aortocoronary bypass grafts were performed. He was symptom free at follow-up.

(3) A 59-year-old man was referred with exertional angina and a soft ejection systolic murmur. His chest radiograph was normal; the ECG showed lateral T wave inversion. Cardiac catheterisation disclosed a 5 mm Hg peak gradient across the perceptibly calcified aortic valve, left ventricular inferoapical hypokinesia, and widespread coronary disease. In June 1974 he had a double aortocoronary bypass operation. In November 1978 his angina recurred. Soon afterwards he developed left ventricular failure. His pulse was 120 beats/min and of small volume, the heart was enlarged, and a third sound and soft ejection systolic murmur were audible. The chest radiograph showed cardiac enlargement and pulmonary oedema. His ECG was little changed (figure). There was a gradient of 60 mm Hg across the now heavily calcified aortic valve, a left ventricular end-diastolic pressure of 35 mm Hg, diffusely impaired left ventricular contraction, and a cardiac index of 2·3 l/min/m^2. Both grafts were satisfactory with no change in the native coronary circulation. Operation confirmed the diagnosis of severe calcific bicuspid aortic stenosis. The valve was replaced. At follow-up he was symptom free.

Comment

The pressure gradient across the aortic valve is influenced not only by its area but also by flow, which in turn is determined by stroke volume, and ejection time. In these patients (in whom all measurements were made with the same recording apparatus) it provided clear evidence of the rapid development of severe obstruction. The importance of recognising such progression is underlined by the successful results of surgery. While the diagnosis may be obvious from the physical signs and electrocardiogram[2] this was not so in two of the patients (cases 2 and 3) whose cardiograms showed T wave inversion throughout, presumably as a result of the coexistent coronary disease. In one patient (case 3) the development of cardiac failure obscured the physical signs, and the hope that it might be attributable to increased outflow obstruction rather than to progressive coronary disease seemed forlorn.

Patients with mild aortic stenosis require regular follow-up. Deterioration is likely to result from progressive obstruction.

I thank Drs M Honey and R Balcon for permission to report the case histories of patients under their care and for their advice. Mr M F Sturridge operated in cases 1 and 2, and Mr J E C Wright in case 3.

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Primary or secondary sicca complex? Investigation in primary biliary cirrhosis by histocompatibility testing

Sicca complex (xerostomia and xerophthalmia) reportedly occurs in up to 72% of patients with primary biliary cirrhosis (primary non-suppurative destructive cholangitis).[1] The reason is obscure, though salivary and lachrymal tissue may be subject to attack by immune-complex-mediated events.[2] Primary or isolated sicca complex may now be separated from secondary or disease-associated sicca complex by histocompatibility-antigen testing. We have therefore reviewed patients with primary biliary cirrhosis with particular reference to histocompatibility antigens in associated sicca complex and also renal tubular acidosis, which occurs as another extrahepatic manifestation in 50-60% of patients.

Subjects, methods, and results

Seventy-four unrelated British patients (four men, 70 women) satisfying the clinical, histological, and immunological criteria for primary biliary cirrhosis[3] were compared with 561 unrelated cadaveric kidney donors from the London area. Tissue typing was performed on peripheral blood lymphocytes with a standardised (Terasaki) microcytotoxicity assay and international workshop sera. Sicca complex was diagnosed from the history and the finding of deficient tear secretion on Schirmer filter-paper testing.[4] Renal tubular acidosis of the distal type was diagnosed from a positive Wrong-Davies ammonium chloride loading test accompanied by normal serum electrolyte concentrations. We used conventional statistical methods to evaluate the results and a modification of Bodmer's technique to correct derived probabilities for the number of HLA alleles tested (14 on the A locus, 16 on the B locus).

The table gives the results. Apart from an excess of HLA-B18 in the patients with primary biliary cirrhosis (which we do not regard as important, since the prevalence of this antigen in the controls was lower than in most European series) the prevalences of the antigens and linkage disequilibrium indices were similar to those in the controls. HLA antigen pattern showed no relation with disease severity, sex, age at onset, autoantibody titre, DNA binding, or immunoglobulin concentration. Sicca complex was confirmed in 24 (41%) out of 58 patients tested, but the slight deficit of BW40 was not significant. In particular, the prevalence of B8 was similar to that in the controls and patients without sicca complex. Renal tubular acidosis was found in 16 (46%) out of 35 patients tested; again no significant differences emerged between these patients and the controls or patients without renal tubular acidosis.

HLA antigens in primary biliary cirrhosis, controls, and associated renal tubular acidosis and sicca complex

Antigen		Patients with primary biliary cirrhosis (n=74)	Controls (n=561)	Patients with renal tubular acidosis (n=16/35)	Patients with sicca complex (n=24/58)
A1		23	184	4	9
A2		36	288	8	11
A3		17	163	6	6
AW23	A9	3	7	0	1
AW24	A9	9	83	2	4
AW25	A10	3	12	0	2
AW26	A10	5	26	2	2
A11		6	69	1	1
A28		5	56	1	1
A29	A19	5	58	3	1
AW30	A19	5	28	0	2
AW31	A19	3	16	0	1
AW32	A19	6	38	1	1
AW33	A19	0	0	0	0
B5		4	44	0	1
B7		13	141	5	6
B8		22	140	3	8
B12		17	170	5	6
B13		4	18	1	1
B14		6	58	2	1
B18		11*	30	3	4
B27		6	50	1	2
BW15		10	83	2	2
BW16		5	39	0	2
BW17		3	58	1	1
BW21		4	22	0	2
BW22		3	26	2	1
BW35		9	90	2	1
BW37		1	20	0	0
BW40		8	62	0	2

*Significant excess compared with controls: pc = 0·035.

Comment

The clinical and immunological heterogeneity of sicca complex is well known. Moutsopoulos *et al*[5] proposed that a primary and secondary group could be defined on the basis of coexisting disease and showed that significant differences in the distribution of HLA and other histocompatibility antigens existed between the two types. Thus increased prevalences of HLA-B8, the lymphocyte alloantigen DRW3, and the IR-analogous antigens Ia172, Ia35, and Ia715 were found in primary sicca but not in the secondary form. B8 is in linkage disequilibrium with DRW3, Ia172, and Ia35, so that our findings complement the clinical evidence for sicca in primary biliary cirrhosis being of true secondary type. The development of the two conditions is therefore probably not subject to independent genetic control. The normal distribution of HLA antigens in renal tubular acidosis suggests that this complication is also secondary to hepatobiliary disease processes.

The importance of these observations is, firstly, that sicca complex in primary biliary cirrhosis is not an overlap phenomenon but a secondary manifestation, which may yield to treatment of the underlying bile duct lesion; and, secondly, that in a large series of patients collected in a single centre HLA type did not differ from control

values. The implications for the taxonomy of primary biliary cirrhosis are far reaching, as it is hereby differentiated from a similar condition in which sicca complex occurs—namely, chronic active hepatitis. In that condition the prevalence of B8 is greatly increased, and the genesis of both the liver disease and the sicca syndrome itself may well be on an alternative basis.

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Unprocessed bran and its effect on urinary calcium excretion in idiopathic hypercalciuria

Idiopathic hypercalciuria occurs in 50-60% of patients with urolithiasis.[1] It results from either increased intestinal absorption of calcium (absorptive hypercalciuria) or an abnormality of the renal tubular handling of calcium (renal hypercalciuria). Increasing the fluid intake and restricting dietary calcium are important means of reducing calcium excretion, but long-term reduction by dietary methods is achieved in only about 20% of patients.[2] Sodium cellulose phosphate and thiazide diuretics have been used successfully in idiopathic hypercalciuria but may cause side effects[1 3 4] and require patient compliance and medical supervision.

Phytic acid combines with calcium to form the insoluble salt calcium phytate and reduces urinary calcium excretion.[5] Since unprocessed bran contains phytic acid (1·7 g/100 g bran) we decided to study urinary calcium excretion in patients with idiopathic hypercalciuria treated with unprocessed bran.

Patients, methods, and results

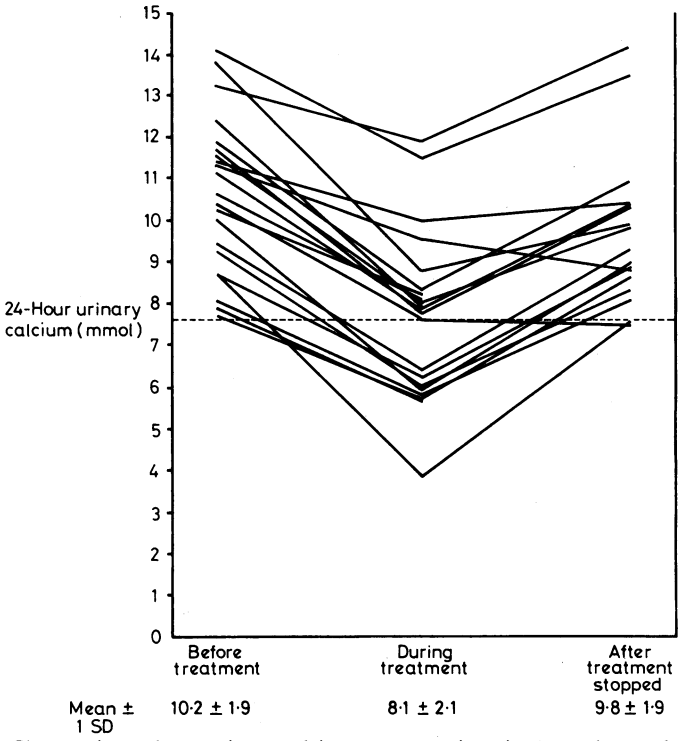
Thirty patients (28 male, 2 female) with idiopathic hypercalciuria (urinary calcium concentration exceeding 7·5 mmol (300 mg)/24 h on two occasions) were entered into the study. Most were aged 40-50 years (range 15-70). Serum and 24-hour urinary calcium, phosphate, magnesium, urea, and creatinine concentrations were measured before, during, and after treatment. A daily sachet of 24 g unprocessed bran was prescribed in divided amounts with meals. Patients continued with a normal diet throughout.

All serum measurements were normal before and during treatment. The mean pre-trial urinary calcium concentration ($\pm$1SD) was 10·6$\pm$1·9 mmol (424$\pm$76 mg)/24 h. Of the 30 patients, 22 achieved a reduction in urinary calcium with unprocessed bran. The improvement during treatment was highly significant ($p > 0·001$; paired *t* test). The eight patients who failed to respond included the two women. In the 22 patients urinary calcium excretion rose after treatment had been withdrawn for one month.

Comment

If urinary calcium excretion can be reduced to normal for a long period in idiopathic hypercalciuria the incidence of recurrent stone formation can be reduced.[3] An effective dietary regimen is ideal for patients with hypercalciuria as it avoids the possible side effects of drug treatment. Dietary restriction of calcium is difficult to maintain, however, as long-term low calcium diets are intolerable to most patients.

In our study 22 patients (73·3%) (figure) reduced their urinary calcium excretion by 20-25%, which could well reduce the risk of stone recurrence by 30-50% over a long period. Possibly larger doses of unprocessed bran would further reduce urinary calcium excretion. The dose used here, however, was close to the upper limit acceptable.



Changes in 24-hour urinary calcium concentrations in 22 patients who responded to treatment. (Urinary calcium: 1 mmol/24 h$\approx$40 mg/24 h.)

The eight patients who did not respond to bran treatment might have had "renal" hypercalciuria; we did not, however, attempt to distinguish between the two conditions.

We postulate that three factors may be responsible for the reduction in urinary calcium excretion: (*a*) the binding effect of phytic acid on dietary calcium may reduce its absorption; (*b*) a decrease in intestinal transit time produced by dietary fibre may reduce the time available for calcium absorption; (*c*) bran may have a direct binding effect on dietary calcium.

Unprocessed bran is effective in reducing urinary calcium excretion in most patients with idiopathic hypercalciuria. Bran is inexpensive, free from serious side effects, and should be taken as part of a dietary regimen aimed at reducing intestinal calcium absorption.

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