselective	-	Vasoconstricting
Less pronounced effect on lipid levels			
Acebutolol	Nonselective	ISA	Vasoconstricting
Penbutolol	Nonselective	ISA	Vasoconstricting
Pindolol	Nonselective	ISA	Vasoconstricting
No effect on Lipid levels			
Carvedilol	Nonselective	α -blocking	Vasodilating
Labetolol	Nonselective	α -blocking	Vasodilating
Nebivolol	β 1 Selective	-	Vasodilating

Thiazide diuretics and β -blockers are important agents for other cardiovascular indications. β -blockers are effective in reducing cardiovascular morbidity and mortality in congestive heart failure and CAD and diuretics are vital for symptomatic management of many CV comorbidities. While it is important to assess for increased lipid levels caused by these agents, with other

compelling indications, it remains prudent to continue them while continuing to monitor serum lipid levels.

Table 3. Potential Mechanism of β-blocker Induced Dyslipidemia
Inhibition of insulin release
Insulin resistance
Weight gain
Inhibition of lipolysis
Reduced activity of lipoprotein lipase enzyme
Endothelial dysfunction

OTHER CARDIOVASCULAR MEDICATIONS

Amiodarone

Amiodarone, a potent antiarrhythmic drug, increases plasma cholesterol levels, reported in case reports.^{30,31} Amiodarone increases LDL-C levels as a result of a decreased expression of the LDL-receptor gene.^{30,32,33} In addition, amiodarone induced hypothyroidism can cause alterations in lipid metabolism as hypothyroidism is one of the most common causes of secondary hyperlipidemia. Amiodarone contains 39.4% iodine on weight basis which may cause hyperthyroidism or hypothyroidism.³³ Research demonstrates that long-term amiodarone treatment induces a dose-dependent increase in plasma cholesterol, in part due to thyroid hormone deficiency and a decrease in the number of LDL receptors.^{34,35}

DIABETES MEDICATIONS

Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors

The SGLT2 inhibitors lower blood glucose and hemoglobin A1c (HbA1c) through inhibiting SGLT2 in the proximal tubule, thereby blocking reabsorption of glucose and increasing the renal excretion of glucose.³⁶ There are currently four SGLT2 inhibitors available and approved for the treatment of type 2 diabetes mellitus (Table 4). In addition to their effects on glucose lowering, SGLT2 inhibitors have been shown to have positive effects on other metabolic parameters, including body weight and blood pressure.³⁶ Although data is mixed and the individual agents appear to affect the lipid profile to a varying degree, these agents have shown to increase LDL-C while also increasing HDL-C with variable effects (decreasing or no effect) on TG (Table 4). While a decrease in weight could explain the favorable effects seen on HDL-C and TG, it remains unclear what the mechanism behind the modest dose-related increase in LDL-C is.³⁷ One possibility is that SGLT2 inhibitors cause a switch from carbohydrate to lipid utilization causing an increase in hepatic fatty acid levels to induce ketone production and hepatic total cholesterol levels.³⁷ How this impacts CV health is uncertain. To date, canagliflozin and empagliflozin have demonstrated an improvement in CV outcomes (composite of CV mortality, nonfatal myocardial infarction (MI), or nonfatal stroke) and a reduction in heart failure hospitalizations in subjects with high CV risk.³⁸ For information on the effect of other glucose

lowering drugs on lipids and lipoprotein see the chapter in the Diabetes section of Endotext entitled “Role Of Glucose And Lipids In The Cardiovascular Disease Of Patients With Diabetes”.³⁸

Table 4. Sodium-glucose co-transporter 2 (SGLT2) inhibitors and their effects on low density lipoprotein cholesterol (LDL-C)³⁹⁻⁴²

Generic	Brand	Dose-Related Effects on LDL-C
Canagliflozin	Invokana®	4.5% - 8.0%
Dapagliflozin	Farxiga®	2.9%
Empagliflozin	Jardiance®	2.3% - 6.5%
Ertugliflozin	Steglatro®	2.6% - 5.4%

STEROID HORMONES

Estrogens and Progestins

Oral estrogens have been shown to be important regulators of lipid metabolism.^{43,44} Premenopausal women are protected from diseases such as CAD, hypertension, diabetes and dyslipidemia. This is seemingly due to estrogens having a protective effect, as unopposed estrogens beneficially affect the lipid profile. They lower TC (2-10%) and LDL-C levels (7-20%) and increase HDL-C levels (5-20%) in a dose-related manner.^{3,9} Studies have also shown a decrease in lipoprotein(a) levels, which is an independent risk factor for coronary heart disease (CHD), with both estrogen and progestin therapy.⁴⁵ However, they also increase TG levels up to 40%, and can increase the risk of pancreatitis in women with overt hypertriglyceridemia.⁴⁶ Ethinyl-estradiol has a more pronounced effect on lipoproteins than natural estradiol.⁴⁷ Oral estrogen therapy increases TG plasma levels by increasing production of very-low density lipoprotein (VLDL), reducing the concentrations of lipoprotein lipase and hepatic lipase, resulting in a reduction of TG clearance, and potentially through a change in insulin resistance.^{43,46} Triglyceride levels vary over time in women who are taking cyclic hormone regimens and it is assumed that the increase is enhanced among those with preexisting hypertriglyceridemia. Elevations in TGs are not usually observed with transdermally administered estrogens, as the transdermal application is thought to reduce the hepatic first pass effect and reduced impact on hepatic protein synthesis.^{3,48,49}

Progestins antagonize the estrogen-induced lipid changes, and can have a negative effect on TC and HDL-C.^{48,50,51} Serum lipid levels depend on the androgenic effects of the progestin.⁹ Progestins with more androgenic effects, such as levonorgestrel, are theorized to have larger effects on lipid levels than those with less androgenic effects.⁵² Newer, “third generation” progestins (desogestrel, gestodene) with higher specificity have been developed to reduce this risk and have demonstrated favorable effects on LDL-C levels and HDL-C levels, but they can also increase TGs.^{47,53} There remains insufficient evidence that third generation agents lower risk of ASCVD. Also, in recent years, the dose of ethinyl estradiol has been decreased from 50 down to just 20-30 mcg in current formulations, to also reduce adverse metabolic changes.

Therefore, the effect varies with oral contraceptives based on their estrogen and progestin content and more specifically the potency of the estrogen and the androgenicity of the progestin. Selective estrogen-receptor modulators, including raloxifene and tamoxifen, appear to have less impact on lipids, but can still elevate TG levels.⁴⁸ There have been several case reports in the literature describing tamoxifen-induced hypertriglyceridemia causing acute pancreatitis.^{6,7,54,55}

The American Heart Association recommends that lower estrogen-containing preparations or other forms of contraception should be considered in women who develop hypertriglyceridemia while taking therapy.⁴⁸ Postmenopausal women with hypertriglyceridemia who require hormone therapy are encouraged to switch to transdermal preparations. It is not clear if transdermal application influences cardiovascular outcomes.⁴⁸ In addition, oral contraceptives (OC) with low doses of estrogen should be used in women with controlled dyslipidemia, as studies of low dose triphasic OC have resulted in no significant changes or only mild elevations in TC, LDL-C, and TG levels. Contraceptives can be considered for women with uncontrolled LDL-C levels or multiple CV risk factors, including using non-androgenic or anti-androgenic progestins as they have minimal influence on the lipid profile.⁵⁰

In postmenopausal women, hormone therapy with estrogen alone or estrogen combined with a progestin is utilized for the treatment of hot flashes and other menopausal symptoms. Similar to studies evaluating OC, oral estrogen has also been shown to increase HDL-C and TG levels, and reduce LDL-C.⁴⁹ Combined hormone replacement therapy regimens have similar effects on TC levels and LDL-C as estrogens.⁹ Studies have shown that unopposed estrogen has a more beneficial effect on HDL-C than estrogen and progestin in combination but both similarly lowered LDL-C and increased TG in postmenopausal women.⁴³ There is conflicting evidence if hormone replacement therapy is associated with a protective cardiovascular effect in postmenopausal women and more recent data from a systematic review demonstrated that estrogen only increased the risk of a stroke (RR 1.34; 95% CI 1.07 to 1.68) and venous thromboembolism (RR 1.32; 95% CI 1 to 1.74), and there was no significant difference compared to placebo in risk of coronary events.⁵⁶ Combined hormone therapy compared to placebo demonstrated a significant increase in coronary events (RR 1.89; 95% CI 1.15 to 3.1), stroke (RR 1.38; 95% CI 1.08 to 1.75), and venous thromboembolism (RR 4.28; 95% CI 2.49 to 7.34).⁵⁶ Data has also shown that the effects of hormone therapy on CV outcomes are influenced by age and time since onset of menopause and that estrogen may slow down the early stages of atherosclerosis and have more favorable effects in women with more recent onset of menopause.⁵⁷ Overall, long term data suggests that hormone therapy may have a harmful effect on CHD risk in older women, and the results in younger women remain inconclusive. At this time, treatment for the purpose of prevention of coronary heart disease or chronic disease prevention is not recommended. For postmenopausal women, short-term therapy should be used at the lowest effective dose.⁵⁸ For those with hypertriglyceridemia, the use of transdermal estrogen may be a preferred alternative to oral.

ANABOLIC STEROIDS

Danazol

Danazol is a synthetic steroid indicated for endometriosis and fibrocystic breast disease as well as for prophylaxis in patients with hereditary angioedema (HAE).^{59,60} A review of data for the treatment of endometriosis showed that danazol treatment can result in a rapid reduction in HDL-C by up to 50% and increase in LDL-C by 10-40%.⁶¹ However, these levels return to baseline levels after stopping therapy and there is only a concern in prolonged therapy for 12 months or greater or in patients with a high risk of CV disease.⁶⁰ This effect is consistent in the literature.⁶²⁻⁶⁵ The mechanism is likely from its effects on hepatic lipase, LDL receptor, and lecithin cholesterol acyl transferase activity. Data also supports an altering of lipoprotein levels in women treated for endometriosis, but there may not be an effect in the treatment of HAE.⁶⁶ Some possible explanations for this difference are that HAE doses are lower than doses used for the treatment of endometriosis, the duration of therapy is longer and often lifelong versus 2-6 months for endometriosis, and men are also treated for HAE. A randomized trial evaluated danazol on HDL-C in healthy volunteers and patients with HAE. Patients with CV disease or significant risk factors for CV disease were excluded in the healthy volunteer study. Short-term use in healthy subjects (n=15) demonstrated a 23% decrease in HDL-C levels; however, these were normalized by 4 weeks of treatment. There was no effect seen on LDL-C or TG. Longer-term use in patients with HAE did not appear to decrease HDL-C levels compared to matched healthy controls. This study supports the belief that the differences in study populations as well as varying duration and doses of danazol impact the effect danazol has on the lipid profile. However, other studies have shown conflicted results and also demonstrated decrease in HDL-C (as well as apolipoprotein Apo A-I; the major component of the HDL particle) and increase in LDL in long term use for the prevention of HAE.^{66,67} However, this negative effect was not shown to translate into an increased risk of atherosclerosis.⁶⁷

Androgens

Similarly, studies of bodybuilders and weight lifters using anabolic steroids have revealed reductions in HDL-C levels by 20-70% accompanied by decreases in apo A-I levels, as well as elevations in LDL-C by approximately 20%.⁶⁸⁻⁷¹ The misuse of anabolic steroids in strength athletes has previously been associated with CV events which may be in part due to the adverse lipid effects associated with their use. One small study confirmed that self-administration of anabolic steroids produced unfavorable effects on lipids and lipoproteins, including a decrease in serum concentrations of HDL-C, and Apo-A1.⁷⁰ Serum LDL-C levels may increase through induction of hepatic triglyceride lipase and the catabolism of VLDL. Through this process, HDL-C serum levels are also reduced. A more recent literature review described 49 reports of 1,467 athletes using anabolic-androgenic steroids corroborating the link and reports that these changes can occur within 9 weeks of self-administration and the effects seem to be reversible and normalize within 5 months after discontinuation.⁷² The majority of the evidence is based on small, observational studies or single case reports and may reflect significant publication bias. However, use of anabolic-androgenic steroids has also been linked to elevated blood pressure, left ventricular hypertrophy, acute myocardial infarction, and sudden death and awareness of these potential adverse effects may benefit athletes and increase recognition of young otherwise healthy individuals with CV abnormalities.

Androgen deprivation therapy (ADT) is hormone therapy used for the treatment of prostate cancer and is associated with a variety of metabolic adverse events, including lipid alterations.⁷³ This can be done by surgical castration or medical castration with gonadotropin-releasing hormone (GnRH) agonists (also called luteinizing hormone-releasing hormone (LHRH) agonists). These agents can cause changes in lipid levels, including increases in TC, TG, and HDL-C.⁷³ Studies have shown different changes on LDL-C; with some showing an increase and others with no significant changes. Small studies have demonstrated increases in TGs of up to 25% and HDL-C increases of up to 11%. Furthermore, a longer term study over 1 year observed these changes did not persist after 6 months.⁷⁴ Given that ADT may increase the risk of lipid changes as well as obesity and insulin resistance, studies have also evaluated the effects of ADT on CV disease and observational studies have suggested an association between ADT and a greater risk of CV disease.⁷⁵ One explanation for this association is that ADT interferes with the cardioprotective property of testosterone and therefore, increases the risk for adverse events. In 2010, the FDA released a drug safety communication informing of the increased risk of diabetes and certain CV diseases (heart attack, sudden cardiac death, stroke) in men receiving GnRH agonists for the treatment of prostate cancer based on their review of several published studies.⁷⁶ However, this was based on mostly small observational studies and RCTs have remained conflicted on this relationship, as seen in a recent meta-analysis of randomized trials.⁷⁷

Testosterone replacement products are approved for men who have low testosterone levels caused by various medical conditions. Nonetheless, the use of testosterone therapy is increasing, including for men who have low testosterone simply due to aging.⁷⁸ Recent studies have shown that the risk of MI and other CV-related events may be increased with the use of testosterone therapy and that testosterone therapy should be avoided in certain high risk patients.^{78,79} However, most of the data remains observational and many report conflicting results. Further RCTs are needed to clarify the concern. If treatment with testosterone does increase the development of arteriosclerotic heart disease, one potential mechanism is through an adverse effect on serum lipids and apolipoprotein levels. However, studies to date have not demonstrated a significant effect on lipid or lipoprotein levels, with possibly a slight decrease in HDL-C occurring due to changes in the HDL protein composition.⁸⁰⁻⁸²

GROWTH HORMONE

Adults with growth hormone deficiency frequently have lipid abnormalities, decreased insulin sensitivity and an increased CV morbidity and mortality. Treatment with recombinant human growth hormone, or somatropin, for adults with growth hormone deficiency has contributed to positive lipid changes, including decreased levels of TC and LDL-C by 10-25%.⁸³⁻⁸⁸ There appears to be no significant effect on TG levels and data is conflicted on changes in HDL-C, with most studies demonstrating an increase in serum HDL-C.⁸⁴ Conversely, studies have showed no effect on HDL-C, as well as a decrease by approximately 20% has been reported.⁸⁹ There is some data to suggest that individual response to growth hormone on lipid metabolism is partly influenced by genetic polymorphisms in genes related to lipid metabolism.⁹⁰

A recent prospective, open-label, single-center study reports the effects of 15 years of growth hormone replacement in 156 adults with growth hormone deficiency.⁸⁴ After prolonged therapy, there were decreases in serum levels of TC and LDL-C; with corresponding increases in HDL-C ($p < 0.001$ for all vs. baseline levels). There were no significant changes in serum TG levels. This long observational study demonstrates that treatment of growth hormone deficiency in adults results in sustained improvements in the serum lipid profile. This could be due to improvements in body composition or direct effects on lipid metabolism. Studies suggest that growth hormone may increase the expression of LDL receptors, improves the catabolism of LDL, increase the turnover of LDL, and increase apo B-100 turnover. Nonetheless, evidence that these improvements result in decreased mortality from ASCVD remains unknown.

RETINOIDS

Retinoids are synthetic analogues of Vitamin A effective for the treatment of psoriasis, severe acne and other related skin disorders caused by abnormal keratinization. Oral isotretinoin was first reported to cause hypertriglyceridemia; most likely due to a reduction in the clearance of VLDL particles, which interferes with lipoprotein lipase-mediated lipolysis.^{91,92} Retinoids have also been shown to increase plasma apo C-III concentrations by increasing the transcriptional activity of the human apo C-III gene via the retinoid X receptor (RXR), ultimately contributing to the development of hypertriglyceridemia.^{93,94} Isotretinoin has been established as effective treatment for severe nodular acne that is unresponsive to conventional therapy, including systemic antibiotics. However, it has been reported to cause a variety of adverse events with some potential serious consequences, including case reports of pancreatitis.⁹⁵ Patients with significantly elevated TG levels are more likely to develop pancreatitis and therefore, patients with preexisting hypertriglyceridemia should avoid retinoid therapy or use with extreme caution until TG levels can get better controlled. In addition, a baseline lipid profile should be obtained in all patients and TG levels checked at least once after four weeks of therapy. Patients with a higher risk of developing hypertriglyceridemia should be monitored more frequently.

Studies with isotretinoin have demonstrated a rise in VLDL-C, TG, LDL-C, and TC with a slight decrease in HDL-C.³ One study evaluated the subsequent risk in ASCVD in 104 men and women using isotretinoin for severe acne using the ratio of TC/HDL-C.⁸⁴ The results showed that in otherwise healthy individuals, the changes in lipid metabolism did not influence the overall risk of ASCVD significantly.

ANTIPSYCHOTICS

Antipsychotic medications can be highly effective in controlling psychiatric illnesses. However, some of these are also associated with metabolic adverse events that can increase the risk for ASCVD.⁹⁶⁻⁹⁹ One such adverse event includes dyslipidemia, with increases primarily occurring in TG levels. Phenothiazines, which are first generation or 'typical' antipsychotics, were found to elevate serum TG and TC levels soon after their approval, with a greater effect on TG levels. Studies have shown an increase of up to 22% after a year of treatment with chlorpromazine.³

Further studies have observed similar effects with trifluorinated phenothiazines and haloperidol. The main limiting adverse effects of first generation antipsychotics are extrapyramidal symptoms and other movement disorders due to their high-affinity of dopamine D₂ receptors. Still, the possibility that these drugs also contribute to lipoprotein abnormalities should be considered in patients with dyslipidemia or high CV risk.

Second generation, or 'atypical' antipsychotics were later developed to reduce relapse rates and adverse events. Compared to first generation antipsychotics, they have lower affinity for the D₂ receptors and instead act namely on serotonin and norepinephrine. They have become first line treatment due to a lower potential risk of extrapyramidal symptoms. However, metabolic side effects including an increase in serum TG levels as well as minor increased in TC, has also been demonstrated with the use of second generation antipsychotics. Some studies suggest this is a result of increased leptin levels; an adipocyte hormone that corresponds with a decrease in the synthesis of fatty acid and TG and an increase in lipid oxidation.¹⁰⁰ There are many other possible mechanisms for the drug induced hyperlipidemia and the exact mechanisms are not fully understood. Clozapine, a second-generation antipsychotic, was the first agent shown to increase serum TG levels.¹⁰¹ A retrospective study reviewed patients on clozapine and found that men on clozapine had an average 48.13% increase in TG level and women 35.38% and there was a significant interaction between drug and gender over time ($p<0.05$).¹⁰¹

In addition, weight gain is a common adverse effect of using atypical antipsychotics which can also lead to an increase in both leptin and TG levels.¹⁰⁰ The 5-HT_{2c} receptor-blocking and/or histamine antagonism action of these medications is a possible cause of the related weight gain. One study demonstrated a significant increase in weight and serum TG and leptin levels with olanzapine and clozapine, with minimal and moderate changes in those on risperidone and quetiapine, respectively.¹⁰⁰ However, this was an extremely small study ($n=56$) that and it is difficult to translate these results to the general population. This is consistent with the overall evidence and it appears that clozapine and olanzapine have the greatest effect on the risk of hyperlipidemia, followed by quetiapine. Risperidone, ziprasidone and aripiprazole have a relatively low risk of hyperlipidemia associated with their use.¹⁰¹ As access to general and preventive care remains a limitation for patient populations with schizophrenia, these adverse effects can be of great concern for a population already at increased risk of CV complications. Therefore, checking baseline lipid levels and screening for the duration of therapy may be necessary in patients receiving therapy with atypical antipsychotics. If a patient develops elevated TG levels or dyslipidemia, they should be offered lipid-lowering therapy or if possible, switched to a less offending agent.

ANTICONVULSANTS

Changes in serum lipid levels have been reported with the use of various anticonvulsants with variability and inconsistency in the literature. Some observational studies have reported elevated levels of LDL-C and HDL-C while others have shown no significant effects. Triglyceride levels are not influenced by treatment with anticonvulsants. Since most anticonvulsants induce

the hepatic cytochrome P450 (CYP) enzymes, it is theorized that competition between the medication and cholesterol for the enzyme occurs which results in a decreased breakdown of cholesterol to bile acids and an increase in TC.⁹ This inconsistency has been noted in studies in both adults and pediatrics with epilepsy and it appears differences may exist based on the individual anticonvulsant used. In addition, the influence of therapy on development of atherosclerosis remains debatable.

Epilepsy often requires lifelong therapy and the long-term administration of some antiepileptic drugs (AEDs) is associated with metabolic side effects from dysfunction of the vessel wall. In particular, carbamazepine and phenobarbital have shown to cause alterations in the lipid profile. In children and adolescents with epilepsy, carbamazepine has demonstrated a consistent increase in TC and LDL-C levels, while some individual studies have also shown an increase in HDL-C as well as TG levels.^{102,103} Treatment of epilepsy in children with phenobarbital has also shown increased TC, LDL-C and HDL-C, as well as lower TG levels. Valproic acid appears to have little effect, or even a slightly favorable effect, on the lipid profile.¹⁰²

IMMUNOSUPPRESSIVES

Corticosteroids

It has been generally postulated that chronic glucocorticoid excess is a secondary cause of dyslipidemia, but the degree of lipid abnormalities in clinical conditions is extremely variable and studies have remained conflicted and inconsistent.¹⁰⁴ Observational studies of steroid treatment in patients with asthma, rheumatoid arthritis, or connective tissue disorders have shown elevations in TC, LDL-C, and serum TG levels.^{3,105} These are all illnesses that may require long-term treatment with corticosteroids. However, a large survey demonstrated no association with an adverse lipid profile and glucocorticoid use.¹⁰⁶ One study found that pre-menopausal females who were taking corticosteroids for a mean of 3.1 years had a significant elevation in TC and decrease in HDL-C. Conversely, a study in female patients with asthma noticed a significant increase in serum TG but no changes in TC.¹⁰⁷ The potential mechanisms of the effect on the lipid profile is multifactorial. One theory for this increase in TG is due to the redistribution of body fat caused by corticosteroid treatment to the upper trunk and face with a loss of fat in the extremities resulting in cells with fewer glucocorticoid receptors in addition to the stimulation of both lipolysis and lipogenesis.¹⁰⁴ This results in a spared effect on glucose transport in cells with fewer receptors resulting in an accumulation of glucose and TG secondary to a rise in insulin levels.¹⁰⁸ Insulin resistance also plays a role in lipid abnormalities. In the liver, glucocorticoids cause hyperglycemia, increase VLDL production, enhance hepatic lipogenesis and inhibit fatty acid β -oxidation. Furthermore, they increase the synthesis and secretion of apolipoprotein AI.

Changes in lipid metabolism due to corticosteroid treatment has also been evaluated in women with systemic lupus erythematosus (SLE).¹⁰⁹ Patients with SLE may be at an increased risk for atherosclerotic CAD, which could be potentiated by the changes in lipid serum levels from corticosteroid administration. When compared to women with SLE not treated with prednisone, patients on prednisone had higher TG, TC, and LDL-C levels.¹⁰⁹ It appears that women may be

more prone to these changes than men, and in many of these chronic illnesses, the use of corticosteroids is unavoidable. It is prudent to educate patients about the risks and benefits associated with long-term therapy with corticosteroids and to support life-style changes that help prevent ASCVD.

Cyclosporine and Tacrolimus

Cyclosporine and tacrolimus are immunosuppressant agents used as mainstay therapy for solid organ transplant recipients. Several metabolic abnormalities are associated with the use of both of these medications, including glucose intolerance, bone loss, and elevations in TC and LDL-C and apo B-100 levels. Effects on HDL-C levels are inconsistent, but trials have also demonstrated increases in HDL-C.⁹ Hyperlipidemia can occur in up to 60% in post-transplant patients.¹¹⁰ This is due to a combination of factors, including post-transplant obesity, multiple drug therapy (including steroids and other immunosuppressants) and diabetes. These drug effects are much greater with cyclosporine than tacrolimus, which has minimal effects on TC and LDL-C, and smaller effects on TG levels than cyclosporine.¹¹¹ A randomized prospective trial compared a tacrolimus-based regimen to a cyclosporine-based regimen in patients undergoing a cardiac transplant. After 12 months of therapy, serum TC, LDL-C, HDL-C and TG were significantly higher in the cyclosporine group compared to tacrolimus and more patients received medical treatment for elevated lipids (71% vs. 41%; $p=0.01$).¹⁰⁰ The impact of cyclosporine on lipid levels appears to be dose dependent and trough blood levels correlate with the elevations in TC and LDL-C, as well as reductions in HDL-C levels.¹¹² The mechanisms by which cyclosporine causes hyperlipidemia are unclear, as the effects in humans are confounded by many other factors in transplant patients.

Due to the complex state of transplant patients and the increased risk of ASCVD, attention should be given to these adverse events and other risk factors. Serum drug levels should be monitored during treatment as increases in drug levels are associated with negative adverse events. In addition, if appropriate, conversion from cyclosporine to tacrolimus can be considered if post-transplant hyperlipidemia occurs, and several studies have demonstrated this.¹¹³⁻¹¹⁵ Although patients may benefit from therapy with a HMG-CoA reductase inhibitor, concomitant use of cyclosporine and HMG-CoA reductase inhibitors has been shown to increase the risk of myopathy and rhabdomyolysis due to a potential drug-drug interaction through inhibition of the CYP3A-mediated metabolism of simvastatin and cyclosporine inhibition of the organic anion transporter protein (OATP1B1)-mediated hepatic uptake of simvastatin.^{116,117} As pravastatin and fluvastatin are not significantly metabolized by CYP enzymes, they may be a favorable choice in this patient population due to the decreased risk of drug-drug interactions.¹¹⁸ However, pravastatin and fluvastatin doses should still be lowered due to cyclosporine inhibition of the OATP1B1-mediated hepatic uptake. Furthermore, fluvastatin has been shown to reduce CV events and lower LDL-C concentrations in transplant recipients receiving immunosuppressive therapy with cyclosporine.¹¹⁹

ANTIVIRAL THERAPY

Protease Inhibitors

Protease inhibitors (PIs) are potent antiretroviral drugs used in combination with other therapy as part of a antiretroviral regimen for the treatment of human immunodeficiency virus (HIV).¹²⁰ These PIs have substantial clinical benefits, but can also produce lipodystrophy, hyperlipidemia, and insulin resistance.^{121,122} The hyperlipidemia is thought to be caused by increases in VLDL production and intermediate density lipoproteins (IDL) with the potential to cause endothelial dysfunction and atherosclerosis. Enzymes imperative for the removal of triglyceride rich lipoproteins are also decreased in HIV patients. This includes lipoprotein lipase and hepatic lipase. PI associated insulin resistance and abnormal expression of the apolipoprotein C-III gene may also induce dyslipidemia.¹²³

Studies evaluating PIs have shown increases in TC as well as triglycerides with little to no effects on HDL-C and inconsistent increases in LDL-C levels.¹²⁴ There is insufficient evidence directly linking dyslipidemia and the risk of CHD in HIV infected individuals. The main increase being in triglyceride-containing lipoproteins supports the mechanism of a release of free fatty acids and resulting increase in synthesis of VLDL causing these changes. While all PIs can change lipid levels, ritonavir appears to have the greatest effects and has also been reported to cause cases of extreme hyperlipidemia. During a randomized, 4-week double blind study, ritonavir was associated with at least a doubling of the serum triglyceride level in 24 (61%) patients compared to only 4 (19%) patients on placebo ($p=0.003$) and seven subjects had triglyceride levels exceeding 1000 mg/dl.¹²⁵ Patients with high serum triglyceride levels are at a higher risk of pancreatitis, which has been reported after protease inhibitor therapy.¹²⁶ Therefore, the long-term complications of elevated lipids in the setting of HIV should be taken into consideration in patients treated with PIs. Guideline supported lipid lowering therapy and efforts to modify other CV risk factors should be initiated in patients.¹²⁷ Guidelines from the HIV Medicine Association and Infectious Disease Society of America (IDSA)/Adult Aids Clinical Trials Group recommend pravastatin or atorvastatin as initial therapy for elevated LDL-C to avoid potential drug-drug interactions with PIs mediated through the CYP450 enzyme system.¹²³ Gemfibrozil or fenofibrate are recommended when triglyceride concentrations are greater than 500 mg/dl.¹²³ In higher risk patients, switching to a treatment regimen without a PI is another option.

Direct Acting Antivirals

Regimens of direct acting antivirals (DAAs) have vastly changed the treatment of chronic hepatitis C (CHC) since the approval of sofosbuvir in 2014. The DAAs have shown to be more effective than previous standard of care (interferon-based treatments such as pegylated interferon and ribavirin) in producing sustained virologic response (SVR) of $\geq 90\%$ and are associated with fewer side effects.¹²⁸ There are currently four classes of DAAs, defined by their mechanism of action and therapeutic target (NS3/4A inhibitors, protease inhibitors [PIs], NS5B inhibitors and NS5A inhibitors).¹²⁸ Recommended regimens today consist of multiple antivirals that target different sites to improve efficacy and decrease resistance rates.

While the hepatitis C virus itself can impact lipid metabolism, treatment with a DAA regimen has been associated with short term increases in LDL-C, TC, and HDL-C.¹²⁹ There do not appear to be any significant effects on TG's. This effect may result from a cancellation of the suppressive effect from HCV viral replication or from direct pharmacologic activity of the DAA's themselves.¹³⁰ The magnitude of effect does seem to vary based on DAA regimen with an increase in LDL-C of up to 27% reported. More studies are needed to elucidate the exact mechanism of action and which regimens have the greatest impact.

Since treatment duration is defined and short term (12-24 weeks), it is unlikely that these changes will negatively impact long term CV health. However, it is important to acknowledge that many of these agents have pharmacokinetic drug-drug interactions with statins. Clinicians may elect to temporarily hold statin therapy which may also contribute to changes in the lipid profile during the treatment period.

INTERFERONS

Interferons are associated with a wide range of systemic complications including neuropsychiatric changes, fatigue, and bone marrow suppression. Although metabolic side effects are less frequent, α interferon is known to inhibit lipoprotein lipase, stimulate hepatic lipogenesis and is associated with an increase in TG.^{131,132} A cohort study of patients with chronic hepatitis C on treatment with various forms α interferon were evaluated for changes in TG and TC.¹³² Overall, mean serum TG levels rose 40% at 12 weeks and returned to baseline by 24 weeks after stopping therapy. However, the effect on individual patients was variable and 41 patients (27%) experienced TGs that more than doubled from baseline. There was no significant change in TC noted. The long-term complications of this have not been evaluated and no patients in the study developed acute pancreatitis. It appears that any significant clinical consequence from this rise in TG is extremely rare. There did not seem to be a difference in change in levels based on the specific form of α interferon that was used, including the long-acting PEGylated forms.

As the landscape for the treatment of chronic hepatitis C transitions to interferon-free regimens with DAAs, this may be irrelevant in these patients. However, this effect on TG has been seen in the treatment with interferons for other illnesses, including chronic myelogenous leukemia and other cancers.^{133,134} It has recently been elucidated that interleukin-10 plays a key role in the linkage between inflammation and lipoprotein metabolism and that patients with cancer or other autoimmune diseases associated with elevated interleukin-10 levels can present with markedly decreased HDL-C, low LDL-C and elevated TG.¹³⁵ Patients receiving interferon treatment for the treatment of cancer can be considered for anti-dyslipidemic medications to manage secondary hypertriglyceridemia.¹³⁶

OTHER DRUGS THAT AFFECT LIPOPROTEIN LEVELS

Various other drugs have been reported to affect lipid and/or lipoprotein levels (Table 4). Lipid changes from these drugs are based on limited data, are reported inconsistently, and could be due to other disease related aspects. Thus, the effects on serum lipid levels cannot fully be substantiated.

Table 4. Other Drugs that Affect Lipid and/or Lipoproteins
Antacids
Ascorbic Acid
Aspirin
Cimetidine/ranitidine
Cyclophosphamide
Interferons
Ketoconazole
L-asparaginase
Neomycin
Aminosalicylic acid

MANAGEMENT

Several medication classes or individual medications can affect the lipid profile, both positively and negatively. Risk factors include elevated lipid levels at baseline and high cardiovascular risk patients. Identifying potential medications as the cause of these changes and monitoring the lipid profile while on therapy can provide value to the care of the patient. However, the long-term implications of these drugs on ASCVD mortality and morbidity remains unknown and there is limited evidence on the overall impact of these drug-induced changes.

A thorough risk-benefit analysis of each treatment should be done based on individual patient factors. In general, if negative changes in the lipid profile are observed during therapy, replacement with an equivalent alternative therapy can be recommended. If no equivalent therapy is available and treatment must be initiated, then monitoring of serum lipid levels is vital. The use of existing guidelines for the management of dyslipidemia in the general population can be referred to and in extreme cases; the use of the suspected medication should be reassessed.

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