The Management of Hyperuricaemia

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There is an enormous literature relating to gout, hyperuricaemia and their sequelae; changes in medical practice, however, necessitate reappraisal of their management. Past reports related only to those who sought treatment on account of illness but, during the last 25 years, increasing numbers of 'well' people have had a serum urate estimation as part of a routine 'health check' or in relation to epidemiological surveys, and many others suffering non-urate related disorders have a serum urate estimation included in a biochemical profile. The problem is what should be done about those found to have a raised serum urate without symptoms attributable thereto. Studies in the USA[1-4] have given valuable guidance, but a ten-year survey in this country of 229 'well' males belonging to social class I may provide data more appropriate to practice in the UK.

Patients and Methods

This series comprises 229 male executives aged 29-65 required, as a condition of their employment, to have an annual medical examination that includes biochemical and lipid profiles, blood count, chest radiography, electrocardiography and urinalysis. Most have been seen annually over a period of 10 years but some over a shorter period by reason of death, retirement or leaving, or only being recently recruited to their employing organisation.

Serum urate was determined by the phosphotungstate reduction method of Sobrinho-Simões[5]; the limits of the reference range being 200-500 μmol/litre.

One of the 229 subjects was in severe heart failure resulting from rheumatic heart disease, and was excluded, as the high serum urate was thought to be attributable to his cardiac status. None of the other 228 had evidence of cardiac or renal failure or haematological disease, but three were taking diuretics for mild hypertension. All were examined, and their blood samples taken, in the morning after an overnight fast.

Results

The serum urate levels of the 228 subjects, related to age, body weight and alcohol intake, are shown in Table 1. In compiling this and other tables the highest serum urate recorded and the related age have been used as in the Framingham survey[1]. Table 1 also shows those in whom no discernible factors affecting the serum urate were apparent.

Table 1. Serum urate levels related to age, body weight and alcohol intake.

Serum urate (μg/litre)	200-299	300-399	400-499	500 +
No. of subjects	6	90	107	25*
Mean age (years)	52.0	46.2	46.8	48.6
Percentage with weight 10% or more above normal	33.3	25.5	40.2	60.0
Percentage with a high alcohol intake	0	4.4	14.1	60.0
Percentage with weight within 10% of normal, low alcohol intake and no diuretics	66.7	72.2	50.5	16.0

*3 taking diuretics for mild hypertension

Scrutiny of all who had had five or more serum urate estimations showed that those with high serum urates maintained their high levels unless treated, while those with low levels remained low. In one half of the individuals the levels varied less than 10 per cent around the mean of all their estimations while in the remainder only three varied more than 20 per cent.

The spread of the serum urate levels in the 228 subjects is shown in Table 1 and Fig. 1: only 25 were above the upper limit of the reference range. The mean serum urate of the whole group was 407.6 μmol/litre.

The incidence of gout, albuminuria and urinary calculus formation in the 228 subjects is shown in Table 2 and the association of hypertension, hyperlipidaemia and myocardial infarction in Table 3.

In the three subjects taking diuretics for mild hypertension no effect on serum uric acid levels was evident.

Discussion

Table 1 shows no relationship between age and serum urate levels as we[6] and others[1,7] have previously

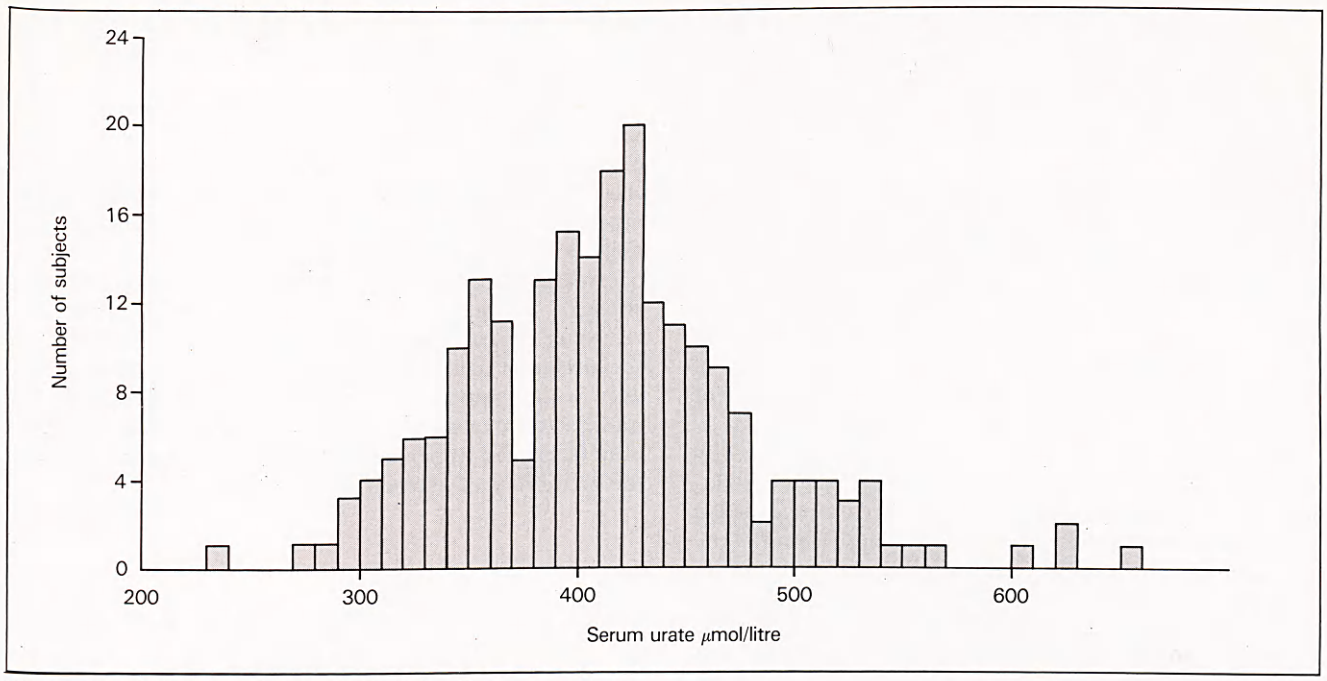

Fig. 1. *Spread of serum urate levels in the 228 subjects.*

Table 2. Serum urate levels related to incidence of gout, albuminuria and urinary calculi.

Serum urate (μg/litre)	200-299	300-399	400-499	500 +
Percentage with gout	0	1.1*	0.9	8.0
Percentage with albuminuria	0	3.3	0.9	16.0
Percentage with urinary calculi	0	1.1†	0	0

*Taking allopurinol when first seen.
†Type of stone not known. Highest serum urate 345 μg/litre.

Table 3. Serum urate related to hypertension, hyperlipidaemia and myocardial infarction.

Serum urate (μg/litre)	200-299	300-399	400-499	500 +
Percentage with hypertension	16.6	14.4	15.0	44.0
Percentage with				
hypercholesterolaemia	0	1.1	2.8	4.0
hypertriglyceridaemia	0	5.6	9.3	20.0
Percentage with myocardial infarction	0	5.6	2.8	12.0

reported; it does, however, demonstrate a clear association of serum urate with body weight and alcohol intake as previously recorded[1-4,6-8]. Table 1 also shows those in whom there was no evident cause for hyperuricaemia; 16 per cent of those with serum urate levels above the upper limit of the reference range fall into this category. These presumably had specific enzyme abnormalities or a genetic tendency to hyperuricaemia which in this survey have not been investigated further. It is acknowledged that these factors may also have operated in some subjects in whom body weight and alcohol intake appeared to be the responsible influences. The fact that over a decade the serum urate in any individual shows so little variation is not unexpected. Genetic tendencies and enzyme abnormalities cannot be altered and body weight and alcohol intake are unlikely to change to any great extent.

Only 11 per cent of the 228 subjects had a serum urate above the upper limit of the reference range (Table 1) but it is unrealistic to suggest that a level can be defined below which is 'normal' and above which is 'abnormal'. It is much more meaningful to examine and quantify the complications of hyperuricaemia than its exact levels. Table 2 shows that only four subjects had gout, two had serum urates above 500 μmol/litre, in one it was 466 μmol/litre and the fourth was already taking allopurinol and had a serum urate of 352 μmol/litre when first seen. In none of the four was gout a significant disability; it was in fact only a temporary nuisance which responded rapidly to appropriate treatment.

Only one of the 228 patients had a urinary calculus. His highest serum urate was 345 μmol/litre, the stone had been passed 15 years previously and had not been analysed. It appears unlikely to have been a uric acid stone.

The incidence of albuminuria is also shown in Table 2. While some relationship with serum urate levels is evident, it cannot be accepted as invariably attributable to hyperuricaemia; often a more likely explanation is that albuminuria is derived from hypertension with which hyperuricaemia is commonly associated[2,4,9,10], the high serum urate being thought to be secondary to hypertension, though the mechanism is uncertain. Of the eight patients with albuminuria six had hypertension, one had an uncoiled aorta, an enlarged left ventricle and other

evidence of arterial degenerative change and the remaining one had a serum urate of only 325 μg/litre. In all the eight patients the albuminuria was slight and none of them nor the other 220 patients showed any evidence of azotaemia. These findings accord closely with those of Fessel[11].

The association of high serum urate levels with hypertension[2,4,9,10] and hypercholesterolaemia[2,4,7-10, 12-15] is well known. Our survey fully confirms the previous reports but the hypertension was mild, the highest level being 190/120, and the hyperlipidaemia showed itself as hypertriglyceridaemia approximately four times more frequently than as an elevation of cholesterol levels, doubtless reflecting the association of hyperuricaemia with increased body weight (Table 3).

Myocardial infarction is less likely to be causally related to serum urate levels. Table 3 suggests a correlation, but only three of the 12 who suffered a myocardial infarct had serum urate levels above the upper limit of the reference range and the apparent link between serum urate and coronary artery disease probably derives from mutual associations, particularly hypertension, hyperlipidaemia, increased body weight and high alcohol intake, rather than from hyperuricaemia itself. Other risk factors were certainly present in nine of the 12, and the serum urate levels of the other three were 423, 369 and 369 μmol/litre. Our findings and interpretation thereof accord with others writers[2-4,16].

What should be done when the physician is faced by the incidental finding of a high serum urate? Its common association with obesity, a generous intake of alcohol, and hypertension should trigger appropriate advice and therapy if such factors are thought to be responsible and important. Albuminuria, renal stone and impaired renal function appear to be rare sequelae of hyperuricaemia[17,18] but recurrent uric acid calculi clearly call for treatment to lower the serum uric acid, though this may dislodge previously static calculi and lead to their ureteric impaction. The only other indication is frequent and disabling attacks of gout. Allopurinol reduces the serum urate even in those addicted to alcohol and prevents gout but in a minority it produces rashes or more severe allergic reactions. Its use should be restricted to those who have a genuine disability. Hyperuricaemia is a common and benign biochemical abnormality which does not often warrant therapeutic interference.

Not surprisingly, our findings and opinions are in close accord with those of Scott, who has studied hyperuricaemia, gout and their complications for many years[8,10,17].

It is widely believed that gout and hyperuricaemia are associated with greater than average intelligence, achievement and drive[17,19,20]. Our 228 subjects from social class I would therefore be expected to have higher serum urate levels than the average population, especially as their larger disposable income might also lend itself to over-eating and a generous intake of alcohol. Of our subjects, 11 per cent had a serum urate above the reference range, compared with 9.2 per cent of men of all social classes in the Framingham survey[1]. This difference would appear to support the hypothesis, but the multifactorial origins of hyperuricaemia and the difficulty of defining the upper limit of the reference range impair the credibility of all such comparisons.

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