Drug-Induced Dyslipidemia

15

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Introduction

Evaluation of patients with dyslipidemia must include a thorough investigation for secondary causes which may be exacerbating a primary lipid disorder. Lifestyle factors including diet, activity, and smoking, as well as comorbidities such as diabetes, hypothyroidism, liver, and kidney disease may contribute to elevated cholesterol and triglyceride levels. Similarly, medications used in the treatment of a variety of diseases may have adverse effects on lipid metabolism. The effects may vary from a thiazide-induced mild increase in serum cholesterol with unclear long-term consequences to a dramatic increase in serum triglycerides due to retinoid therapy leading to acute pancreatitis. A large group of medications have been identified to cause or worsen dyslipidemia, and since a growing number of patients are on polypharmacy, it is very important to be aware of the potential contribution of concomitant medications on hyperlipidemia. This brief chapter focuses on the magnitude, mechanisms, and management of lipid abnormalities induced by medications. The salient effects of some commonly used drugs on plasma lipids are summarized in Table 15.1.

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Antihypertensives

Beta-Adrenergic Blockers

Beta-adrenergic blockers are commonly used in the treatment of hypertension and coronary artery disease. Despite their proven efficacy in reducing cardiovascular morbidity and mortality, they are well known to cause unfavorable changes in lipid profile. Tanaka et al. [1] observed nearly 40 years ago that while acute administration of propranolol led to reduced free fatty acid levels, chronic treatment resulted in elevated serum triglycerides and reduced post-heparin-lipolytic activity, an effect that was reversed 10 days after drug withdrawal. Subsequent studies in the next decade showed a 24–46% increase in serum triglycerides with propranolol therapy [2, 3], a 18–36% increase with atenolol therapy [4, 5], and a 16% increase with metoprolol [6]. All these studies also showed a modest reduction in serum high-density lipoprotein (HDL) cholesterol, but no significant effect on total or low-density lipoprotein (LDL) cholesterol.

Nonselective beta-adrenergic blockers such as propranolol have generally been held to cause greater dyslipidemia than cardioselective (beta 1)-adrenergic receptor blockers [7, 8]. However, the new third-generation beta-adrenergic blocker, carvedilol, which is a nonselective beta 1- and beta 2-adrenergic receptor antagonist besides being a weak alpha 1-adrenergic receptor antagonist, is not associated with similar adverse effects

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Table 15.1 Effect of some commonly used medications on serum lipid levels

Drug	TC	LDL-C	TG	HDL-C
Beta blockers				
Atenolol, Metoprolol, Propranolol	N	N	↑	↓
Carvedilol	N	N	N	N
Diuretics				
Thiazides	↑	↑	↑-↑↑	↓
Loop diuretics	↑	↑	↑	N
Potassium sparing	N	N	N	N
Steroids				
Glucocorticoids	↑	↑	↑	↑-↑↑
Estrogens	↓	↓	↑-↑↑↑	↑
Tamoxifen	↓	↓	↑-↑↑↑	N-↑
Clomiphene	N	N	↑-↑↑↑	N
Progestogens	N-↑	N-↑	N-↓	N-↓
Androgens	N-↑	N-↑	↓	↓
Immunosuppressants				
Cyclosporine	↑-↑↑	↑-↑↑	↑-↑↑	↓
Tacrolimus	N-↑	N-↑	N-↑	N
Sirolimus	↑	↑	↑-↑↑↑	↓
Antineoplastic agents				
Retinoids	↑	↑	↑-↑↑↑	N-↓
Interferons	N-↑	N-↑	↑-↑↑↑	N-↓
Capecitabine, L-asparaginase	N-↑	N-↑	↑-↑↑↑	N-↓
Antipsychotics, atypical	N	N	↑-↑↑↑	↓
Antiepileptics	N-↑	N-↑	N	N-↑
Protease inhibitors	↑	N-↑	↑-↑↑↑	N-↓
Propofol	N-↑	N	↑-↑↑↑	↓

↑ increase, ↓ decrease, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *N* no change, *TC* total cholesterol, *TG* triglycerides

on lipid profile. A post hoc analysis of the Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) trial showed favorable lipid effects of carvedilol compared to metoprolol in over 1200 subjects with diabetes [9]. Sharp et al. [10] analyzed 12 carvedilol studies, 6 of which compared carvedilol with selective beta 1-adrenergic antagonists and found that carvedilol had either a neutral or a mild beneficial effect on serum lipids. This difference may be due to the alpha 1-antagonist action as alpha-adrenergic blockers such as prazosin have been consistently shown to reduce serum triglycerides and increase HDL cholesterol [2, 11, 12]. Alpha-adrenergic stimulation is known to inhibit lipoprotein lipase activity [13], and the reflex increase in alpha-adrenergic activity that occurs during beta-adrenergic blocker therapy may be responsible for impaired triglyceride removal and hypertriglyceridemia.

Interestingly, the adverse effects of beta-adrenergic blocker therapy are most evident in patients with baseline hypertriglyceridemia [14, 15], and recently, beta 2-adrenergic receptor polymorphisms have been shown to influence serum triglyceride levels during metoprolol treatment [16]. While future studies in this direction may help identify patients who are most prone to develop hyperlipidemia during beta-adrenergic blocker therapy, it would be prudent at this time to use these medications cautiously in patients with abnormal lipid levels, and consider using carvedilol in dyslipidemic patients who need beta-adrenergic blocker therapy.

Diuretics

Diuretics are one of the oldest and most commonly used medications for hypertension, and the Joint National Commission on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7) recommends thiazide diuretics as the first line of therapy unless there are compelling indications for other drug classes [17]. However, thiazide diuretics including hydrocholorothiazide and chlorthalidone have been noted to increase both total and LDL cholesterol by 6–7%, increase triglycerides by about 15%, and cause a mild reduction in HDL cholesterol [5, 18–22]. A large meta-analysis of 474 trials involving more than 65,000 patients showed that diuretic therapy increased total cholesterol by an average of 0.29 mmol/L (11 mg/dL), LDL cholesterol by 0.24 mmol/L (9 mg/dL), and triglycerides by 0.35 mmol/L (31 mg/dL), and reduced HDL cholesterol by 0.02 mmol/L (1 mg/dL) [23]. Further, these effects were more pronounced in African Americans and at higher doses, but did not depend on the type of diuretic used. However, limited data from small studies suggest that loop diuretics and potassium sparing diuretics have only a mild or neutral effect [8, 24–26].

The mechanisms by which diuretics induce dyslipidemia are not very clear, but may involve a reflex activation of alpha-adrenergic activity and renin–angiotensin–aldosterone axis as a result of volume depletion [13, 27]. This could lead to increased lipolysis and increase in hepatic very low-density lipoprotein (VLDL) and LDL synthesis. Thiazides are also known to cause insulin resistance [19, 28] and glucose intolerance due to hypokalemia [29, 30] which may also contribute to lipid effects.

The clinical significance of thiazide-induced dyslipidemia is also not very clear. In the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack (ALLHAT) trial, a randomized double-blind study of over 33,000 hypertensive patients, chlorthalidone therapy was associated with higher total cholesterol levels, but with lower cardiovascular events [31]. While this might suggest that the mild dyslipidemia induced by thiazides has no deleterious effects, it is also possible that the lipid effects might have decreased the overall benefits of blood pressure reduction. A safe strategy would be to use thiazides in low doses, especially in subjects prone to dyslipidemia.

Steroid Hormones

Glucocorticoids

Glucocorticoids are another commonly used group of medications which have generally been held to cause an adverse effect on lipid profile, including an elevation in both total and LDL cholesterol and triglycerides [8, 32]. However, it is often difficult to discern if the alleged lipid effects are due to the glucocorticoids or due to underlying disease and other concomitant medications. Studies in healthy volunteers have yielded inconsistent results, with one study reporting a 40% increase in serum triglycerides after 14 days of prednisone therapy [33], while others observed no significant effect on triglycerides, but the study duration was only 7 days [34]. However, both studies [33, 34] reported elevation in HDL cholesterol and no change in LDL cholesterol. A cross-sectional analysis of over 15,000 participants in the Third National Health and Nutrition Examination Survey showed that both oral and inhaled glucocorticoid use was associated with a higher HDL cholesterol level and lower total to HDL cholesterol ratio in subjects over age 60 years, but not with an adverse lipid profile [35]. Two other prospective studies have also shown a similar increase in HDL cholesterol levels with no change in LDL cholesterol or triglycerides [36, 37]. Other studies have shown that patients with systemic lupus erythematosus who are treated with glucocorticoids have a higher LDL cholesterol and serum triglycerides [38, 39]. A clear dose–response relationship between glucocorticoid dose and serum triglycerides and LDL cholesterol has been observed in hypopituitary patients on glucocorticoid replacement therapy [40]. Marked elevation in both total cholesterol and triglycerides is also noted in organ transplant recipients receiving glucocorticoid-inclusive

immunosuppression. This has been observed in patients undergoing renal transplantation [41, 42], cardiac transplantation [43, 44], and liver transplantation [45]. It must however be noted that these effects are not uniform, and many transplant recipients do not demonstrate any lipid abnormalities [46, 47]. Underlying medical conditions such as uremia and other concomitant medications such as cyclosporine and rapamycin may modulate the effect of glucocorticoids on serum lipids. Overall, it appears that the most consistent direct effect of glucocorticoids is to increase serum HDL cholesterol, sometimes by up to 20–40%, with a more variable effect on LDL cholesterol and triglycerides noted in only some patients.

The mechanism by which glucocorticoids raise HDL cholesterol is not well known, but may be secondary to an increase in lipoprotein lipase activity [34]. Further, most conditions requiring glucocorticoid therapy are associated with systemic inflammation and low HDL cholesterol, and glucocorticoids may raise HDL by their anti-inflammatory effect [48]. Glucocorticoids also increase lipolysis, hepatic steatosis, and insulin resistance [49] which can increase VLDL production and thus increase serum triglycerides and LDL cholesterol.

Estrogen and Related Compounds

The lower incidence of coronary heart disease in premenopausal women compared to men, and the increase in LDL cholesterol in women after menopause, suggests a beneficial effect of estrogens on the lipid profile. Indeed, unopposed estrogen administration does lead to reduction in total and LDL cholesterol and increase in HDL cholesterol [50, 51]. However, these and other studies [52–54] have also shown a 30–40% increase in serum triglyceride levels. The hypertriglyceridemic effect of estrogens is dose dependent, and most prominent in patients with baseline hypertriglyceridemia. In the large Postmenopausal Estrogen/Progestin Interventions (PEPI) trial, about 1.5% of the subjects had serum triglycerides above 500 mg/dL [51], and there are many instances of estrogen-induced pancreatitis from hypertriglyceridemia in patients with underlying lipid disorders such as type I hyperlipoproteinemia [55, 56] and lipodystrophy [57]. Estrogens increase VLDL production [58] which accounts for the hypertriglyceridemic effect despite a direct modest increase in clearance of apolipoprotein B-containing particles. In subjects who already have impaired clearance of these particles (type I or type III hyperlipoproteinemia), or have increased VLDL secretion (lipodystrophy, metabolic syndrome), further increase in VLDL production leads to severe hypertriglyceridemia. Unlike oral estrogen, transdermal estrogens, which do not undergo first-pass metabolism in the liver, have only minimal effects on lipid levels [59].

Estrogens are often administered in combination with progesterone, such as in combined oral contraceptives, which modifies their effect on lipids. Both natural progesterone and its synthetic derivatives have a weak androgenic effect. When used alone in high doses, they increase LDL cholesterol and decrease triglycerides and HDL cholesterol [60], but low doses such as progesterone-only pill have minimal effects [61], while depot medroxy progesterone acetate preparations cause a 15–30% decline in serum HDL cholesterol levels [62, 63]. More recent long-term studies showed that the HDL-lowering effect of depot medroxy progesterone acetate was temporary and improved after 6 months even when the drug use was continued [64]. Progestogens, like androgens, are thought to decrease HDL cholesterol levels by increasing the activity of hepatic lipase leading to increased HDL catabolism [65]. The effect of combined oral contraceptives on lipids depends on the "androgenicity" of the progestogen being combined with estrogens. Oral contraceptives containing the older second-generation progestogens such as levonorgestrel and norethisterone, which have strong androgenic effects, increase LDL cholesterol and triglycerides and decrease HDL cholesterol [66, 67]. The newer third-generation progestogens such as desogestrel and gestodene are least androgenic and do not cause unfavorable effects on LDL and HDL cholesterol, but may cause hypertriglyceridemia [68–70]. Even the combined contracep-

tive vaginal ring containing ethinylestradiol and etonogestrel (NuvaRing) has been noted to increase serum triglycerides and apolipoprotein B levels in comparison with levonorgestrel containing combined oral contraceptives which increase LDL cholesterol [71]. In women at risk for severe hypertriglyceridemia, progesterone-only methods such as levonorgestrel intrauterine device, the etonogestrel implant, or progesterone-only pills containing desogestrel or levonorgestrel do not exacerbate the elevation in triglyceride levels [72–74]. Despite the mild increase in LDL cholesterol, combined oral contraceptives are unlikely to pose a significant cardiovascular risk, even in subjects with metabolic syndrome [75].

The selective estrogen receptor modulator tamoxifen also causes a modest reduction in total and LDL cholesterol [76], but may sometimes cause severe hypertriglyceridemia and acute pancreatitis [77–79]. Liu and Yang [80] sequentially followed 116 patients with breast cancer on tamoxifen therapy, and reported that 102 patients had clinically insignificant rise in serum triglycerides and there was improvement in 10 other subjects after dose reduction. Apolipoprotein E polymorphisms may influence triglyceride levels during tamoxifen therapy [81]. Raloxifene, another selective estrogen receptor modulator, has generally not been associated with severe hypertriglyceridemia, and has been even shown to reduce total cholesterol and apolipoprotein B levels in hypertriglyceridemic subjects [82]. Nonetheless, limited data suggest caution in using this drug also in patients who have experienced estrogen-induced hypertriglyceridemia [83]. Clomiphene is another synthetic estrogen analog which is structurally similar to tamoxifen and has been used to induce ovulation. Severe hypertriglyceridemia has been reported in three patients with polycystic ovarian disease during treatment with clomiphene, two of whom developed acute pancreatitis [84–86]. One of the patients was eventually diagnosed to have familial dysbetalipoproteinemia [85]. It is therefore important to screen patients for baseline dyslipidemia before starting this medicine. The aromatase inhibitors are not associated with hypertriglyceridemia, and though anastrazole has been reported to cause mild hypercholesterolemia, their effects on lipids is generally mild and clinically insignificant [87].

Androgens

Androgen replacement therapy in hypogonadal men has many beneficial effects including increase in lean body and bone mass, but is also noted to consistently lower HDL cholesterol by 10–20% [88–90]. The total and LDL cholesterol levels do not change much, or may decrease slightly. More dramatic changes are seen with administration of oral testosterone preparations with more than 50% decline in HDL cholesterol levels and a concomitant increase in LDL cholesterol, especially in athletes who abuse anabolic steroids [91–93]. Some studies have not shown significant change in HDL cholesterol when supraphysiologic doses of testosterone are administered parenterally in normal healthy men [94], but others have noted both a decrease in HDL cholesterol and an increase in LDL cholesterol [95, 96]. Supplementation of oral dehydroepiandrosterone (DHEA), a weak androgen, in both men and postmenopausal women has also been shown to reduce HDL cholesterol levels [97, 98]. Androgens have been shown to increase the activity of hepatic lipase and thus accelerate catabolism of HDL particles, besides decreasing apolipoprotein A1 synthesis, thus leading to low HDL cholesterol [99]. Single intramuscular dose of 500 mg of testosterone in healthy volunteers has been shown to increase the expression of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase enzyme and cause hypercholesterolemia [100]. It is important to closely monitor lipid levels in men on androgen replacement therapy, and to create awareness about these adverse effects among potential androgen abusers. Similarly, the use of leuprolide and other gonadotropin releasing hormone agonists for androgen deprivation therapy may cause elevation in total cholesterol, triglycerides, and HDL cholesterol besides other metabolic complications such as insulin resistance [101, 102].

Immunosuppressive Drugs

Recent advances in the development of new immunosuppressant drugs have greatly decreased acute rejection rates following solid organ transplantation. However, as the life span of organ transplant recipients improves, there is increasing awareness of long-term complications including dyslipidemia and accelerated atherosclerosis. Following cardiac transplantation, over 60% of subjects develop hyperlipidemia within a month, and the prevalence increases to over 90% by 10 years [47, 103]. Similarly, more than half of renal and liver transplant recipients also develop hyperlipidemia [104–107]. While multiple factors including underlying disease, comorbidities, diet, physical activity, and other host factors play a role in the genesis of posttransplantation dyslipidemia, immunosuppressive medications are probably the most important cause. Besides glucocorticoids, whose effects have already been discussed, cyclosporine and sirolimus are commonly associated with adverse lipid effects, while azathioprine and mycophenolate mofetil have only minimal effects.

Cyclosporine

The calcineurin inhibitors, cyclosporine and tacrolimus, suppress the transcription of inflammatory genes in the T cells by inhibiting the translocation into the nucleus of a critical transcription factor called nuclear factor of activated T cells (NFAT) [108]. They form the backbone of most immunosuppressive regimen, especially in renal transplant recipients. Cyclosporine can cause mild to moderate elevation in both total and LDL cholesterol and serum triglycerides [109–111]. Change in serum triglycerides and concomitant lowering of HDL cholesterol is less consistent than elevation in total and LDL cholesterol. Some studies have shown a correlation between lipid levels and cyclosporine levels and dosages, while others have not [104, 112–114]. Interestingly, cyclosporine-induced dyslipidemia has been observed to improve over time [115]. Elevation in total and LDL cholesterol has also been seen in non-transplant patients treated with cyclosporine [116, 117].

The exact mechanism by which cyclosporine increases cholesterol and triglyceride levels is not known, and may involve multiple pathways (Fig. 15.1). In vitro studies suggest that cyclosporine decreases LDL receptor activity [118, 119], and may also decrease the conversion of cholesterol to bile acids by inhibiting the enzyme cholesterol 27-hydroxylase [120, 121]. Inhibition of this enzyme and the resultant decrease in levels of its product 27-hydroxycholesterol can further worsen hypercholesterolemia as 27-hydroxycholesterol is involved in the negative feedback inhibition of HMG CoA reductase, and increased activity of HMG CoA reductase could account for decreased LDL receptor activity [122, 123]. Interestingly, it has been shown that this reduction in LDL receptor activity can be reversed by administration of HMG CoA reductase inhibitors in an in vitro cell culture model [124] which establishes a basis for statin therapy for cyclosporine-induced hypercholesterolemia. Clinical trials have indeed shown the efficacy of statin therapy in both reducing cholesterol levels and increasing survival in heart transplant recipients on cyclosporine-based immunosuppression [125–127]. However, cyclosporine can increase the serum levels of statins such as lovastatin, simvastatin, and atorvastatin by competing with the hepatic cytochrome CYP3A4 enzymes involved in their metabolism. Fluvastatin and pravastatin may be safer to use in combination with cyclosporine [128–130].

Tacrolimus is also a calcineurin inhibitor like cyclosporine, but with much less effect on lipid metabolism. Lower levels of total and LDL cholesterol and triglycerides are seen in patients on tacrolimus-based therapy compared to cyclosporine, and improvement in lipids are noted when cyclosporine is switched to tacrolimus [131–134]. Thus, patients with significant cyclosporine-induced dyslipidemia can be managed either with cautiously dosed statin therapy [135] or by switching to tacrolimus which does not affect the efficacy of immunosuppression.

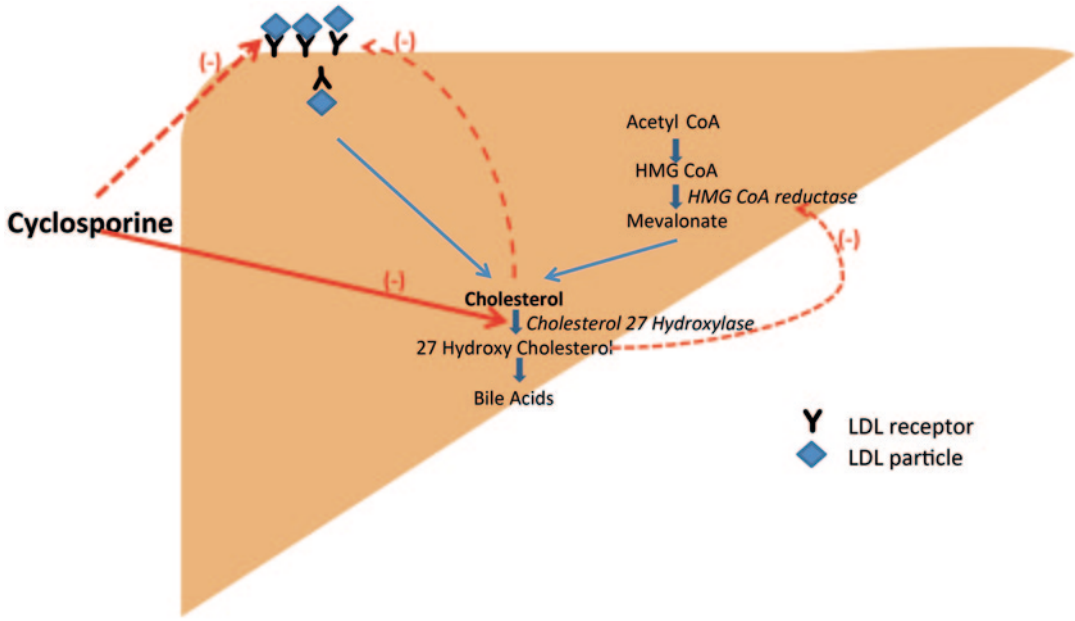

Fig. 15.1 Mechanisms of cyclosporine-induced hypercholesterolemia. Cellular cholesterol is derived from two sources, receptor mediated endocytosis of LDL particles and synthesis from acetyl CoA. Cholesterol is converted to bile acids in the hepatocytes for excretion. Cyclosporine interferes with the catabolism of cholesterol to bile acids by inhibiting the enzyme cholesterol 27-hydroxylase. In the process, it also decreases the production of 27-hydroxy cholesterol, which normally inhibits HMG CoA reductase, the rate-limiting enzyme in cholesterol biosynthesis. As a result of increased cellular cholesterol synthesis and decreased breakdown, there is inhibition of LDL receptor expression. Cyclosporine may also directly affect binding of LDL particle to the receptor

Sirolimus

Sirolimus or rapamycin is a newer immunosuppressive agent which is structurally similar to tacrolimus, but acts in a calcineurin-independent manner. It binds to the kinase enzyme, mammalian target of rapamycin (mTOR), leading to cell cycle arrest at the G1 to S phase of cell cycle, and subsequent inhibition of T cell activation and proliferation in response to cytokine stimulation [136]. Since it complements the action of calcineurin inhibitors, and has a different side-effect profile, it is often advantageous to combine low doses of these two classes of medications. However, use of sirolimus and other mTOR inhibitors such as everolimus and temsirolimus is also associated with many adverse effects [137] including hyperlipidemia. Dose-dependent elevation of serum triglycerides by up to 20% in 50–75% of renal and liver transplant patients on sirolimus has been reported [138–140]. In some patients, more marked serum triglyceride elevations up to 2000 mg/dL may be noted [141]. Reduction of sirolimus dosing and therapy with fibrates or statin may be helpful in some cases, while the medication had to be discontinued in other subjects to control the hypertriglyceridemia [141]. Mild increase in total cholesterol and reduction in HDL cholesterol may also occur. The mechanisms by which sirolimus causes dyslipidemia (Fig. 15.2) are not clear, but may involve both an increase in apolipoprotein B and VLDL synthesis and a decrease in triglyceride hydrolysis due to increase in apolipoprotein CIII levels [142–144]. Further, inhibition of mTOR has been shown to increase the expression of PCSK9 which leads to reduced LDL receptors and an increase in LDL/VLDL cholesterol [145].

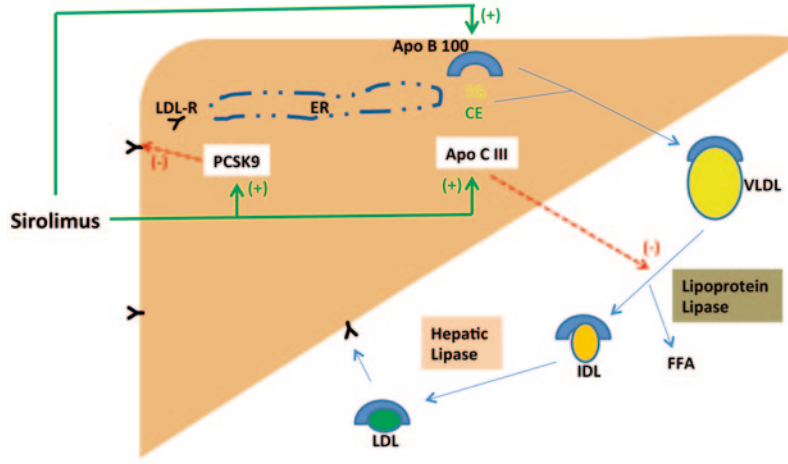

Fig. 15.2 Mechanisms of sirolimus-induced hyperlipidemia. Sirolimus increases *Apo B* levels and thus *VLDL* secretion. In addition, it increases production of *Apo C III* which inhibits the activity of lipoprotein lipase leading to decreased *VLDL* triglyceride hydrolysis. Both these actions cause hypertriglyceridemia. Further, it can increase *PCSK9* expression leading to increased destruction of LDL receptors (*LDL-R*), decreased clearance of *LDL* particles, and resultant hypercholesterolemia

Antineoplastic Agents

Retinoids

Retinoids have been used both locally and systemically in the treatment of a variety of skin disorders including acne, psoriasis, cutaneous T cell lymphoma and other hyperkeratotic disorders. They are vitamin A derivatives and include isotretinoin (13-cis retinoic acid), tretinoin (all-trans retinoic acid), acitretin, alitretinoin, and bexarotene.

Isotretinoin is a naturally occurring metabolite of retinol used in the treatment of severe acne vulgaris. Marked elevation in serum triglycerides and a mild elevation in serum total cholesterol may however occur with this therapy, and may also increase risk for diabetes mellitus or metabolic syndrome in the future [146–148]. A large retrospective analysis of over 13,000 patients with no baseline lipid abnormalities showed that 44 % of the subjects developed hypertriglyceridemia, 31 % had elevation in total cholesterol levels, and 11 % an increase in hepatic transaminase levels [149]. These abnormalities were however generally transient and reversible, but marked hyperlipidemia and acute pancreatitis can also occur [150]. Patients with baseline elevations of cholesterol and triglycerides are more likely to experience more severe elevations, and frequent monitoring of lipid levels is necessary in such patients if they are started on isotretinoin [151].

Acitretin is a synthetic derivative of retinoic acid used in the therapy of psoriasis which can also cause hyperlipidemia, but to a lesser degree [152, 153]. Bexarotene is also a synthetic derivative of retinoic acid which is used in the treatment of cutaneous T cell lymphoma. Over half of these patients have been reported to develop hypertriglyceridemia and central hypothyroidism [154, 155]. Interestingly, when bexarotene was used in a phase III trial of advanced non-small cell lung cancer, subjects who developed hypertriglyceridemia had longer survival which was associated with certain genetic polymorphisms [156].

The mechanism by which retinoids induce hyperlipidemia is thought to involve their interaction with nuclear receptors, Retinoid receptors (RAR) and retinoid X-receptor (RXR), and the nuclear transcription factor, FOXO1, which leads to decreased hepatic fatty acid oxidation and increased VLDL synthesis and secretion. There is also decreased triglyceride hydrolysis due to increased apolipoprotein CIII [157, 158]. Some of

these actions can be antagonized by peroxisome proliferator-activated receptor-α agonists which have opposing effects on fatty acid oxidation and VLDL secretion. Indeed, fibrates and fish oil supplementation have been reported to improve hypertriglyceridemia in patients treated with retinoids [159–161], but it would be best to avoid using them in patients with baseline hypertriglyceridemia.

Central hypothyroidism may also contribute to hyperlipidemia in bexarotene-treated patients, and it is important to check both thyroid-stimulating hormone (TSH) and free thyroxine levels in these patients. Among 27 patients with cutaneous T cell lymphoma on bexarotene therapy, 26 developed reversible TSH suppression, and 19 developed overt clinical hypothyroidism [162]. A single dose of bexarotene has also been shown to suppress TSH levels without any effect on other pituitary functions [163]. Data from mice studies suggest that this is due to direct suppression of transcription of TSH β subunit gene in the pituitary thyrotrophs [164]. Therefore, before employing lipid-lowering therapy in bexarotene-treated patients, adequate levothyroxine replacement should be given to maintain serum-free thyroxine levels near the mid-normal or even high-normal range.

Interferons

The use of interferon-α in the treatment of chronic hepatitis C infection, and as an adjuvant to chemotherapy and radiotherapy in certain malignancies is becoming increasingly popular. One of the adverse effects of interferon therapy is hypertriglyceridemia [165–168]. Serum triglycerides increased by nearly 70% during 1 year of interferon therapy for chronic hepatitis C, but returned to normal when the drug was discontinued [169]. While none of these patients developed significant hypertriglyceridemia, marked hypertriglyceridemia leading to acute pancreatitis has been reported [170]. Elevation in serum triglycerides is usually noted within 4 weeks of treatment initiation and is not dose dependent and can occur in patients with normal baseline triglycerides. Interferons have been shown to reduce hepatic triglyceride lipase activity which may be responsible for the hypertriglyceridemic effect [171, 172]. In vitro studies have also shown that they can stimulate hepatic triglyceride synthesis [173] which may also be contributing to elevated triglyceride levels. Patients with significant triglyceride elevations can be treated effectively with low-dose fibrates if lifestyle modification is not sufficient [174].

L-Asparaginase

L-Asparaginase (L-asp) is used in the treatment of hematological malignancies such as acute lymphocytic leukemia (ALL) where it works by reducing the availability of the essential amino acid L-asparagine to the malignant lymphoblastic cells. More than 60% of patients treated with this medicine develop mild hypertriglyceridemia which is usually benign and transient [175–177]. However, severe hypertriglyceridemia leading to acute pancreatitis or hyperviscosity syndrome causing neurological complications can also occur [178–182]. Some of these patients required plasmapheresis or intravenous insulin-dextrose infusion to correct the acute, severe hypertriglyceridemia, but many patients can be managed conservatively by fasting or low-fat diet [177]. Drug therapy using fibrates, omega-3 fatty acids, and acarbose have also been reported to be beneficial [177, 183–185]. Dexamethasone is often used along with L-asp and may exacerbate the hyperlipidemia. Avoidance of concomitant dexamethasone has been reported to improve serum triglyceride levels despite continuation of L-asp [186]. Interestingly, rechallenge with L-asp has been reported to have not led to recurrent hypertriglyceridemia in three children with ALL [187]. L-asp has been shown to inhibit lipoprotein lipase action which is responsible for the chylomicronemia and hypertriglyceridemia [188]. Some investigators have also shown an increase in ratio of apolipoprotein CIII to apolipoprotein CII before the onset of hypertriglyceridemia, thus suggesting that increased apolipoprotein CIII activity may also contribute to decreased triglyceride clearance [189].

Capecitabine

Capecitabine is a novel oral antineoplastic agent used in the treatment of colorectal carcinoma and other metastatic gastrointestinal and breast cancers. It is a prodrug which leads to increased levels of 5-flurouracil within the cells. While 5-flurouracil is itself not known to cause any adverse lipid effects, there have been about a dozen reports of severe hypertriglyceridemia due to capecitabine [190–196]. Serum triglycerides normalized after drug discontinuation and increased on rechallenge. A prospective study in over 200 patients on capecitabine showed that 3.7% of the patients developed clinically significant hypertriglyceridemia [197]. Most patients responded well to fenofibrate therapy without any need for drug discontinuation, and there were no cases of pancreatitis. However, capecitabine has been reported to cause pancreatitis without triglyceride elevation [198, 199]. The mechanism by which capecitabine leads to triglyceride elevation is not known, post-heparin plasma lipolytic activity has been reported to be normal [196].

Atypical Antipsychotics

The second-generation (atypical) antipsychotics have gained popularity over phenothiazines because of their better efficacy and less extra-pyramidal side effects. However, they are increasingly recognized to cause weight gain and lead to the metabolic syndrome [200–204]. Weight gain due to increased appetite may be mediated by the combined blockade of H1 histamine and serotonin 2C receptors on the hypothalamic neurons regulating feeding behavior [205, 206]. Dyslipidemia in the form of elevated serum triglycerides and low HDL cholesterol could be secondary to obesity and diabetes, but direct lipid effects independent of obesity are also thought to be at play. Increased transcriptional activity of lipid biosynthetic enzymes such as fatty acid synthase and steroyl CoA desaturase has been observed in peripheral blood cells of patients being treated with olanzapine [207]. In vitro studies have also shown the ability of atypical antipsychotics to directly impair insulin signaling and fatty acid uptake and release in cultured adipocytes [208]. The most consistent clinical effect noted is a slight increase in serum triglycerides and reduction in HDL cholesterol leading to increased ratio of LDL to HDL cholesterol, but severe hypertriglyceridemia and pancreatitis can also occur [209–211].

A pharmacovigilance study of pooled, spontaneously reported adverse events showed that, of the 192 patients who developed pancreatitis when on antipsychotic medications, more than 90% were on one of the three atypical antipsychotics, clozapine, olanzapine or resperidone, even though maximum patient exposure was to haloperidol [212]. Among the different antipsychotics, clozapine and olanzapine are associated with the highest risk for metabolic complications followed by resperidone and quetiapine, while ziprasidone and aripiprazole have the least risk [206, 213].

There is lot of interest in trying to identify genetic risk factors which predispose to dyslipidemia during treatment with these medications, and polymorphisms in apolipoprotein A5, leptin, and leptin receptor gene have been reported to increase the risk [214, 215]. While further studies in this direction may help identify at-risk patient, it is important at this time to monitor lipids at regular intervals in patients being treated with second-generation antipsychotics. Similarly, some of the selective serotonin receptor reuptake inhibitors used in the treatment of depression such as sertraline and paroxetine may rarely cause mild elevations in cholesterol and triglyceride levels, which need to be monitored.

Antiepileptic Drugs

The effect of chronic antiepileptic therapy on atherosclerotic risk factors and incidence of coronary heart disease is controversial. Some studies have reported a lower risk of death from coronary heart disease in patients on antiepileptic drugs [216], while others have shown an increased risk [217]. While many factors may play a role in determining the overall cardiovascular risk and thus explain these discrepancies, the effect of these med-

ications on lipid profile is also not very clear. In general, majority of studies have shown that carbamazepine and phenobarbital modestly increase total and LDL cholesterol, often accompanied by an increase in HDL cholesterol as well [218–222]. Most studies did not show significant effect on serum triglycerides, though some did report a significant increase with carbamazepine [223, 224].

The mechanisms by which these medications cause dyslipidemia are not clear. Since these drugs are metabolized by the hepatic cytochrome P450 enzymes, it has been proposed that they competitively interfere with the catabolism of cholesterol to bile acids which is also catalyzed by the same enzyme system [218, 225]. Hypercholesterolemia could also be augmented by the mild hypothyroidism often seen in association with these drugs [226].

Valproic acid and other newer antiepileptics such as topiramate and oxcarbazepine have minimal adverse effects on lipid profile, and some studies have even reported a modest improvement [218, 222, 224, 227]. Whether long-term antiepileptic therapy in children adversely effects cardiovascular risk is still not clear, but it may be advisable to use newer agents such as oxcarbazepine and topiramate in children with strong family history of cardiovascular disease [228].

Propofol

Propofol is an anesthetic agent used for long-term sedation in critically ill patients. It is administered in a lipid emulsion and has been associated with a moderate to severe triglyceride elevation [229, 230]. Pancreatitis has also been reported to occur, though it may be independent of hypertriglyceridemia [231]. A retrospective analysis of 159 intensive care patients treated with propofol infusion for over 24 h showed that 18% of patients developed serum triglyceride elevations over 400 mg/dL [232]. Six of these patients had serum triglycerides over 1000 mg/dL and three developed pancreatitis. The median time from start of propofol therapy to identification of hypertriglyceridemia was 54 h. A recent prospective observational study also identified propofol administration as the strongest risk factor for hypertriglyceridemia in 1300 patients admitted consecutively to the intensive care unit [233]. It is recommended that triglyceride levels be checked at least twice a week when patients are on propofol. It is not clear if the triglyceride increase is due to the lipid emulsion or a direct effect of propofol on lipid metabolism.

Protease Inhibitors

The role of human immnuodeficiency virus-1 protease inhibitors in the genesis of hyperlipidemia in association with lipodystrophy has been discussed in another section.

Conclusions

A variety of commonly used drugs including antihypertensives, steroids, immunosuppressants, antineoplastic agents, antipsychotics, and others can cause mild to severe alterations in serum lipid levels. It is important to recognize these effects when evaluating patients with dyslipidemia. The optimal treatment of drug-induced dyslipidemia would obviously be discontinuation of the medication if possible. But sometimes, clinical circumstances may dictate continued use of such medicines. The overall cardiovascular risk profile needs to be considered when managing such patients. Mild hypercholesterolemia due to diuretic use may not have adverse long-term effects. If the medication is being used only temporarily, like isotretinoin for treatment of acne, then it may be sufficient to just monitor lipid levels unless there is risk of acute complications like pancreatitis. Hypolipidemic therapy in addition to lifestyle measures may be necessary in many cases, such as in post-transplant patients, and it is important to be aware of potential drug interactions when doing so. Finally, it must be realized that other drugs, new and old, not discussed here can also potentially affect lipid levels, and clinicians should always consider drug-induced dyslipidemia in the differential diagnosis of hyperlipidemic disorders.

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