Review Article

Corticosteroids: do they damage the cardiovascular system?

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Summary: Since their introduction for the treatment of rheumatoid arthritis, corticosteroids have become widely used as effective agents in the control of inflammatory diseases. Although there have been undoubted benefits upon mortality in diseases such as systemic lupus erythematosus, many patients survive only to suffer a high incidence of premature atherosclerosis. There is also evidence of increased rates of vascular mortality in other corticosteroid-treated diseases, such as rheumatoid arthritis, reversible airways obstruction and transplant recipients. Possible mechanisms of damage include elevated blood pressure, impaired glucose tolerance, dyslipidaemia, and imbalances in thrombosis and fibrinolysis. This paper reviews the clinical evidence supporting the contention that there is an excess cardiovascular mortality in steroid-treated patients and the underlying mechanisms, and points to further areas of research.

Introduction

Corticosteroids are comparable to endogenous glucocorticoids both in structure and function, they bind to the physiological glucocorticoid cytosolic receptor and influence DNA transcription in all parts of the body. Since they were introduced into British medical practice in 1948 for the treatment of rheumatoid arthritis (RA), the potent anti-inflammatory and immunosuppressive properties of corticosteroids have led to their use in a variety of rheumatic and other diseases. There is even a current debate as to whether such drugs should be prescribed more widely in RA. Even from the earliest days, it has been recognized that corticosteroid therapy is associated with many undesirable side effects but, since therapy was employed to control severe diseases with high morbidity and mortality, the risk of these complications was considered acceptable. However, today there are often alternatives to steroid therapy and the risk to benefit ratio of this class of drugs requires closer scrutiny before treatment is considered. The prognosis of systemic lupus erythematosus (SLE), for example, has greatly improved in the post-steroid era. However, despite a better prognosis for lupus-related complications, many patients survive only to suffer a high rate of

premature cardiovascular complications, prompting us to question whether these events may be a consequence of therapy – in particular, prolonged treatment with oral corticosteroids.

Such a hypothesis deserves further analysis. The demonstration of increased cardiovascular disease due to corticosteroid therapy would have major implications for patients with a variety of other less pernicious diseases sometimes controlled by steroids, such as mild RA. In this article, we discuss the evidence that corticosteroids induce vascular damage and highlight the mechanisms that might underlie this association by linking our current understanding of the actions of glucocorticoids with the pathophysiology of vascular disease.

Evidence for steroid-related damage

The potential problems and benefits of steroid therapy can be assessed by examining its impact on morbidity and survival in chronic steroid-responsive diseases (Table I).

The outlook for patients with SLE has improved greatly during the last few decades since the introduction of corticosteroids. The survival rate has risen from less than 50% at 4 years in the early 1950s,¹ to more than 70% at 10 years by 1980² and has continued to improve. The improved survival has been paralleled by an increased usage of

corticosteroids, although earlier diagnosis of SLE, together with improvements in nephrology services, antibiotics and anti-hypertensive agents are likely to have had some influence on these figures. In 1976, Urowitz and colleagues noted a bimodal distribution of mortality amongst their series of 81 patients with SLE.³ The early deaths in six patients were primarily due to active lupus or intercurrent infection: whereas the late deaths were primarily due to atherosclerotic cardiovascular disease, in the absence of active disease. This finding prompted the question as to whether atherosclerosis of the coronary arteries is a particular problem in patients with SLE and, if so, how is atherogenesis facilitated?

Several authors have produced anecdotal reports of premature atherosclerotic myocardial infarction in patients with SLE.⁴⁻⁹ In one cohort of 133 SLE patients followed up for 6 years, as many as eight myocardial infarctions occurred, including two in young women.¹⁰ This compared with an anticipated infarct occurrence of 0.87. Furthermore, those sustained cardiac events had used corticosteroids for an average 81% of the study duration compared with 46% amongst the rest of the group.

In a large study of 552 patients, Ginzler and Berg¹¹ found that as many as 10% of deaths were due to myocardial infarction, and others could have occurred as a consequence of atheroma, such as dissecting aortic aneurysm and cerebrovascular accidents. Accelerated, non-fatal atherosclerosis was also suggested by the finding of 45 cases of angina or myocardial infarction in a follow-up of 507 SLE patients.¹² Amongst these, three premenopausal women required coronary artery bypass surgery.

Various anatomical studies of the coronary circulation have been performed. Necropsies in 36 corticosteroid-treated patients were compared with specimens from the presteroid era.¹³ It was observed that the lumen of at least one major coronary vessel was narrowed more than 50% by atherosclerotic plaques in nearly a half of the cases receiving corticosteroids for more than a year, and none of the cases on steroids for less than a year. The authors pointed out that coronary atheroma was rarely described in the presteroid necropsies. A study of 2,856 necropsies performed on young Japanese found that those with collagen diseases including SLE had more severe atheroma especially in the second decade.¹⁴ Atheroma also appears to be more common in SLE patients than controls at angiography.¹⁵

Steroid damage in other rheumatic diseases

If corticosteroids have an adverse effect on the cardiovascular system in SLE, does the same

phenomenon occur in other steroid-treated illness? After the publication of the first trials of therapy in RA,¹⁶ corticosteroids became popular for disease suppression. Some authors are trying to rekindle a greater enthusiasm for their use.¹⁷

Mortality in RA has been the subject of a number of recent studies. Scott *et al.*¹⁸ followed 112 RA cases at one centre over 20 years, by which time 37 had died. Nearly a third of the deaths were ascribed to cardiovascular disease and the authors suggested that this may have been due to steroids. Mutru *et al.*¹⁹ used a case-control technique to follow 1,000 cases of RA over 10 years. During that time, 352 cases and 221 controls died, with a significantly greater incidence of cardiovascular mortality amongst cases compared to controls. A number of other studies have also reported an increased incidence of cardiac deaths in RA.²⁰⁻²³ An effect of corticosteroids on the heart in RA is also implied by a report of an increased incidence of electrocardiographic (ECG) abnormalities in patients on low-dose steroids when compared to non-steroid treated controls.²⁴ This group found ST and T wave abnormalities five times more frequent in those controlled on steroids. Peripheral vascular disease was also found to be considerably more common in a corticosteroid-treated group (60%) than a group of controls (20%).²⁵ Necropsy studies of patients with RA have also noted a high incidence of coronary disease.^{26,27}

Steroids and non-rheumatic disease

Corticosteroids became widely available in 1955 for use in the treatment of reversible airways obstruction and remain effective in controlling airway inflammation. Robinette and Fraumeni²⁸ examined the 'all cause' mortality over a 29-year period in a cohort of 9,550 war veterans hospitalized with asthma during 1944-1945. When compared with a control group hospitalized at the same time with 'acute nasopharyngitis' the relative risk of death from ischaemic heart disease was 1.46 ($P < 0.001$) and from stroke was 1.51 ($P < 0.05$).

Table I Steroid-responsive diseases

Systemic lupus erythematosus
Rheumatoid arthritis
Graft rejection post-transplantation
Asthma
Sarcoidosis
Inflammatory bowel disease
Nephrotic syndrome
Polyarteritis nodosa
Wegner's granulomatosis
Temporal arteritis/polymyalgia rheumatica

The authors were unable to offer a good explanation for this interesting finding.

Corticosteroids have been widely employed in transplant units as immunosuppressive agents. Recipients of heart transplants are at risk of graft failure as a result of accelerated coronary atherosclerosis, although the aetiology of this problem remains unclear. Becker *et al.*²⁹ noted a high incidence of dyslipidaemia amongst their transplant patients and showed by linear regression analysis that cumulative prednisone dosage was the strongest predictor of both total and low density lipoprotein levels. Renal transplant patients are also at increased risk of developing atherosclerosis. Kariska³⁰ reported that the incidence of vascular disease in a series of renal transplant recipients was significantly related to the number of acute rejection episodes, all treated with high doses of corticosteroids.

Steroids and peripheral vascular disease

Most of the studies relating corticosteroids to the incidence of cardiovascular disease have focused on myocardial infarction, although the steroid effect may not be restricted to coronary arteries. Amongst cases of RA, atherosclerosis of the peripheral arteries was three times as common in those treated with corticosteroids as those who were not.²⁵ Other studies have implied that cerebrovascular events may be associated with corticosteroid treatment. The reports on mortality in RA by Mutru *et al.*¹⁹ and Reilly *et al.*³¹ both point to an increase in the incidence of stroke. The Oxford Community Stroke Project,³² recorded the fact that at least nine of their cases of first stroke were currently or recently treated with steroids for presumed arteritic diseases. The West Birmingham Stroke Project found the relative risk of stroke to be 6.4 in those who reported that they had been regular users of oral corticosteroids during the year preceeding their stroke.³³

Finally, the endogenous overproduction of glucocorticoids, Cushing's syndrome, is also known to be associated with premature atherosclerosis and death from myocardial infarction and stroke.³⁴ Data from animal models also support a role for glucocorticoids in accelerating atherogenesis.³⁵ Both cortisone and adrenocorticotrophic hormone (ACTH) are capable of causing vascular injury³⁶ and glucocorticoids have been also shown to promote direct endothelial cell damage.³⁷

Mechanisms of steroid-induced vascular damage

If corticosteroid administration is a risk factor for cardiovascular disease, how is the damage medi-

ated? Knowledge of the method of action of steroids has grown rapidly over the last few years, providing greater understanding of both beneficial and unwanted effects. Some of these actions might be seen as harmful to heart and circulation (Table II) and will be reviewed in more detail.

Hypertension

Hypertension was one of the features of Cushing's original report of endogenous hypercortisolism³⁸ and there is still widespread acceptance that high blood pressure is a sequel of glucocorticoid excess from whatever cause.³⁹ Several studies have suggested that long-term low-dose corticosteroid therapy can cause hypertension.⁴⁰⁻⁴³ Beevers *et al.*⁴⁴ found a highly significant rise in systolic blood pressure (135.9 to 147.0, $P < 0.001$) in 195 patients with either asthma or RA treated for at least one year with prednisone or prednisolone compared to those not on steroids.

Insulin resistance

Glucocorticoid excess causes insulin resistance,^{45,46} mediated by a reduced affinity of insulin receptors,^{47,48} which produces a tendency towards hyperglycaemia and hyperinsulinaemia. Thus even mild corticosteroid-induced diabetes may have many of the adverse effects on the cardiovascular system traditionally associated with the typical type II hyperinsulinaemia *per se* as a risk factor for coronary artery disease⁵⁰⁻⁵³ and this may also be true of children and premenopausal women.^{54,55}

Effects of lipid metabolism

Disturbances of blood lipid levels following corticosteroid treatment have been well documented.^{29,56-59}

Table II Possible mechanisms contributing to corticosteroid-induced vascular damage

Hypertension
Hypercholesterolaemia
Hypertriglyceridaemia
Insulin resistance
Hyperinsulinaemia
Obesity
Electrolyte disturbances
Avascular necrosis
Hypercoagulability
Endothelial-platelet balance disturbed
Endothelial cell damage
Catecholamine potentiation
Monocyte-macrophage function
Corticosteroid cytotoxicity
Corticosteroid vasculitis

The most usual finding is a rise in low-density lipoprotein cholesterol and to a lesser extent, very low-density lipoprotein cholesterol. Both changes might be expected to affect the risk of coronary disease adversely.⁶⁰ Studies on patients with SLE suggest the overall levels of apolipoprotein B-containing particles were greater in those treated with prednisone.⁶¹

The corticosteroids are also amongst several hormones capable of stimulating 'hormone-sensitive' tissue lipase, possibly by potentiating the effects of catecholamines⁶² and leading to an overall increase in availability of circulating fatty acids, which may also be harmful to the heart.

Obesity

There is a well-established relationship between hypercortisolism and obesity both in man and experimental animals.^{63–65} This association is also seen with corticosteroid therapy.^{66,67} Patients with Cushing's syndrome tend to exhibit obesity with a characteristic deposition of fat in the upper body.³⁸ Altered distribution of adipose tissue has also been reported in patients treated with corticosteroids, particularly in the upper body.⁶⁸ The distribution of excess body fat seems to be a significant factor in relation to cardiovascular disease (reviewed by Kaplan⁶⁹). There appear to be two distinct patterns: central (upper body, male, android) obesity with waist/hip ratio greater than 0.85 or peripheral (female, gynoid) pattern with waist/hip ratio less than 0.85. There is considerable evidence that, at a given weight, individuals with central obesity have an increased risk of cardiovascular disease.^{70–74} This group also have higher blood pressures, serum triglycerides and glucose, peripheral insulin resistance and hyperinsulinaemia, and lower high-density lipoprotein levels.^{75–79}

Avascular necrosis of bone

This phenomenon is known to be associated with the use of corticosteroids and seems to result from a disruption of the vascular supply of the femoral head.⁸⁰ The association was noted by Zizic *et al.*⁸¹ who documented Cushingoid changes in 86% of patients with SLE with avascular necrosis and only 15% of SLE patients without avascular necrosis ($P < 0.0001$). The duration of steroid therapy,⁸² the total cumulative dose⁸³ or the highest daily dosage⁸⁴ have all been implicated as relevant factors.

Several causes for avascular necrosis have been proposed but altered vascular function seems to be the most likely. Some authors pointed to the induction of a hypercoagulable state by corticosteroid^{85–87} suggesting that microvascular clots may cause local ischaemia. Another popular theory is that corticosteroids can induce fat emboli, which

obstruct the subchondral arterioles.^{88–91} Indeed, Fisher and Bickel⁹² had reported fat emboli in the subchondral arterioles of up to half of the specimens examined.

The coagulation system

Several reports have suggested that corticosteroids produce a state of hypercoagulability^{85,86} manifested as a shortening of the activated partial thromboplastin time⁸⁷ (Table III). This finding is significant since occlusive thrombus formation is likely to be the final event leading to acute myocardial infarction or ischaemic stroke.

The potential effect of corticosteroids on fibrinogen deserve particular mention. Fibrinogen is now emerging as a major risk factor in stroke⁹³ and myocardial infarction,^{94–97} and may be a closer predictor of cardiovascular death than serum cholesterol.⁹⁸ Fibrinogen, an acute phase protein is produced in the liver. *In vitro* cultured rat liver cells will increase the synthesis of fibrinogen mRNA when incubated with glucocorticoids.⁹⁹ Fibrinogen production has been shown to increase in response to glucocorticoids both *in vitro*^{100–102} and *in vivo*.^{103,104}

The natural defence to fibrin deposition and clot formation is the fibrinolytic system, initiated by tissue plasminogen activator. Although there are no studies of the overall changes in fibrinolytic activity in response to corticosteroids, cellular production of plasminogen activator by both the mouse macrophage and human neutrophil is blocked by corticosteroids.^{105,106} Clearly this aspect of glucocorticoid activity may be crucial to intravascular pathology and requires further investigation.

There is further potential for corticosteroids to cause disruption of the thrombosis–fibrinolysis balance by their effects on limiting the availability of arachidonic acid for prostacyclin synthesis in the vascular wall.^{107,108} Glucocorticoids stimulate DNA transcription to produce lipocortin, a protein that inhibits phospholipase A2.^{109–114} This prevents the formation of products of both the cyclooxygenase and lipoxygenase systems, including prostaglandins, prostacyclin, leukotrienes and thromboxanes. It would appear that there is a proportionally

Table III Factors contributing to a steroid-induced hypercoagulability

Increased cellular production of fibrinogen
Reduced cellular plasminogen activator formation
Inhibition of phospholipase A2 formation and arachidonic acid release – prostacyclin/thromboxane imbalance

greater inhibition of prostacyclin synthesis by glucocorticoids than the thromboxanes^{115,116} and this occurs at therapeutic doses.¹¹⁷ A relative deficiency of prostacyclin may allow dominance of platelet thromboxanes at the endothelial surface and favour vasoconstriction, thrombus formation and release of platelet-derived growth factors stimulating local cellular proliferation and atheroma. Some have advocated the simultaneous use of anti-platelet agents, such as aspirin concurrently with corticosteroids, in an attempt to restore the balance.¹¹⁸

Leucocyte function

The egress of monocytes from the vascular lumen and eventual uptake of lipid deposits seems to underly the atherosclerotic process.^{119,120} Glucocorticoids inhibit the responsiveness of tissue macrophages to cytokines, depress bactericidal activity and prevent normal chemotaxis.^{121–123} If the failure to complete the phagocytic process adequately included other materials such as lipids, one could envisage that the transition from tissue scavenger to lipid laden 'foam' cell might be facilitated.

Conclusions

In view of their adverse effects on a number of cardiovascular risk factors, it is surprising that a

possible relationship between corticosteroid usage and cardiovascular damage has not been more thoroughly investigated. A considerable body of evidence has been presented that, at the very least, casts suspicion about the effects of the agents currently in widespread use. The lack of attention previously given to this subject probably reflects the fact that therapy is usually given to those of older age who are already prone to the high incidence of age-related atheroma or to younger patients with serious multi-system diseases often involving widespread vasculitis. Under these circumstances a small but genuine effect could be masked.

In summary, there is good evidence in the literature to support the contention that regular systemic treatment with corticosteroids is associated with an increase in the incidence of major cardiovascular disease. Several mechanisms may predispose corticosteroid users to an increased risk of atherosclerosis and thrombosis and further research is required to test this hypothesis. As physicians we are obliged to consider the situation and the therapeutic options carefully before starting our patients on long-term steroid therapy.

It is hoped that, in the future, safer and less toxic steroid-sparing agents will be available. In the mean time, although steroids may have a life-saving role in general diseases, their dosage should be reviewed regularly by prescribers to lessen the subsequent complications of long-term therapy.

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