Oral retinoids and plasma lipids

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ABSTRACT: Retinoids and rexinoids are prescribed for conditions ranging from acne vulgaris to hyperkeratosis to cutaneous T cell lymphoma. Dyslipidemia is a frequent consequence of the use of these drugs, with more than one-third of patients manifesting aberrations in triglyceride (TG) levels. The efficacy of retinoic acid derivatives is linked to their influence on lipid metabolism in the skin, which can impair systemic lipid trafficking and metabolism in some patients. Thus, baseline screening for preexisting dyslipidemia and regular follow-up lipid panels are mandated, especially when powerful agents such as bexarotene are used. Dietary modification, increased physical activity, and weight management are the cornerstones of initial management for mild hypertriglyceridemia, which is a contributor to cardiovascular risk. More severe impairments (fasting TG > 500 mg/dL) warrant pharmacologic interventions early on to reduce the risk of pancreatitis. Retinoic acid derivative action, lipid metabolism, and treatment of incident dyslipidemias are reviewed to empower prescribers in management of adverse lipid effects.

KEYWORDS: drug-induced dyslipidemia, retinoid, rexinoid, secondary hypertriglyceridemia.

Introduction

Plasma lipid levels, though highly dependent on genetic and epigenetic influences, are sensitive to the effects of many acquired factors, including dietary choices, exercise level, body weight, comorbidities, and use of pharmaceutical agents for other conditions. Systemic dermatologic therapies such as retinoids and rexinoids are among the drugs that can strongly and quickly affect lipid parameters. In order to empower the dermatologist to provide these effective treatments safely, we will review lipid metabolism, the mechanism of influence of vitamin A derivatives on triglycerides (TGs), screening recommendations, and treatment options for patients who experience adverse lipid effects.

Synopsis of lipid metabolism

Abundant production of cholesterol and proper regulation of its trafficking and recycling pathways are critical to life due to the need for cholesterol in cell membrane building and repair, myelin formation, and steroid hormone and vitamin D synthesis. The skin is a particularly active site for synthesis of cholesterol, sphingolipids, ceramides, and fatty acids, because lipids are an essential component of its physical and antimicrobial barrier properties (1). Lipid flux in the bloodstream is controlled through two main pathways: the exogenous, via intestinal assembly of absorbed dietary lipids, and the endogenous, via hepatic assembly of lipoproteins from internal fuel in the fasting state.

Because lipids are insoluble in plasma, they must be combined with proteins (called apoproteins) for transport in the circulation. Dietary fats, mostly in the form of TGs, are broken down into fatty acids and glycerol to enter the intestinal epithelium, and then are reassembled into TGs and combined by the action of microsomal triglyceride transfer protein (MTP) with a structural protein
called apolipoprotein B48 to form chylomicrons, which are secreted into the lymphatic system for transport via the thoracic duct and into the systemic circulation. As chylomicrons travel in plasma, additional apolipoproteins, such as apoCII, apoCIII, apoAV, and apoE, are incorporated into the surface of the particle. Chylomicrons have the task to distribute dietary fats to sites of use (skeletal muscle) or storage (adipose tissue). This is accomplished by a well-designed strategy of targeted lipolysis in the capillary beds of these tissues, where chylomicrons connect with highly concentrated lipoprotein lipase (LPL) attached to the endothelial surface via glycosyl-phosphatidyl-inositol-anchored HDL-binding protein 1, and activated by apoCII (2). LPL activity is regulated by insulin and thyroid hormone; this is clinically relevant because insulin resistance and hypothyroidism can lead to decreased clearance of chylomicron remnants, leading to hypertriglyceridemia.

The liver synthesizes and secretes TG-rich lipoproteins known as very low density lipoproteins (VLDLs), smaller in size compared with chylomicrons and carried by a similar but larger structural protein called apoB100. In the circulation, VLDL TGs are hydrolyzed by LPL in the capillary districts of muscle and fat tissues, similar to chylomicrons. Unlike chylomicrons, they are also susceptible to the action of hepatic lipase, which releases additional fatty acids and results in the formation of remnant particles known as intermediate density lipoprotein, which can either be directly cleared by the liver or further metabolized by LPL and hepatic lipase to form the cholesterol ester-rich particle and nescessary of the arterial wall known as low density lipoprotein (LDL). The LDL particles are eventually removed from the blood via receptor-mediated endocytosis by the LDL receptor (LDLR). Blood levels of LDL-cholesterol (LDL-C) are controlled by the liver, which accounts for two-thirds of the body’s LDLR expression (3).

Treatment recommendations for cardiovascular risk reduction mostly target LDL-C levels, with goals of <130, 100, or 70 mg/dL depending on whether the patient is at intermediate, high, or very high risk, respectively (4). However, all apoB100-containing lipoproteins are atherogenic, and levels of apoB100 have been shown to improve cardiovascular risk prediction algorithms based on LDL-C. Non-HDL (high density lipoprotein) cholesterol (i.e., total cholesterol minus HDL-C) is a secondary target of therapy useful in the setting of hypertriglyceridemia because LDL cannot be calculated when TGs are above 400 mg/dL. The goal for non-HDL as a target for therapy is 30 points above LDL-C goal (4). Increasing evidence supports that high levels of serum TGs are an independent risk factor for atherosclerotic cardiovascular disease (5). However, more severe hypertriglyceridemias (i.e., those with TG > 500 mg/dL) are associated with more immediate risk of pancreatitis (6) than with increased risk of heart attacks or stroke.

Peripheral cholesterol is cycled back to the liver in a process called reverse cholesterol transport. Cholesterol and phospholipids from cell membranes are transferred to the HDL protein, apoAI, to form cholesterol-rich particles that can exchange their cargo with VLDL through cholesteryl ester transfer protein (CETP), or with the liver cell through the HDL receptor scavenger receptor class B member 1. Although higher levels of HDL-C are generally associated with lower cardiovascular risk (7), functional defects in HDL may commonly diminish the cardioprotective role of these particles (8). Moreover, no proof for the HDL hypothesis has been thus far provided, as clinical trials of HDL-raising agents such as CETP inhibitors (torcetrapib and dalcetrapib) and niacin have failed to further protect high-risk patients on statin therapy (9,10).

### Cholesterol metabolism in the skin

To maintain its protective barrier and antimicrobial function, the skin secretes lipids into the extracellular matrix of the epidermis as ceramides, sphingolipids, and cholesterol from lamellar bodies, specialized organelles within keratinocytes in the stratum corneum (1,11). People with severe elevation of cholesterol or TGs, or with defective cellular cholesterol efflux (HDL abnormalities), can develop xanthomas and xanthelasma, external deposits of these excess inert substances; conversely, congenital absence of enzymes necessary for formation of necessary lipids in the skin leads to pathology and pigmentation changes as seen in lysosomal storage diseases such as Gaucher and Niemann-Pick type C.

### Retinoic acid derivatives in clinical practice

Retinoic acid derivatives bind directly to their corresponding receptors, 9-cis-retinoic acid/retinoid receptor (RXR) and all-trans-retinoic acid.
receptor (RAR), and directly affect transcription of metabolically related genes. They are indicated for hyperkeratotic disorders like psoriasis, lichen planus, and cystic acne, and can be used as chemotherapeutic agents in acute promyelocytic leukemia and cutaneous T cell lymphoma. Clinicians must be aware that along with their efficacy come potential adverse effects, including metabolic abnormalities that require close laboratory monitoring. The prescriber must keep in mind that metabolic side effects are more common among those with predisposing conditions such as obesity and insulin resistance. In one series, those who developed retinoid-induced hypertriglyceridemia were more likely to have had baseline dyslipidemia, truncal obesity, hyperinsulinemia, and family history of hypertriglyceridemia (12).

Peroxisome proliferator-activated receptors (PPARs) are transcription factors that regulate the expression of dozens of metabolically related genes, including those producing rate-limiting enzymes in the oxidative pathways of fatty acids. These nuclear hormone receptors are part of a family that also includes the RXR, RAR, vitamin D receptor, thyroid hormone receptor, and others (13). PPARs are strongly expressed by cells in the skin and sebaceous glands (14).

RAR activation leads to increased secretion and decreased catabolism of TG-rich particles, causing plasma accumulation of TGs and secondary decreases in HDL-C (15). RXR activation leads to increased apoCIII synthesis, resulting in reduced LPL activity and hypertriglyceridemia (16). As keratinocytes differentiate, the ATP-binding cassette protein ABCA12 necessary for normal lamellar body formation is upregulated; PPARs and liver X receptors activators increase ABCA12 as well (17).

The transcription factor FOXO1 is also stimulated by retinoid therapy and inactivated via phosphorylation by insulin; this inactivation leads to reduced gluconeogenesis and VLDL release by the liver in the fed state. MTP and apoCIII are stimulated by FOXO1, leading to activation of particle assembly and inhibition of LPL, two causes of higher plasma TGs. Interestingly, the retinoid effect on FOXO1-dependent increase in apoCIII is inhibited by PPAR (18). Thus, PPAR-α agonists like fibrates should be as effective in treating retinoid-induced hypertriglyceridemia as they are in the management of more common forms.

TG elevation is common and affected 44% of patients treated with isotretinoin in one series (19). Elevated LDL-C and low HDL-C are also relatively common. Although more than 30% will have significant hypertriglyceridemia (TG > 175 mg/dL) while on retinoid therapy, levels rarely rise to the range of severe hypertriglyceridemia; in one analysis, only 1.5% of patients surpassed 400 mg/dL (16,20). Liver function tests will become abnormal in 25–30% of subjects on therapy (21). Most of these changes are mild and may be managed by the prescribing dermatologist without the use of medications. Lipid aberrations reach their peak 6–8 weeks after initiating therapy; later lipid panels are usually stable (22).

Most patients receiving bexarotene develop hyperlipidemia, and fatal cases of cholestasis and pancreatitis have been reported (23). Because of the increased severity of bexarotene adverse effects, lipid panels should be checked at baseline, weekly for 2–4 weeks, then monthly after a stable pattern has been established. Bexarotene can also cause central hypothyroidism, which can exacerbate hypertriglyceridemia, so thyroid function testing should be repeated as well. Notably, due to the high proportion of patients whose bexarotene treatment courses are complicated by central hypothyroidism and hypertriglyceridemia, the British Association of Dermatologists recently recommended starting prophylactic levotyroxine and fenofibrate for all patients receiving this therapy (24).

Baseline lipid panel with weekly follow-up testing until lipid response has been established is recommended for other systemic retinoids, with follow-up testing in 48 weeks. Only one case of pancreatitis in an individual being treated with isotretinoin has been reported, and the affected woman likely had an underlying genetic hypertriglyceridemia because she also had a history of pregnancy-induced pancreatitis (25). In all cases, a final lipid panel should be checked 4–8 weeks following discontinuation of therapy, and serial lipid panels should be rechecked in the case of dose increases (16). Topical retinoids have very little systemic absorption and are not expected to cause hypertriglyceridemia, and thus routine lipid screening during topical retinoid therapy is not currently recommended.

Though lipid aberrations and other adverse effects are not uncommon for patients treated with vitamin A derivatives, these drugs provide considerable relief from physically and emotionally scarring conditions. Patients should be counseled of the potential for abnormal cholesterol and TGs and plan for the course if hyperlipidemia occurs. If mild hyperlipidemia develops, lifestyle changes should be initiated and the retinoid or rexinoid dose should be decreased. Medical therapy of the
dyslipidemia should be considered if appropriate. If TGs surpass 800 mg/dL, the retinoid or rexinoid should be discontinued. These therapies, if necessary, may be restarted following successful medical management of hyperlipidemia (21). Overall consideration to increased cardiovascular and pancreatitis risk should be approached on a patient-by-patient basis. The importance of dietary control cannot be overemphasized.

**Preexisting dyslipidemias**

Every person who is treated with retinoic acid derivatives should have a baseline fasting lipid panel drawn. Normal lipid parameters are outlined in Table 1. Dyslipidemias are common and likely to be detected on routine screening laboratory testing. Based on the most recent National Health and Nutrition Examination Survey data, about 30% of Americans have hypertriglyceridemia (26). One in 500 people have familial hypercholesterolemia, an autosomal codominant genetic disease that causes elevations in LDL-C (27). One in 200 patients have familial-combined dyslipidemia, which can cause high LDL-C, high TG, and low HDL-C (28). About 35% of Americans are affected by metabolic syndrome, a constellation of obesity, insulin resistance, hypertension, low HDL-C, small, dense LDL-C, and elevated TG (29). Familial hypertriglyceridemia causes TGs in the 200–500 mg/dL range and often manifests in the presence of an exacerbating factor such as pregnancy, binge drinking, diabetes mellitus, or drugs affecting lipid metabolism (30).

Pure genetic hypertriglyceridemias are rarer; for instance, LPL deficiency affects fewer than 1 in 1,000,000 individuals, manifests in childhood, usually causes TG much greater than 1000 mg/dL, and is associated with increased risk for pancreatitis (31). However, secondary elevations in TGs may be observed due to uncontrolled diabetes mellitus, hypothyroidism, nephrotic syndrome, and cholestatic liver disease. Beyond retinoids and rexinoids, pharmaceuticals ranging from antipsychotic medications to protease inhibitors for human immunodeficiency virus treatment can cause hypertriglyceridemia; several known causes of hypertriglyceridemia are listed in Table 2. Excessive alcohol intake is among the most common causes of hypertriglyceridemia. Importantly, oral estrogens, which are often concurrently prescribed to women of childbearing years due to the high teratogenicity of retinoids or rexinoids, can also increase TGs. Transdermal estrogens do not seem to have this effect (32).

If baseline dyslipidemia is identified, the patient should be referred to his or her primary care physician for dietary or pharmacologic management prior to initiation of retinoid therapy, and more frequent monitoring during treatment should be planned. Secondary dyslipidemia should be ruled out by reviewing history and current therapies. Furthermore, thyroid stimulating hormone, free thyroxine (free T4), and urinalysis should be checked, and hepatic function should be evaluated via transaminase levels. Those at higher risk for developing hypertriglyceridemia due to underlying metabolic syndrome, including overweight or obese patients or those with acanthosis nigricans on physical exam, should start on a lower dose and perhaps be screened more often for lipid derangements throughout therapy.
Treatment strategies

Though long-term exposure to high TGs is expected to increase risk of cardiovascular disease, short-term mild hypertriglyceridemia in the context of therapy with retinoic acid for acne or vitamin A derivatives for chemotherapy may be tolerated as long as short-term risks of elevated TGs are avoided in an otherwise healthy patient. Pancreatitis is the most serious risk for patients with TGs greater than 500 mg/dL. Even though pancreatitis often occurs in context of much higher levels (TG > 2000 mg/dL), it is important to keep in mind that TG levels can rise dramatically and quickly if the patient is not instructed on the proper diet.

The first-line therapy for hypertriglyceridemia and hypercholesterolemia is lifestyle modification. Medications should be reviewed for secondary causes of hyperlipidemia, and treatable causes such as diabetes should be appropriately managed. Weight loss should be recommended in nearly every patient because 5–10% reduction in weight can reduce TGs by about 20% (33). This approach is admittedly slow, but patients treated with retinoic acid derivatives may be particularly motivated to reach weight loss goals in order to continue these beneficial therapies. Fortunately, strategies to decrease TGs are additive, and other approaches can be taken as part of the weight reduction plan.

Moderate to vigorous physical activity usually has drastic and rapid beneficial effects, as TGs are used for fuel by the skeletal muscle. Aerobic exercise is most effective for lowering TGs when it is combined with other efforts sufficient for weight reduction.

Total dietary fat content, especially saturated and trans fats, should be restricted, and refined carbohydrates reduced. The American Heart Association recommends a Mediterranean diet for TG reduction; this plan is rich in fruits, vegetables, nuts, and whole grains with 28% of total calories from fat, most of which is unsaturated (33). Alcohol intake should be eliminated. For very severe hypertriglyceridemia, more drastic fat, sugar, and caloric restriction is necessary, with total dietary fat limited to less than 20 g daily. Consultation with a dietitian improves the efficacy of lifestyle interventions.

In addition to lifestyle changes, supplementation with high-dose omega-3 fatty acids (docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)) is recommended. Omega-3 fatty acids decrease hepatic secretion of VLDL and increase clearance of TG-rich particles, resulting in lower serum TGs (34). The maximum dose recommended to treat hypertriglyceridemia in adults is 4 g daily; at this dose, TGs should be expected to fall 20–50% (35). Prescription strength omega-3-acid ethyl esters (Lovaza®, GlaxoSmithKline, Research Triangle Park, NC, USA) may be used, though this branded formulation may not be covered by every insurance. A new formulation containing only EPA has been recently approved by the Food and Drug Administration and will soon be available in the United States with the trade name of Vascepa.

Many supplements are available directly to consumers. Verifying the strength of the preparation is important because the amount of omega-3 fatty acids is more commonly about one-third of total oil represented in each pill. For instance, popular single-strength fish oil supplements contain 500- to 1200-mg fish oil but only 360 mg of DHA plus EPA. Of note, sources such as krill oil or flaxseed oil are not equivalent substitutes as they contain very little omega-3 fats. Gummy and liquid preparations of these supplements also contain very little DHA or EPA. Fish oil supplements often cause nausea or unpleasant aftertaste; taking the supplements with food and storing the capsules in the freezer may decrease these side effects. Though advertising campaigns assert that certain brands are mercury free, mercury contamination is not a concern with fish oil supplements because mercury is not lipid soluble. High-strength supplements are now available with as much as 70% of total as omega-3 fats.

Obviously, fish oil supplements have not been evaluated in randomized controlled trials of either pancreatitis or heart disease prevention. Branded formulations have shown promising results in trials of cardiovascular disease prevention (36,37) and of TG reductions in subjects with more or less severe hypertriglyceridemia (38,39). In the Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico study, long-term ingestion of 1 g of omega-3 fats reduced death and nonfatal cardiovascular events in survivors of recent myocardial infarction by 10–15% (36). The Japan Eicosapentaenoic acid (EPA) Lipid Intervention Study found a 19% reduction in relative risk of cardiovascular disease in hypercholesterolemic patients treated with omega-3 fatty acids and statin when compared with similar patients given statin monotherapy (37). Other EPA-only studies include the ANCHOR trial, which showed significant TG lowering in patients with mild hypertriglyceridemia, and the MARINE trial, where patients experienced a significant TG reduction.
from a high baseline (in many cases TG > 800 mg/dL). Both trials attained this goal without increasing LDL-C (38,39). The additional advantage of supplemental and prescription omega-3 capsules for the dermatologist is in the easy acceptance from patients due to the well-publicized but not so well-documented improvements in skin health.

Fibrate therapy follows lifestyle modification (40). Gemfibrozil and fenofibrate are PPAR-α activators that enhance the action of LPL and decrease TGs by 30–60% (41). These drugs are generally well tolerated but care should be taken when combining with other common agents, particularly statins. Importantly, gemfibrozil should not be given concurrently with bexarotene because both are metabolized by cytochrome P450 3A4 and bexarotene levels would be expected to rise, increasing risk for toxicity.

Niacin reduces TGs via several mechanisms, including reducing secretion of VLDL particles and inhibiting diacylglycerol-acyltransferase-2, the rate-limiting enzyme for TG synthesis in the liver. Though niacin is quite effective, it is associated with the prominent side effect of cutaneous flushing, which is reduced but not abolished in the extended release formulation, Niaspan. No-flush versions of niacin should be avoided because they may be associated with increased risk for hepatitis and are ineffective in lipid lowering. Extended-release niacin has recently failed to proved benefits in subjects with high cardiovascular risk in the AIM-HIGH and HSP2-THRIVE studies (http://www.thrivestudy.org), and thus the use of this medication in lipid management is expected to dwindle (9).

Statins act through decreasing HMG-CoA reductase activity, primarily affecting LDL-C with dose-dependent TG lowering effects of up to 40% reduction at the higher doses. Despite one case report outlining successful TG reduction in one patient given a statin following isotretinoin-induced hypertriglyceridemia, statins are not the first-line pharmaceutical option for hypertriglyceridemia, though they are first-line treatment for elevated LDL-C after lifestyle measures have failed (42). Combination therapy may be necessary for management of extremely high TGs, or in patients with combined dyslipidemia or those with high cardiovascular risk and inappropriate LDL-C. Statins are also metabolized through the CYP3A4 pathway and should be used with caution alongside retinoids and rexinoids because of the risk of toxicity; simvastatin should not be coadministered, and there is potential for interaction with atorvastatin.

Conclusion

The close relationship of cholesterol metabolism and healthy skin implies that pharmaceuticals that impact one have potential to affect the other. Though lipid derangements while on vitamin A derivative therapies are relatively common, careful attention to high-risk patients, routine lipid screening, and prompt management of dyslipidemia allow prescribers to safely provide effective management of dermatologic disease.

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