CLINICAL ALERT

The influence of glucocorticoids on lipid and lipoprotein metabolism and atherosclerosis

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Glucocorticoids have multiple therapeutic uses, but their impact on lipid metabolism and cardiovascular disease risk is not always considered during long-term treatment. Genetic variations, environmental factors and the reasons for glucocorticoid treatment all influence the lipid profile and atherosclerosis. Responses to glucocorticoid treatment may therefore be variable and unpredictable. Despite the frequency with which pharmacological doses of glucocorticoids are used, surprisingly few publications examine their effects on lipid metabolism and atherosclerosis. Patients managed with glucocorticoids should have their cardiovascular risk assessed, especially if long-term treatment is planned. While some apparent favourable changes have been reported in high-density lipoprotein metabolism, very-low-density lipoprotein and low-density lipoprotein responses seem unfavourable. The impact of glucocorticoids on atherosclerosis, which is often viewed as an inflammatory process, is unclear. Glucocorticoid treatment should be undertaken for appropriate indications, but in some instances special attention should be given to management of dyslipidaemia, as long-term survivors of treatment are likely to encounter atherosclerosis.

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Lipid transport

Lipoproteins transport lipids in the circulation in four major pathways: (*i*) a postprandial (exogenous) pathway for chylomicrons; (*ii*) an endogenous pathway involving very-low-density lipoprotein (VLDL) for triglyceride (TG) transport from the liver; (*iii*) a low-density lipoprotein (LDL) pathway from a proportion of VLDL as a source of cholesterol for cells; and (*iv*) a reverse cholesterol transport pathway by high-density lipoprotein (HDL).[1] These pathways and the reported effects of glucocorticoids are shown in Fig. 1.

Exogenous TG pathway

Chylomicrons, comprising 85 - 90% TG and containing apolipoprotein B (apo B)-48 (apoB48), apolipoprotein Ai (apoAi) and apolipoprotein Aiv (apoAiv), are produced in enterocytes, traverse the thoracic duct and ultimately reach the systemic circulation. Lipoprotein lipase anchored on cells by heparan sulphate proteoglycans hydrolyses TG at the vascular endothelium, yielding non-esterified fatty acids (NEFAs) and remnants, proportionately richer in cholesterol esters. Chylomicron remnants are rapidly cleared by liver remnant receptors,[2] as a result of apolipoprotein E (apoE) acquired in the circulation. Dietary fat restriction will have a significant impact on severe hypertriglyceridaemia.

Endogenous TG pathway

VLDL is assembled on apolipoprotein B-100 (apoB100) and comprises 50% TG, 20% cholesterol esters, 15% phospholipids and 15% protein. Secretion is enhanced by increasing delivery of NEFAs from adipose tissue during starvation or in diabetes.[3] VLDL is also hydrolysed by lipoprotein lipase. These remnants and other small lipoproteins (LDL and HDL) can undergo hydrolysis of TG by hepatic lipase, forming progressively smaller particles. VLDL remnants are proportionately richer in cholesterol, and some form LDL.[1] The release of fatty acids from adipose tissue and their uptake in the liver will enhance VLDL production and may cause hypertriglyceridaemia.

LDL pathway

LDL contains the majority of cholesterol in the plasma. Its mass comprises 35% cholesteryl ester, 10% unesterified cholesterol (UC), 10% TG and 20% phospholipids. ApoB100 almost entirely accounts for the 25% of protein. Most circulating LDL is taken up by hepatocyte LDL receptors. Increased VLDL could increase LDLC while also resulting in modulation of particle size. This process requires cholesterylester transfer protein (CETP) to enrich with TG, after which hepatic lipase hydrolyses the TG. The plasma LDL concentration may also be raised by decreased clearance (by LDL receptors) in familial hypercholesterolaemia.

Reverse cholesterol transport

HDL is the smallest of the lipoproteins. About half is lipids (25% phospholipids and 15% cholesterylester, while UC and TG both constitute 5%). The remainder is chiefly apoAi and apolipoprotein Aii (apoAii). The liver and intestine secrete apoAi that may initiate particle formation, which may also result from lipolysis of TG-rich lipoproteins[4] when apoAi and the relative excess of phospholipids pinch off from the lipoprotein. Lecithin-cholesterol acyltransferase

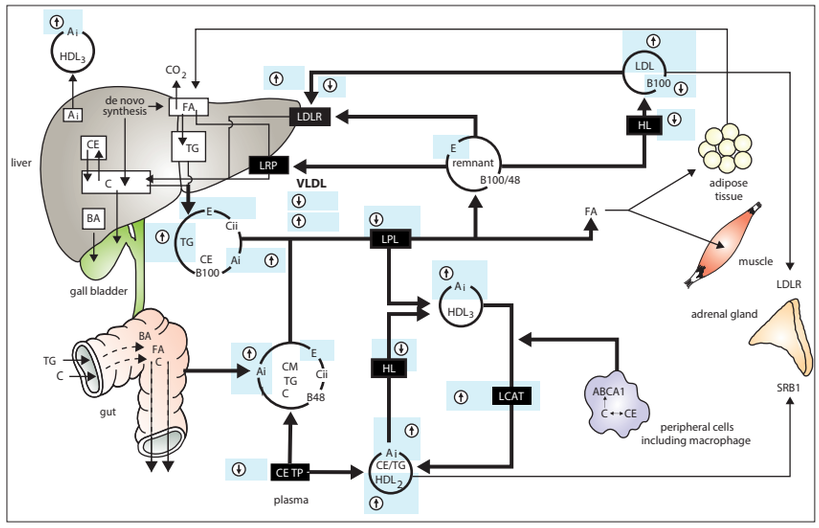

Fig. 1. Schematic view of lipoprotein metabolism including the effects of glucocorticoids. Adapted with permission from Marais.[1] (ABCA1 = adenosine binding cassette transporter A1; apoE = apolipoprotein E; Ai = apolipoprotein Ai; BA = bile acid; B100 = apolipoprotein B100; C = cholesterol; CE = cholesteryl ester; CETP = cholesterylester transfer protein; CM = chylomicron; Cii = apolipoprotein Cii; FA = fatty acids; HDL_2 = high-density lipoprotein 2; HDL_3 = high-density lipoprotein 3; HL = hepatic lipase; TG = triglyceride; LDL = low-density lipoprotein; LDLR = LDL receptor protein; LPL = lipoprotein lipase; LRP = low-density lipoprotein receptor protein; LCAT = lecithin cholesterol acyltransferase; SRB1 = scavenger receptor B1; VLDL = very-low-density lipoprotein.)

(LCAT) esterifies UC, using long-chain fatty acids from phospholipids. Cholesteryl esters migrate to the core, forming more mature spherical particles (HDL3) and later larger and less dense HDL. CETP transfers cholesteryl ester from HDL2 to TG-rich lipoproteins, permitting delivery of cholesterol to the liver, and in exchange HDL receives TG.[4] Hepatic lipase hydrolyses TG, regenerating smaller HDL3 particles. Exchange of TG into LDL similarly produces smaller particles. In HDL, esterification of UC permits more UC to be accepted from cells or other lipoproteins. HDL delivers cholesterol directly to the liver, leading to its excretion in bile.[5]

Lipid and lipoprotein changes with corticosteroids

Dyslipidaemia, hyperglycaemia and hypertension are the most significant cardiovascular adverse effects resulting from glucocorticoid therapy,[6] but mechanistic insights are incomplete. Documented changes in human lipid profiles on varying doses of prednisone[7-10] include elevated VLDL, TG and LDL cholesterol, and either increased or decreased HDL cholesterol.

Animal studies of lipid changes in steroid use

Hydrocortisone (single dose) administered to rabbits with atherosclerosis raised TG but not total cholesterol (TC),[11] suggesting increased VLDL production or possibly decreased metabolism. In rats, dexamethasone and triamcinolone (but not hydrocortisone) increased plasma TC and TG.[12] Hydrocortisone administered to rats at 100 µg/g of body mass reduced TC. Hydrocortisone, triamcinolone and dexamethasone increased apoAi, with the greatest increases documented for triamcinolone and dexamethasone. Dexamethasone raised apoAiv the most, and triamcinolone caused the greatest increase in apoE, yet reductions in apoE levels occurred in rats receiving hydrocortisone.[12] Methylprednisone administered to normal rats for 8 days increased TG and almost doubled TC,[13] probably owing to a reduction in lipoprotein lipase activity and decreased HDL cholesterol.[14] ApoE decreased with hydrocortisone, either as a result of less hepatic secretion or increased catabolism of apoE-containing lipoproteins, but lower production of apoE by extrahepatic tissues has also been proposed.[15] The brain, spleen and kidney produce apoE, aiding redistribution of cholesterol from cells with an excess of cholesterol to those requiring it.[15] ApoAi increased with most glucocorticoids, but especially with triamcinolone and dexamethasone, resulting in increased HDL cholesterol.[12,15] Hepatic apoAi mRNA increased in cultured rat hepatocytes exposed to glucocorticoids.[16] Transient down-regulation of LDL receptors in rats followed methylprednisolone administration, accounting for elevated LDL and TC.[17] Overall, animal models illustrate marked effects on HDL and some adverse effects on LDL, as well as differences between the drugs.

Human studies with glucocorticoids

The impact of glucocorticoid hormones on lipoprotein metabolism can be examined in normal variation, acute and chronic dosing, replacement therapy, and hypercortisolism. Positive correlations exist between LDL cholesterol and endogenous plasma cortisol in healthy men aged between 52 years and 67 years.[18] Glucocorticoids alter plasma lipids within 14 days.[10] Acute effects of 3 mg dexamethasone (twice daily simulating acute stress) in young men included lower highly sensitive C-reactive protein levels and increased HDL cholesterol; LDL cholesterol, NEFA and TG were not altered.[19] Glucocorticoids reduce hepatic lipase and CETP, resulting in elevated HDL cholesterol after cardiac transplantation.[20] In the third National Health and Nutrition Examination Survey, glucocorticoid use was associated with higher HDL and lower TC/HDL cholesterol ratios.[21] Both glucocorticoid use and endogenous hypercortisolism (Cushing's disease) resulted in elevated TC and LDL cholesterol. Glucocorticoid replacement in hypopituitary patients lowered VLDL, LDL cholesterol, LCAT and CETP.

Based on animal and human studies, exposure to glucocorticoids may produce either increased or decreased HDL cholesterol. Changes in reverse cholesterol transport or other effects may modulate atherosclerosis. Some studies corroborate up-regulated hepatic LDL receptor activity, explaining a decrease in LDL cholesterol. While glucocorticoids are known to have pleiotropic actions on physiological and pathological processes, lipoprotein responses and homoeostasis are varied, but are potentially atherogenic (Table 1).

Hypercortisolism stimulates the production of VLDL.[6] Subclinical Cushing's syndrome has been associated with dyslipidaemia. Rheumatoid arthritis sufferers frequently have high TC and LDL cholesterol and decreased HDL cholesterol. Untreated rheumatoid arthritis patients may have lower HDL cholesterol levels relating to inflammation and acute-phase response. Treatment with glucocorticoids may dampen inflammation favourably, though this

Table 1. Changes in lipid and lipoprotein metabolism attributable to glucocorticoid treatment

Lipid parameter	Increase	No change	Decrease
TC (composite of all lipoproteins)	Methyl-prednisolone administered for 8 days raised total cholesterol. Over-replacement of hypopituitary patients	In response to glucocorticoids in rats	In hypopituitary individuals
VLDLC (reflects most of fasting plasma TG)	Rabbits: increased TG by 80%; increased VLDLC	A short-term study showed no change in VLDL with glucocorticoids	Hydrocortisone in hypopituitary patients
	Rodent increased VLDL size		
	Decreased lipoprotein lipase activity responsible for increased TG		
	Remarkably supraphysiological doses used		
LDLC (bulk of plasma cholesterol in humans)	Reduction in LDL-receptor mRNA	One study with dexamethasone showed a neutral effect on LDLC	Corticotrophin decreased LDLC and apoB
	Human plasma cortisol proportional to LDLC: human study, Cushing's disease		
LDL particle size	Increased small dense LDL		Decreased small dense LDL
HDLC (contains apoAi and substrate for LCAT and CETP)	Low-dose glucocorticoid in women with rheumatoid arthritis: apoAi unchanged, but HDLC increased by 15%		Promotes atherogenic ratio
	ApoAi increased by 18% and HDLC increased by 28% following prednisone after 2 weeks		
	ApoAi increased with hydrocortisone, triamcinolone and dexamethasone variably but only dexamethasone increased apoAiv in rats		
	ApoAi increased after exposure to dexamethasone		
	Increase of HDLC by 10%		
	Increased phospholipids, only esterified cholesterol and apoE, reduced CETP and hepatic lipase, LCAT unchanged		
	ApoAi significantly higher atheroprotective ratios in the elderly		
	Increased after corticotrophin and dexamethasone in healthy humans		
	In human hypopituitary patients		

TC = total cholesterol; VLDLC = very-low-density lipoprotein cholesterol; TG = triglycerides; VLDL = very-low-density lipoprotein; LDLC = low-density lipoprotein cholesterol; LDL = low-density lipoprotein; apo B = apolipoprotein B; HDLC = high-density lipoprotein; apoAi = apolipoprotein Ai; LCAT = lecithin-cholesterol-acyl-transferase; apoAiv = apolipoprotein Aiv; CETP = cholesterylester transfer protein.

may not apply to atherogenesis.[7] A meta-analysis found an increase of cardiovascular and cerebrovascular disease by 59% and 50%, respectively, compared with the general population. Accelerated atherosclerosis in systemic lupus erythematosus has been attributed to the disease or to glucocorticoid therapy.

Hypopituitary patients on replacement therapy (hydrocortisone, thyroxine and sex steroids) are subject to increased morbidity and mortality from accelerated atherosclerosis. Optimally replaced patients had adverse lipid profiles, with increased TG, TC and LDL cholesterol compared with controls. Daily hydrocortisone supplementation of less than 20 mg/d in growth hormone-replaced patients had the least metabolic consequences.

Clinical approach to glucocorticoid treatment

Doctors considering glucocorticoid treatment in patients with chronic disorders should be aware that cardiovascular risk may increase. Chronic inflammatory conditions can predispose to vascular disease, and treatment may aggravate risk through dyslipoproteinaemia or other mechanisms. Until further studies inform otherwise, prevailing guidelines should be followed. Risk calculations based on clinical parameters and lipid profiles as suggested guidelines offer the best guidance on the threshold for treatment, but may not be accurate. The premorbid lipid profile as well as levels during the illness may guide management. Exercise and dietary recommendations should be the norm.

Table 2. Dyslipidaemia and glucocorticoid treatment

Primary
Dominant disorders, familial combined hyperlipidaemia, familial hypercholesterolaemia, dysbetalipoproteinaemia
Variably penetrant disorders, apoE_2 homozygosity, lipoprotein lipase deficiency
Secondary
Diabetes mellitus
Hypothyroidism
Nephrotic syndrome
Autoimmune, e.g antibodies to LPL
Chronic inflammation (atherogenic lipoprotein phenotype)
Glucocorticoid prescription
Physiological increases in VLDL, LDL and HDL
Anti-inflammatory therapy (low and high dose); altered acute-phase response
Iatrogenic
General effect
Unmasking underlying lipid disorder

ApoE_2 = apolipoprotein E_2; LPL = lipoprotein lipase; VLDL = very-low-density lipoprotein; LDL = low-density lipoprotein; HDL = high-density lipoprotein.

Detailed clinical assessments of a personal and family history of premature cardiovascular disease, physical signs and lipoprotein profiles will assist in the diagnoses listed in Table 2. Physical signs are not invariably present. Certain recessive disorders, e.g. dysbetalipoproteinaemia in subjects homozygous for apolipoprotein E_2 (apoE_2), manifest only when metabolic stress occurs. Partial lipoprotein lipase activity in heterozygotes may predispose to hypertriglyceridaemia. It is expected that glucocorticoid therapy will have a small impact on the lipoprotein profile in patients with normal genetic constitutions, while benefiting the chronic inflammatory condition. Occasionally, severe dyslipidaemia may be precipitated by glucocorticoid treatment, and in this setting special treatment with statins will be required for LDL hypercholesterolaemia, or fibrates for severe hypertriglyceridaemia. Successful treatment of the nephrotic syndrome with glucocorticoids will result in improved lipid profiles. Precipitation of diabetes by glucocorticoid therapy can affect the lipid profile and cardiovascular risk. Hypertension will similarly require a re-evaluation of risk and preventive actions to combat cardiovascular disease.

Conclusions

Treatment of conditions requiring glucocorticoids together with disease-modifying agents is likely to prolong life expectancy and therefore raise the risk of cardiovascular disease. This risk is related at least in part to lipoprotein responses, as summarised in this article. More studies are required to evaluate cardiovascular risk in replacement and anti-inflammatory treatment, as well as the effects of different doses and forms of corticosteroid.

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