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A Review Article on Hyperlipidemia: Types, Treatments and New Drug Targets

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ABSTRACT

Hyperlipidemia is a medical condition characterized by an increase in one or more of the plasma lipids, including triglycerides, cholesterol, cholesterol esters, phospholipids and or plasma lipoproteins including very low-density lipoprotein and low-density lipoprotein along with reduced high-density lipoprotein levels. This elevation of plasma lipids is among the leading risk factors associated with cardiovascular diseases. In the meantime, statins and fibrates remain the major anti-hyperlipidemic agents for the treatment of elevated plasma cholesterol and triglycerides respectively, with the price of severe side effects on the muscles and the liver. The present review focuses mainly on the types of hyperlipidemias, lipid metabolism, treatments and new drug targets for the treatment of elevated lipid profile. Many agents such as lanosterol synthase inhibitors, squalene epoxidase inhibitors, diacyl glycerol acyl transferase inhibitors, ATP citrate lyase inhibitors have shown a promising potential in the treatment of hyperlipidemia in clinical trials.

Key words: Hyperlipidemia, Lipid metabolism, Hypolipidemic drugs, Squalene epoxidase inhibitors, Lanosterol synthase inhibitors, Diacyl glycerol acyl transferase inhibitors.

INTRODUCTION

Hyperlipidemia is considered one of the major risk factors causing cardiovascular diseases (CVDs).CVDs accounts for one third of total deaths around the world, it is believed that CVDs will turn out to be the main cause of death and disability worldwide by the year 2020[1,2].

Hyperlipidemia is an increase in one or more of the plasma lipids, including triglycerides, cholesterol, cholesterol esters and phospholipids and or plasma lipoproteins including very low-density lipo protein and low-density lipoprotein, and reduced high-density lipoprotein levels[3,4].

Hypercholesterolemia and hypertriglyceridemia are the main cause of atherosclerosis which is strongly related to ischemic heart disease (IHD)[5]. There is a strong relation between IHD and the high mortality rate. Further more elevated plasma cholesterol levels cause more than four million deaths in a year[6].

Atherosclerosis is a process of arteries hardening due todeposition of cholesterol in the arterial wall which causes narrowing of the arteries.Atherosclerosis and atherosclerosis-associated disorders like coronary, cerebrovascular and peripheral vascular diseases are accelerated by the presence of hyperlipidemia [7].

Hyperlipidemiarelates to increased oxidative stress causing significant production of oxygen free radicals, which may lead to oxidative modifications in low-density lipoproteins, which present a significant function inthe initiation and progression of atherosclerosis and associated cardiovascular diseases[3].

Plasma lipoproteins

Composition and structure

Lipoproteins are macro molecules aggregate composed of lipids and proteins; this structure facilitates lipids compatibility with the aqueous body fluids.

Lipoproteins composed from non-polarlipids(triglycerides and cholesteryl esters), polar lipids(phospholipids and unesterified cholesterol) and specific proteins known as apolipo proteins.Apolipoproteinsare amphiphilic proteins that bindto both lipids and the plasma[8].

Lipoproteinclassification

Chylomicrons (CM),verylow-densitylipoproteins (VLDL), low-density lipoproteins(LDL), intermediate-density lipoproteins (IDL) and high-densitylipoproteins (HDL) are the five classes of lipoproteins present in plasma.These classes areheterogeneous; they have different composition, size, and density[8].

As the triglyceride and cholesteryl ester contents of the core increases the lipoprotein size increases,the density of lipoproteins increase also proportionally to their protein contents, and contrariwise to their lipid contents[9].

Lipoprotein Function

Plasma lipoproteins are important for lipid solubilization in order to transporttriglycerides, an importantenergy source, which synthesized and absorbed to places of utilization and storage; and to transport cholesterol between different places of absorption, synthesis, catabolism, and elimination[10].

Enzymes involved in lipoprotein metabolism

Lipoprotein lipase (LPL)

LPL is a multifunctional enzyme expressed on endothelial cells in the heart, muscle, adipose tissue, macrophages and lactating mammary glands. LPL plays a critical role in the hydrolysis of triglyceride (TG) into two free fatty acids and monoacylglycerol. Besides LPL helps in the receptor-mediated lipoprotein uptake of chylomicron remnants, cholesterol-rich lipoproteins, and free fatty acids[11].

Hepatic lipase (HL)

HL is a multifunctional protein that regulate lipoprotein metabolism. It is synthesized by hepatocytes and found in adrenalgl and and ovary. HL hydrolyzes phospholipids and triglycerides of plasmalipo proteins. In addition HL affects cellular lipid delivery by facilitating lipoprotein absorption by cell surface receptors and proteoglycans[12].

Lecithin cholesterol acyl transferase (LCAT)

Lecithin cholesterol acyltransferase,is a crucial enzyme in the metabolism of HDL. It converts free cholesterol into cholesteryl esters which then sequestered into the core of lipoprotein andfinally making mature HDL[13].

Cholesteryl ester transfer protein (CETP)

Cholesteryl ester transfer protein (CETP), also called plasma lipid transfer protein, is a hydrophobic plasma glycoprotein that accelerates the transferring of esterified cholesterol esters (CE) from HDLs to chylomicrons, VLDL and LDL, in exchange for triglyceride. ACETP deficiency is linked to increased HDL levels and decreased LDL levels[14].

Microsomal triglyceride protein (MTP)

Microsomal triglycerideprotein (MTP) is a lipid transfer protein catalyzesthe transfer of neutral lipids, triglycerides and cholesterol esters between membrane of the lumen of microsomes isolated from the liver and intestinal mucosa. Microsomal triglycerideprotein is an essential protein in the assembly of apo B containing lipoproteins. Now it is known that MTP is important in the biosynthesis of glycolipid presenting moleculesand the regulation of cholesterol ester biosynthesis[15].

Acyl Co-A transferase (ACAT)

Acyl Co-A transferase (ACAT) is membrane-bound protein that useslong-chain fatty acyl-CoA and cholesterol as substrates to produce cholesteryl esters. ACAT plays significant roles in cellular cholesterol homeostasis in various tissues and prevents the toxic accumulation of excess cholesterol in a cell. Further more,the importance of ACAT arises from its crucial role in the assembly along with the secretion of apolipoprotein-B containing lipoproteins in the liver and intestines[16].

Lipid metabolism

Almost all the dietary fats are absorbed from the intestinal lumen into the intestinal lymph and packed into chylomicrons. These lipoproteins move into the blood stream where they got hydrolyzed by endothelial lipoprotein lipase which hydrolyzes the triglyceride into glycerol and non-esterified fatty acids. After which the chylomicron remnants are absorbed in the liver and packaged withc holesterol, cholesteryl esters and ApoB100 to form VLDL. After the release of VLDL into the blood stream it will be converted into IDL by the action of lipoprotein lipase and hepatic lipase,where phospholipids and apolipoproteins transferred back to HDL. Furthermore, after the hydrolysis by hepatic lipase, IDL will be converted to LDLand loss more apolipoproteins[17].

Peripheral cholesterol is returned to the liver by reverse cholesterol transport pathway using HDLs which are originally synthesized by the liver and released into the blood. In the blood, HDL cholesterol is esterified by LCAT to cholesteryl ester and transferred to VLDL and chylomicrons to return to the liver through LDL receptor. Cholesteryl ester are transferred to LDL particles by CETP and then subjected to LDL-receptors mediated endocytosis. Finally, cholesteryl esters are hydrolyzed to cholesterol and extracted from the body as bile acid[18].

Hyperlipidemia classification

Hyperlipidemiain general can be classified to:

Primary: it is also called familial due to a genetic defect, it may be monogenic: a single gene defect or polygenic: multiple gene defects. Primary hyperlipidemia can usually be resolved intoone of the abnormal lipoprotein patterns summarized in table 1[19].

Secondary: it is acquired because it is caused by another disorder like diabetes, nephritic syndrome, chronic alcoholism, hypothyroidism and with use of drugs like corticosteroids, beta blockers and oral contraceptives. Secondary hyperlipidemia together with significant hypertriglyceridemia can cause pancreatitis[20].

The main cause of hyperlipidemia includes changes in lifestyle habits in which risk factor is mainly poor diet in which fat intake form saturated fat and cholesterol exceeds 40 percent of the total calories uptake[20].

Symptoms of hyperlipidemia

Generally hyperlipidemia does not have any obvious symptoms but they are usually discovered during routine examination or until it reaches the danger stage of a stroke or heart attack. Patients with high blood cholesterol level or patients with the familial forms of the disorder can develop xanthomas which are deposits of cholesterol may form under the skin, especially under the eyes. At the same time, patients with elevated levels of triglycerides may develop numerous pimple-like lesions at different sites in their body[19].

Complications of hyperlipidemia

Atherosclerosis: Hyperlipidemia is the most important risk factor for atherosclerosis, which is the major cause of cardiovascular disease. Atherosclerosisis a pathologic process characterized by the accumulation of lipids, cholesterol and calcium and the development of fibrous plaques with in the walls of large and medium arteries[21].

Coronary Artery Disease (CAD): Atherosclerosis, the major cause of coronary artery disease, characterized by the accumulation of lipid and the formation of fibrous plaques within the wall of the arteries resulting in narrowing of the the arteries that supply blood to the myocardium, and results in limiting blood flow and insufficient amounts of oxygen to meet the needs of the heart. Elevated lipid profile has been connected to the development of coronary atherosclerosis[22].

Myocardial Infarction (MI): MI is a condition which occurs when blood and oxygen supplies are partially or completely blocked from flowing in one or more cardiac arteries, resulting in damage or death of heart cells. The occlusion may be due to ruptured atherosclerotic plaque. The studies show that about one-fourth of survivors of myocardial infarction were hyperlipidemic[23].

Ischemic stroke: stroke is the fourth leading cause of death. Usually strokes occur due to blockage of an artery by a blood clot or a piece of

atherosclerotic plaque that breaks loose in a small vessel within the brain. Many clinical trials revealed that lowering of low-density lipoprotein and total cholesterol by 15% significantly reduced the risk of the first stroke[24].

Drugs classes for hyperlipidemia

Since LDL is the major atherogeniclipo protein, reduction of this lipoprotein would be expected to reduce atherosclerosis and therefore reduce cardiovascular adverse effects. In addition to high LDL, presence of risk factors and CHD should qualify initiating drug therapy along with life style changing. Monotherapy has been shown to be effective in treating hyperlipidemia, but combination therapy may be required for a comprehensive approach. Currently, antihyperlipidemic drugs contain five major classes (Table 2) that include statins, fibric acid derivatives, bile acid binding resins, nicotinic acid derivatives and drugs that inhibit cholesterol absorption[20].

3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA)reductaseinhibitors (statins).

This class includes (Lovastatin, Simvastatin, Pravastatin, Fluvastatin, Atorvastatin and Rosuvastatin). Statinsare broadly prescribed in the treatment of hypercholesterolemia, can achieve 20%–50% reductions in cholesterol levels and have been linked to the reduced incidence of coronary morbidity and mortality in high-risk adults[25].

Mechanism of action

Thesedrugs are structural analogues of HMG-coenzyme Areductase. They act by inhibiting the rate limiting enzyme (HMG-coenzyme Areductase) in the biosynthesis of cholesterol in the liver. By inhibiting this enzyme, statins significantly reduce plasma levels of total cholesterol (TC),LDL and ApoB. Mean while, statins also cause a modest decrease in plasma triglycerides and a small increase in plasma level of HDL[26].

Other HMG-CoA reductase inhibitors include the diallyldisulfide (DADS) and diallylthiosulfinate. DADS, is an organosulfur compound derived from garlic, has been shown to reduce cholesterol synthesisby 10–25% at low concentrations. Diallylthiosulfinate,a metabolite of allicin, block the formation of 7-dehydrocholesterol and reduced the production of cholesterol. Bis-(3-(4-nitrophenyl)prop-2-ene)disulfide, a new derivatives of diallyldisulfide, is effective in reducing plasma total cholesterol[27].

Side effects

Statins are frequently well tolerated with the most common adverse effects being transient gastrointestinal symptoms, headache, myalgia and dizziness.These symptoms are more common with higher doses and may solve ifa different statin is used[28].

Statins also cause myopathy, rhabdomyolsis and an increase serum transaminase. These substances are harmful to the kidney and often cause kidney damage. Additionally statins may cause cardiomyopathy[29]. Recent clinical trials showed that statin use has been linked to anincrease in type 2 diabetes[30].

Bile acid sequestrants

Bile acid synthesis is the main pathway of cholesterolcatabolism in the liver; it has been estimated that about 500 mg of cholesterolis converted daily into bile acids in the adult humanliver. Bile acids are secreted into the intestine and have an important role in facilitating the absorption of fats from food[31].

Bile acid sequestrants include cholestyramine, colestipol, colestimide,and colesevelam. Cholestyramine and colestipol are the two bile acid sequestrants currently available. Cholestyramineis a quaternary amine composed of styrene and divinylbenzenepolymers. Colestipolis a copolymer of diethylenetriamine and 1-chloro-2,3-epoxypropane[32].

Mechanism of action

Bile acid sequestrants are positively charged resins that bind to the negatively charged bile acids in the intestine to form a large insoluble complex that not absorbed and so excreted in the feces. Excretion is increased up to tenfold when resins are given, resulting in greater conversion of cholesterol to bile acids. Furthermore bile acid sequestrants increase HDL levels[33].

Side effects

Bile acid sequestrants are rarely used as initial therapy because of poor patient tolerance. Gastrointestinal disturbances are the most common complaints of the bile acid sequestrants include constipation, nausea, indigestion,bloating and flatulence[34].

On long-term therapybile acid sequestering agents may cause osteoporosis due to calcium loss. They may aggravate hypertriglyceridemia by an unknown mechanism. Some vitamins minerals deficiencymay occur[32].

Fibric acid derivatives(Fibrates)

Fibrates include clofibrate, gemfibrozil, fenofibrate, and bezafibrate, areawidely used class of antihyperlipidemic agents, results in a significant reduction in plasmatriglycerides and a modest reduction in LDL cholesterol. HDL cholesterol level increases moderately. Angiographictrials results showed that fibrates play an important role in slowing the progression of coronaryatherosclerosis and decrease the incidence of coronary artery disease.

Mechanism of action

Data from studies in rodents and in humans imply fourmain mechanisms of fibrates:

Stimulation of lipoprotein lipolysis.

Fibrates function primarily as ligands for the nuclear transcription receptor, PPAR-α. They increased the expression of lipoprotein lipase, apo, and down-regulate apo C-III, an inhibitor of lipolysis. Fibrates also increase the level of HDL cholesterol by increasing the expression of apo AI andapo AII[35].

Increase hepatic fatty acid (FA) uptake and reduction of hepatic triglyceride production.

Fibrates enhance the production of fatty acid transport protein and acyl-CoA synthetase, which contribute to the increase uptake of fatty acid by the liver and as a result in a lower availability of fatty acids for triglyceride production[36].

Increase removal of LDL particles.

Fibrate, appears to enhance LDL catabolism via the receptor-mediated pathway; LDL particles became larger and more lipid rich and therefore had more affinity for receptors. Fibrates also inhibits the formation of slowly metabolized, potentially atherogenic LDL particles[37].

Increase in HDL production and stimulation of reverse cholesterol transport.

Fibrates increase apo A-I production in the liver which leads to the observed elevation in plasma levels of apo A4 and HDL-cholesteroland a more effective reverse cholesterol transport[38].

Side effects

Generally, fibrates are considered to be well tolerated. Side effects may include

Table. 1: Fredrickson classification of primary hyperlipidemia[19].

Type	Disorder	Cause	Occurrence	Elevated plasma lipoprotein
I	Familial hyperchylomicronemiaOr Primary hyperlipoproteinemia	Lipoprotein lipase deficiencyor Altered ApoC2	Very rare	Chylomicrons
IIa	Familial hypercholesterolemia OrPolygenic hypercholesterolemia	LDL receptor deficiency	Less common	LDL
IIb	Familial combined hyperlipidemia	Decreased LDL receptor	Commonest	LDL and VLDL
III	Familial dysbetalipoprotenemia	Defect in Apo E- 2 synthesis and increased ApoB	Rare	IDL
IV	Familial hypertriglyceridemia	Increased VLDL production and decreased excretion	common	LDL
V	Endogenous hypertriglyceridemia	Increased VLDL production and decreased LPL	Less common	VLDL and chylomicrons

gastrointestinal symptoms, myopathy, arrhythmia, skin rashes and gallstones. Fibrates should be avoided in patients with liver and renal dysfunction[32].

Nicotinic acid derivatives (Niacin)

Niacin,a water-soluble vitamin of type B, is the oldest lipid lowering agent used totreat hyperlipidemia and proved to decrease cardiovascular morbidity and total mortality. It decreases total cholesterol, LDL cholesterol, triglycerides.

Besides, niacin is the most effective therapy available for the treatment of low HDL levels when used in a dose of (H^{-1} gm per day)[39].

Mechanism of action

Niacin inhibits hormone-sensitive lipase which decreases triglycerides lipolysis the main producer of circulating free fatty acids. The liver usually uses these circulating fatty acids as a major precursor for triacylglycerol synthesis. Therefore, niacin inhibits VLDL secretion, in turn decreasing production of LDL.

Furthermore, niacin treatment elevates HDL cholesterol concentrationsby reducing the fractional clearance of apo A-1 and increasing HDL synthesis[32].

Table. 2: Drug therapy for hyperlipidemia[20].

Drugs	Effects on lipids
Statins:	
Lovastatin (10-80 mg)	Decrease TG
Simvastatin (5-40 mg)	Decrease LDL
Atorvastatin (10-80 mg)	Increase HDL
Rosuvastatin (5- 20 mg)	
Bile acid binding resins:	TG generally noteffected
Cholestyramine (4-16 mg)	Decrease LDL
Colestipol(5-30 mg)	Increase HDL
Fibric acid derivatives:	
Gemfibrozil (1200 mg)	Decrease TG
Bezafibrate (600)mg	Decrease LDL
Fenofibrate(200 mg)	Increase HDL
Nicotinic acid derivatives	Decrease TG
Niacin(2-6 gm)	Decrease LDL
	Increase HDL
Cholesterol absorption inhibitors:	Decrease LDL
Ezetimibe (10 mg)	Decrease cholesterol

Side effects

Niacin treatment has been plagued by low compliance rates. The most common side effects areintense cutaneous flush which affect more than three quarters of patients, itching, headache andsome patients experience nausea and abdominal discomfort. Niacin also elevates liver enzymes.

Administering statins in combination with niacin increases the incidence of rhabdomyolysis. Niacin also promotes glucose in tolerance and hyperuricemia which precipitate a gout attack[34].

Selective cholesterol absorption inhibitor (Ezetimibe)

The discovery and development of ezetimibe, the first member of a group of drugs that inhibit intestinal absorption of phytosterols and cholesterol, has improved the treatment of hypercholesterolemia. It inhibits the absorption of cholesterol from the small intestine without any effect on the plasma concentrations of the fat-soluble vitamins[40].

A combination of statins and ezetimibe can achieve a reduction in LDL cholesterol levels by25%, compared to 6% attained by doubling the statin dose[41].

Mechanism of action

Ezetimibe selectively inhibits absorption of cholesterol in the smallintestine, leading to a decrease in the delivery of intestinal cholesterol to the liver by blocking the Niemann–Pick C1-like 1 protein (NPC1L1), a human sterol transport protein. This causes an increase in the clearance of cholesterol from the blood[42].

Side effects

Ezetimibeis usually well tolerated; the most common side effects include headache, abdominal pain and diarrhea. Ezetimibe appears to cause elevations in liver function tests include elevations in alanine transaminase and aspartate transaminase[43].

New potential targets and treatments

Recently, many clinical trials revealed new potential agents with promising antihyperlipidemic activity. In this section, some of these agents will be reviewed.

Acyl-CoA cholesterol acyl transferase inhibitors(ACAT)

Acyl-CoA cholesterol acyl transferase (ACAT) is the enzyme that catalyzes the conversion of intracellular cholesterol into cholesteryl esters. ACAT has two isomers, termed ACAT1 and ACAT2.

ACAT1 contributes to foam cell formation in the arterial wall and the development of atherosclerosis, so ACAT-1 inhibitors may haveantiatherogenic effect and ACAT-2 inhibitors mayplay an important role in reducing cholesterol absorption in the intestine.

Avasimibe and Eflucimibe act by inhibiting ACAT, decrease plasma cholesterol levels and slow the development of atherosclerosis[44,45]. Some of the potent ACAT inhibitors which are currently in clinical development are naphthoqui none derivatives[46].

Microsomal triglyceride transfer protein (MTP) inhibitors

Microsomal triglyceride transfer protein (MTP) has multiple functions including transferring neutral lipids between membrane vesicles, the biosynthesis of CD1, antigen-presenting molecules, as well as in the regulation of cholesterol ester biosynthesis. Therefore, inhibiting MTP causes significant reductions in plasma triglycerides, LDL, and VLDL cholesterol. These findings suggest that inhibitors of MTP might be useful for reducing the atherogenic lipoproteinslevels[15].

A series of newly synthesized phosphonate esters were evaluated for their effects on MTP activity andthey exhibita potent inhibition bothin vitro and in vivo. Data also suggest the potency oflomitapide (AEGR-733, formerly BMS-201038), a novel drug for hypercholesterolemia[47].

Cholesteryl ester transfer protein (CETP) inhibitors

CETP in liver facilitates the transfer of cholesteryl esters from anti-atherogenic HDLs to proatherogenicapolipo protein B containing lipoproteins, including VLDLs and LDLs. Furthermore, most studies showed that there is evidence that CETP may playa proatherogenic role by involving in reverse cholesterol transport and support the idea that inhibition of CETP slows the progression of atherosclerosis[48].

Dalcetrapib and anacetrapib are novel compounds in Phase III of clinical trials. Dalcetrapib reduced CETP activity by 50% and elevated HDL cholesterol levels by 31% without affecting LDL cholesterol levels[49].

Squalene synthase inhibitors

Squalene synthase (SqS) catalyzes farnesyl pyrophosphate to form squalene, Catalysis by SqS is the first committed step in sterol synthesis, and one of these sterols is cholesterol. Pharmacologists regard SqS inhibitors as promising lead compounds in the development of potential agents to treat hyperlipoproteinemia[50].

It has been reported that after oral administration ofBMS-188,494,a potential inhibitor of SqS,the plasma levels of cholesterol was reduced in experimental rats[51]. Concurrently, YM-53601,another inhibitor of SqS,reduces plasma cholesterol and triglyceride levels[52].

Hydroxymethylglutaryl-CoA synthase inhibitors

HMG synthase catalyzes the chemical reaction that converts acetyl-CoA and acetoacetyl-CoA to 3-hydroxy-3-methylglutaryl-CoA. L-659,699 is one of the compounds that have shown a potential HMG synthase inhibitor activity[52].

ATP citrate lyase inhibitors

ATP citrate lyase (ACL)is the primary enzyme accountable for the synthesis of cytosolicacetyl-CoA and oxaloacetate. Synthesis of cytosolicacetyl-CoA and oxaloacetate represent an important step in the synthesis of fatty acids and cholesterol. For this reason, inhibition of ACL is a promising strategy in the treatmentof dyslipidemia[53].

Recently, Li *et al*. described that a chronic administration of BMS-303141, the leading inhibitor of the enzyme ACL in the 2-hydroxy-N-arylbenzene sulfon amides class, in high-fat–fed mice reduced

weight gain and decreased plasma cholesterol, triglycerides, and glucose[54].

Acyl coenzyme A: diacyl glycerol acyltransferase (DGAT)

DGAT is a microsomal enzyme that joins Acyl CoA to 1,2-diacylglycerol in the final step in triglyceride bio synthesis. Two forms ofDGAT(DGAT-1 and 2) have been identified. Several studies showed that inhibition of DGAT1 is a good target in the treatment of hyperlipidemia.

The compound T863 is a potent inhibitor for DGAT1 in vitro; it was shown that a two weeks treatment with compound T863 decreased serum and liver triglycerides, and decreased serum cholesterolin mice[55].

Squaleneepoxidase inhibitors

Squalene epoxidaseis one of the rate-limiting enzymes for the first oxygenation step in sterol bio synthesis. NB-598 competitively inhibits squalene epoxidase andinhibits cholesterol synthesis[56].

Lanosterol synthase inhibitors

lanosterol synthase (LSS) Catalyzes the cyclization of (S)-2,3 oxidosqualene to lanosterol, the initial sterol intermediate in the cholesterol synthesis pathway. LSS inhibitors such as U18666A and Ro 48-8071 have a potential to decrease plasma LDL cholesterol levels[57].

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