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. Responsiveness 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.


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). These pathways and the reported effects of glucocorticoids are shown in Fig. I.

Exogenous TG pathway

Chylomicrons, comprising 85 - 90% TG and containing apolipoprotein B (apo B)-48 (apoB48), apolipoprotein A4 (apoAIV) and apolipoprotein A1 (apoA1), 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, 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. 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. 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 LDL while also resulting in modulation of particle size. This process requires cholesterylster cyclooxygenase 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 apoA1 and apolipoprotein AII (apoAII). The liver and intestine secrete apoA1 that may initiate particle formation, which may also result from lipolysis of TG-rich lipoproteins when apoA1 and the relative excess of phospholipids pinch off from the lipoprotein. Lecithin-cholesterol acyltransferase
Prednisone include elevated VLDL, TG in human lipid profiles on varying doses of corticosteroids. Documented changes to rabbits with atherosclerosis raised TG. Hydrocortisone (single dose) administered steroid use.

Animal studies of lipid changes in hypertension are the most significant. Dyslipidaemia, hyperglycaemia and corticosteroids changes with lipid and lipoprotein metabolism. Permitting delivery of cholesterol to the liver, leading to its excretion in bile.

**Lipid and lipoprotein changes with corticosteroids**

Dyslipidaemia, hyperglycaemia and hypertension are the most significant cardiovascular adverse effects resulting from glucocorticoid therapy,[96] but mechanistic insights are incomplete. Documented changes in human lipid profiles on varying doses of prednisone[87,88] 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 apoA, with the greatest increases documented for triamcinolone and dexamethasone. Dexamethasone raised apoAv the most, and triamcinolone caused the greatest increase in apoE, yet reductions in apoE levels occurred in rats receiving hydrocortisone.[13] Methylprednisolone administered to normal rats for 8 days increased TG and almost doubled TC,[14] probably owing to a reduction in lipoprotein lipase activity and decreased HDL cholesterol.[11] 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.[16] ApoA increased with most glucocorticoids, but especially with triamcinolone and dexamethasone, resulting in increased HDL cholesterol.[12,13] Hepatic apoA mRNA increased in cultured rat hepatocytes exposed to glucocorticoids.[14] 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.[19] 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.[20] Glucocorticoids reduce hepatic lipase and CETP, resulting in elevated HDL cholesterol after cardiac transplantation.[21] In the third National Health and Nutrition Examination Survey, glucocorticoid use was associated with higher HDL and lower TC/HDL cholesterol ratios.[22] 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, 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.[22] Both glucocorticoid use and endogenous hypercortisolism (Cushing’s disease) resulted in elevated TC and LDL cholesterol.

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.[15] Subclinical Cushing’s syndrome has been associated with dyslipidaemia. Rheumatoid arthritis suffers 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...
may not apply to atherogenesis. 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.
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. dysbetalipoproteinemia in subjects homozygous for apolipoprotein E (apoE), manifest only when metabolic stress occurs. Partial lipoprotein lipase activity in heterozygotes may predispense 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.

Table 2. Dyslipidaemia and glucocorticoid treatment

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

References

For a complete set of references, please contact the corresponding author.