

# Hyperlipidaemia and premature coronary artery disease associated with sex-change in a female

C.K. French-Constant\*, F.A. Spengel and G.R. Thompson

Department of Medicine, Royal Postgraduate Medical School and MRC Lipid Metabolism Unit, Hammersmith Hospital, London W12 0HS, UK.

**Summary:** We describe the management of a genotypic female who developed hyperlipidaemia and premature coronary artery disease following bilateral oophorectomy and methyltestosterone administration, and present evidence to suggest that the therapeutic androgenization involved in the sex-change was responsible for the hyperlipidaemia.

## Introduction

Females undergoing oophorectomy before the menopause have an increased incidence of atherosclerosis (Robinson *et al.*, 1959) and an increased all-cause mortality, which is abolished by the use of oestrogens (Bush *et al.*, 1983). The beneficial effect of oestrogens has been attributed in part to their ability to increase high density lipoprotein (HDL)-cholesterol levels in plasma and thus reduce the risk of coronary heart disease (CHD) (Bush *et al.*, 1983). In contrast, androgens are known to affect serum lipoproteins in such a manner as to increase the risk of developing CHD, when given either as methyltestosterone (Russ *et al.*, 1955) or in the form of a progestogen derived from 19-nortestosterone (Hirvonen *et al.*, 1981). It would therefore be expected that a sex-change involving bilateral oophorectomy and the administration of exogenous androgens might result in hyperlipidaemia and premature CHD, although this has not been previously reported. We describe such a case and the subsequent management of these complications.

## Case report

The patient was born a female, with normal establishment of secondary sexual characteristics at puberty. Following increasing transvestite tendencies from age 15, sex-change was initiated at age 34, initially sublingual methyltestosterone (150 mg/d) for two months followed by oral maintenance therapy (100 mg/d). Following satisfactory virilization, hysterectomy,

bilateral oophorectomy and bilateral mastectomy were performed.

Three years later, at the age of 37, the patient developed angina, subsequently sustaining 4 myocardial infarctions between 1975–1977 (age 41–43), following which angina became disabling. Examination in 1978 showed a well virilized, normotensive and obese subject (height 166cm, weight 71 kg) with no stigmata of hyperlipidaemia, who smoked 5 cigarettes a day. There was no family history of CHD and there were no living relatives. Investigation showed serum total cholesterol 9.6 mmol/l (normal 4.0–6.5), triglyceride 1.8 mmol/l (normal female <1.5), high density lipoprotein (HDL) cholesterol 0.65 mmol/l (normal female 1.02–1.78) and an HDL ratio (HDL/total cholesterol minus HDL cholesterol) of 0.07 (normal >0.20). Estimated low density lipoprotein (LDL) cholesterol (Friedewald *et al.*, 1972) was 8.09 mmol/l (normal <4.9 mmol/l). Haemoglobin, fasting glucose and tests of thyroid and liver function were normal apart from a slight rise in aspartate transaminase (55; normal 7–40 IU/l). <sup>99</sup>Tc liver scan was normal. Coronary angiography showed diffuse atheroma with a blocked left anterior descending coronary artery. Methyltestosterone was reduced to 50 mg/d and two vessel coronary artery bypass grafting was performed, with subsequent relief of angina. Hypercholesterolaemia was managed by clofibrate initially, followed by cholestyramine, with reduction in serum cholesterol to 6.9 mmol/l. In 1979 angina recurred and atenolol was introduced. This was accompanied by increases in both serum cholesterol and triglyceride despite the addition of neomycin. Over this two year period angina remained stable and two further angiograms showed patent grafts.

The patient was re-assessed in 1981 to exclude familial hypercholesterolaemia. Skin fibroblast cul-

C.K. French-Constant, M.A., M.R.C.P.; F.A. Spengel, M.D. (Munich) & G.R. Thompson, M.D., F.R.C.P.

\*Present address: MRC Neuroimmunology Project, Dept of Zoology, University College London, Gower Street, London WC1E 6BT, UK.

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ture showed normal HMG-CoA reductase activity (4.8 pmol/mg/min; normal 0.18–5.70) and a normal cholesterol ester: total cholesterol ratio (0.13; normal 0.09–0.24), indicating normal LDL receptor activity and thus excluding familial hypercholesterolaemia (Spengel *et al.*, 1982).

Because of the patient's refusal to discontinue androgens and our failure to control hyperlipidaemia by drugs, a partial ileal bypass was performed (Mr C. Wood). Operative liver biopsy showed some perivenous hepatocyte hyperplasia but no evidence of cholestasis. Three months later serum cholesterol was 6.1 mmol/l, LDL-cholesterol 4.8 mmol/l, HDL-cholesterol 0.55 mmol/l and the HDL ratio was 0.1. Turnover studies of <sup>125</sup>I-LDL and <sup>131</sup>I-LDL-cyclohexanediol (Shepherd *et al.*, 1979) before and 3 months after surgery showed an increase in the total fractional catabolic rate of LDL protein from 0.259 to 0.358/d, with the proportion catabolized via the receptor-mediated pathway increasing from 25% to 39%, and a decrease in LDL synthesis from 12.3 to 9.2 mg/kg/d. All the post-operative indices of LDL turnover are within the normal range. Two years later the patient remains well with stable angina and the serum cholesterol and LDL-cholesterol are both normal. HDL-cholesterol has risen to 1.30 mmol/l and the HDL ratio is now normal (0.277).

## Discussion

This patient's therapeutic virilization was associated with hypercholesterolaemia, low HDL-cholesterol and raised LDL-cholesterol. The hormonal manipulation is a likely cause for these changes. Bilateral oophorectomy in premenopausal women is associated with a significant increase in serum cholesterol and a fall in the ratio of HDL to LDL cholesterol (Robinson *et al.*, 1957). Methyltestosterone in hyperlipaemic men raised cholesterol by 30%, lowered HDL by 55% and raised LDL by 11% (Oliver & Boyd, 1956). A similar study (Russ *et al.*, 1955) showed a fall in the HDL/LDL ratio after androgens with no consistent effect on total serum cholesterol. A solitary oophorectomized

female given methyltestosterone following oestrone showed a similar fall in the HDL/LDL ratio although the total cholesterol fell (Furman & Howard, 1957). The lowered HDL and increased LDL is therefore a consistent feature of methyltestosterone therapy, although effects on total cholesterol are contradictory.

There is no evidence for other factors producing hyperlipidaemia in this patient. Unfortunately there is no record of serum lipids being determined before sex-change but the presence of normal LDL receptor activity in fibroblasts excludes familial hypercholesterolaemia. Long term methyltestosterone can produce cholestatic jaundice but this was not present in our patient, whose only abnormality on liver biopsy was slight perivenous hepatocyte hyperplasia. This is consistent with changes previously reported in other patients on this androgen (Westaby *et al.*, 1977).

The response to partial ileal bypass was similar to that reported by Spengel *et al.* (1981) in patients with familial hypercholesterolaemia. LDL turnover studies showed an increase in receptor-mediated catabolism consistent with an increase in the activity of hepatic LDL receptors resulting from increased conversion of cholesterol to bile acids (Angelin *et al.*, 1983), as occurs after partial ileal bypass (Moore *et al.*, 1969). It is hoped that the complete normalization of this patient's serum lipids and HDL ratio two years after partial ileal bypass, despite maintenance of testosterone therapy, will prevent the onset of the atherosclerotic changes observed in the vein grafts of other patients whose hyperlipidaemia persists following coronary artery bypass surgery (Palac *et al.*, 1982).

The changes in HDL and LDL associated with oophorectomy and exogenous androgen administration would be expected to increase the risk of CHD (Miller *et al.*, 1977), and presumably caused the premature coronary disease observed in this 37 year old patient, whose only other risk factor was a very modest consumption of cigarettes. We conclude that females undergoing artificial virilization may well constitute a high risk group for premature CHD and should be carefully assessed for hyperlipidaemia on this account.

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