Corticosteroid treatment, serum lipids and coronary artery disease

D. B. JEFFERYS
B.Sc., M.R.C.P.

M. H. LESSOF
M.D., F.R.C.P.

M. B. MATTOCK
Ph.D.

Department of Medicine, Guy's Hospital, London Bridge SE1 9RT

Summary

Serum lipids and the cholesterol concentrations in the high density lipoprotein (HDL) fractions were measured in patients receiving long-term corticosteroid treatment for connective tissue disorders and asthma. Patients who were not receiving corticosteroid treatment had blood lipid levels which did not differ from those of healthy people. However, female (but not male) patients who had received prednisolone for a mean period of 3.1 years had a significant elevation in total cholesterol and a large decrease in HDL cholesterol. It seems possible that high levels of corticosteroids may increase the incidence of premenopausal ischaemic heart disease in females.

Introduction

Corticosteroids are frequently used in the long-term management of connective tissue disorders and occasionally in patients with asthma and sarcoid. In addition to the traditional complications of this treatment, Kalbak (1972) showed an increase in peripheral atherosclerosis during corticosteroid treatment for rheumatoid arthritis. As compared to well matched controls, Bulkley and Roberts (1975) found an increased incidence of coronary atherosclerosis at post-mortem in 36 patients who had received corticosteroids for a variety of conditions including systemic lupus and rheumatoid arthritis. An increased incidence of coronary artery disease has also come to be recognized in renal transplant patients on corticosteroids (Evans and Ghosh, 1979).

The mechanism for this accelerated atherosclerosis is unclear. El-Shaboury and Hayes (1973) showed that both triglycerides and cholesterol were increased in 100 female asthmatics on long-term corticosteroid treatment. Current interest in lipid metabolism centres on the high density lipoproteins and their inverse relationship to ischaemic heart disease (Gordon *et al.*, 1977). These levels may be particularly significant if, as has been suggested, high density lipoproteins are responsible for transferring

cholesterol out of the tissue and back into the general metabolic pool, where it may be catabolized.

In this study the authors have looked at the long-term effects of corticosteroids on HDL cholesterol. They have studied 3 groups: patients who are receiving corticosteroids; age-, sex- and disease-matched patients who are not receiving such treatment; and healthy age- and sex-matched controls.

Patients and methods

Subjects

The serum total cholesterol, triglycerides and HDL cholesterol were measured for 16 premenopausal female patients (age range 18-34 years) and 15 males (ages 24-38 years) who were all receiving long-term corticosteroid treatment. The body weights were all within 5% of the predicted weight from standardized life assurance tables. Three of the females were taking an oral contraceptive, whilst only 2 of the males and none of the females were cigarette smokers. None had a known family history of hyperlipidaemia. The average dose of prednisolone was 17.0 mg/day for the females and 17.2 mg for the males. The mean duration of treatment was 3.1 years for the females and 3.4 years for the males.

The patients studied were all in remission from their disease at the time of investigation. This was judged from clinical impression and from sedimentation rates, biochemical profiles and respiratory function tests.

Three of the patients with Behçet's syndrome were taking azathioprine 50 mg twice/day, one of the rheumatoids was taking naproxen 200 mg thrice/day and one patient with urticarial vasculitis was receiving cimetidine 400 mg at night. Apart from the asthmatics, who were using bronchodilator aerosols, the steroid patients were on no other regular medications. In the control group 3 patients were taking azathioprine 100 mg daily.

The conditions for which they were receiving prednisolone were mainly connective tissue disorders, including Behçet's syndrome (13), systemic lupus

(2), rheumatoid arthritis (4), polyarteritis (2), urticarial vasculitis (2), sarcoidosis (4) and asthma (4). The blood samples were taken after a 14-hr fast.

Methods

The fasting serum triglyceride and cholesterol concentrations and the cholesterol concentrations of the high density lipoprotein (HDL) fractions were assayed by standard Technicon Autoanalyser II enzymatic methods.

The HDL fraction was measured in the supernatant following specific precipitation from serum of very low density and low density lipoproteins by sodium phosphotungstate and magnesium chloride (Lopes Virella, Stone and Colwell, 1977). It has been confirmed that this method shows good agreement with a reference ultracentrifugal technique of HDL separation (Mattock *et al.*, 1979).

Results

There was no significant difference between the disease-, age- and sex-matched controls, compared to the healthy controls, in any of the serum lipids (Table 1). A notable difference was found between the male and female patients receiving corticosteroids. The male patients had lower levels of triglycerides and total cholesterol. They had significantly higher levels of HDL cholesterol and of the total cholesterol to HDL cholesterol ratio ($P < 0.001$). Thus long-term corticosteroids appear to reverse the usual higher HDL levels seen in females.

Discussion

The principal finding of this study was the marked sex difference in the effect of long-term corticosteroid administration on HDL cholesterol. Epidemiological studies of ischaemic heart disease have shown that there is an inverse relationship with HDL cholesterol and that the cholesterol

to HDL ratio is one of the most sensitive predictors of coronary artery disease (Miller *et al.*, 1977). In such studies, pre-menopausal women have higher HDL cholesterol concentrations. From the authors' observation, long-term corticosteroid treatment appears to reverse the usual pre-menopausal pattern of HDL cholesterol. Indeed, by generally accepted criteria young female patients in this study were likely to have a considerably increased risk of premature coronary artery disease. In keeping with this, 2 of the female patients have a history of angina pectoris with exercise ECG changes. They had no family history of ischaemic heart disease.

It was felt important to exclude a primary effect of the disease on the serum lipid concentrations, or the influence of other drugs on lipid metabolism. The patients studied were all young and were in remission from their various diseases at the time of investigation. Many had been referred for an opinion as to whether their corticosteroids could be reduced or steroid-sparing drugs introduced. The study was designed to compare the patients on steroids with disease-matched controls and healthy subjects. This was facilitated by the fact that the authors were simultaneously looking at a large group of patients with Behçet's syndrome (Lessof *et al.*, 1979). It could be argued that either the connective tissue disease, or additional drug therapy such as immunosuppressives, would alter the blood lipids. In fact only 3 patients were receiving, or had received, azathioprine in addition to the corticosteroids. Three similar patients on azathioprine were therefore included in the disease-matched control group. Since the patients were in remission it was possible to establish well matched controls. Several of the patients were on inappropriately high doses of steroids and these were subsequently reduced without ill effect.

Attention was also paid to the other factors which are known to influence HDL concentrations. Obesity, cigarette smoking and alcohol consumption

TABLE 1. Results

Serum lipids and high density lipoprotein (HDL) cholesterol all in mmol/l ($\pm$ s.d.)					
Group		Corticosteroid group	Disease-matched controls	Healthy controls	Significance, controls v. steroid group
Total triglycerides (mmol/l)	Male ($n=15$)	1.21 (0.42)	0.90 (0.21)	0.87 (0.56)	NS
	Female ($n=16$)	1.84 (0.55)	0.91 (0.29)	0.90 (0.28)	$P < 0.05$
Total cholesterol (mmol/l)	Male	5.61 (0.28)	5.33 (0.31)	5.28 (0.15)	NS
	Female	6.58 (1.04)	4.81 (0.81)	4.93 (0.57)	$P < 0.05$
HDL cholesterol (mmol/l)	Male	1.40 (0.31)	1.54 (0.15)	1.50 (0.53)	NS
	Female	1.10 (0.26)	1.99 (0.25)	1.78 (0.35)	$P < 0.01$
Ratio of					
Total cholesterol	Male	4.00	3.46	3.71	NS
HDL cholesterol	Female	5.98	2.42	2.78	$P < 0.001$

were found to be similar within the groups. No glucose intolerance was noted. Three of the female patients were taking oral contraceptives but their HDL cholesterol levels were in the range seen in other female patients. It was therefore concluded that the sex difference in HDL concentration was attributable to the corticosteroid treatment rather than to the disease or to other therapy.

The accelerated atherosclerosis seen in patients on long-term corticosteroids has been quoted above. El-Shaboury and Hayes (1973) found a significant increase in serum triglycerides amongst 100 female asthmatics receiving this treatment, and it is of interest that Bulkley and Roberts' (1975) patients with systemic lupus and coronary artery disease—like lupus patients in general—were predominantly female.

Savdie *et al.* (1979) have reported a rise in HDL cholesterol after successful renal transplantation but have provided no explanation for this. In view of the authors' own findings and the other evidence quoted here, it seems likely that the reduction in prednisolone dose after successful transplantation may well have been a factor.

Young women usually have higher HDL cholesterol levels than do men and have a low incidence of ischaemic heart disease. The protective effect of female sex hormones is not simple, however, since the contraceptive pill has an opposite effect (Ory, 1977) and so does exogenous sex hormone administration in animals (Jefferys and White, 1973). However the effect of prednisolone on endogenous sex hormones is unknown.

The female patients receiving long-term corticosteroid treatment appear to have the increased risk of developing coronary artery disease, which the male patients do not have. The mechanism for this protection is not clear but may involve changes in endogenous sex hormone production and transport. Whatever the short-term benefits, the present results also emphasize that corticosteroid treatment is a

disease in itself and, particularly in female patients, should be kept to a minimum.

References

- BULKLEY, B.H. & ROBERTS, W.C. (1975) The heart in systemic lupus erythematosus and the changes induced in it by corticosteroid therapy. *American Journal of Medicine*, **58**, 243.
- EL-SHABOURY, A.H. & HAYES, T.M. (1973) Hyperlipidaemia in asthmatic patients receiving long-term steroid therapy. *British Medical Journal*, **2**, 85.
- EVANS, D.B. & GHOSH, P. (1979) Plasma lipoproteins in renal transplant patients. *British Medical Journal*, **1**, 21.
- GORDON, T., CASTELLI, W., HJORTLAND, M.C., KANNEL, W. & DAWBER, T. (1977) High density lipoprotein as a protective factor against coronary heart disease. *American Journal of Medicine*, **62**, 707.
- GOTTO, A.M., MILLER, N.E. & OLIVER, M.F. (Eds) (1978) *High Density Lipoproteins and Atherosclerosis*. Excerpta Medica, Amsterdam.
- JEFFERYS, D.B. & WHITE, I.R. (1973) The lipid response to female gonadal hormones in rats. *Nutrition Reports International*, **8** (3), 201.
- KALBAK, K. (1972) The incidence of arteriosclerosis in patients with rheumatoid arthritis receiving long-term corticosteroid therapy. *Annals of the Rheumatic Diseases*, **31**, 196.
- LESSOF, M.H., JEFFERYS, D.B., LEHNER, T., MATTOCK, M. & SAUNDERS, M.D. (1979) Corticosteroids and azathioprine: their use in Behçet's syndrome. Chapt. 22. In: *Behçet's Syndrome* (Ed. by Lehner, T. & Barnes, C.G.). Academic Press, London.
- LOPES-VIRELLA, M., STONE, P. & COLWELL, J. (1977) Serum high density lipoprotein in diabetic patients. *Diabetologia*, **13**, 285.
- MATTOCK, M.B., FULLER, J.H., PAMELA, S.M. & KEEN, H. (1980) Lipoproteins and plasma cholesterol esterification in normal and diabetic subjects. *Atherosclerosis* (in press).
- MILLER, N.E., FORDE, O.H., THELLE, D.S. & MOJOS, O.D. (1977) High density lipoprotein and coronary heart disease; a prospective case-control study. *Lancet*, **i**, 965.
- ORY, H.W. (1977) Association between oral contraceptives and myocardial infarction. *Journal of the American Medical Association*, **237**, 2619.
- SAVDIE, E., GIBSON, J.C., STEWART, J.H. & SIMONS, L.A. (1979) High density lipoproteins in chronic renal failure and after renal transplantation. *British Medical Journal*, **1**, 928.