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Renal impairment and gout

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SUMMARY A study of renal function in 51 patients with gout and an equal number of normouricaemic controls revealed significant differences. A relative impairment of the glomerular filtration rate and urine concentrating ability in the gouty subjects could not be wholly explained on the basis of aging or hypertension. Renal dysfunction was generally mild and was not associated with specific clinical characteristics, higher levels of uric acid excretion, or hypertriglyceridaemia. Gout patients excreted urine with a significantly lower pH. This was associated with a relatively high excretion of titratable acid and a deficit of ammonium excretion, which was accentuated by ingestion of an acid load. Urate clearance was significantly reduced in gout, even when expressed as a fraction of the glomerular filtration rate.

Gout remains a common disorder, and despite the availability of effective remedies many patients do not receive long-term treatment.[1] If it were certain that hyperuricaemia caused disease of vital organs, the necessity of regular hypouricaemic therapy would be more compelling. For example, it remains questionable whether gout can cause serious renal impairment and, if so, how often. In a widely quoted study Talbott and Terplan[2] noted that uraemia was the cause of death in 23 of 166 cases of gout. Paradoxically, gout was also said to have no adverse effect on life expectancy.[3] In a recent review Steele[4] has implied that hyperuricaemia by itself has a deleterious effect on kidney function. The evidence is not wholly convincing. Berger and Yu,[5] in a study of gouty patients, failed to detect any harmful effect of untreated hyperuricaemia on renal efficiency, and Fessel *et al.*[6] observed no gross deterioration in subjects with asymptomatic hyperuricaemia over a 4-year period. On the other hand Klinenberg *et al.*[7] claimed that hyperuricaemia may induce renal impairment even in the absence of symptoms.

In an attempt to clarify these anomalies we have compared the renal function of a largely untreated population of gouty patients with that of normouricaemic subjects. In a preliminary report we noted that there were no major differences in 29 patients compared with age matched controls.[8] We have expanded our observations to an additional 27 gouty patients and their controls.

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Subjects and methods

Renal function of 51 patients with primary gout was compared with that of an equal number of normouricaemic subjects matched for age and sex. All the gouty patients had a history of sustained hyperuricaemia and at least 1 episode of acute arthritis. The study was confined to patients who had received sporadic or no hypouricaemic therapy. Only colchicine was prescribed during the period of investigation. Twelve gouty patients had a history of hypertension (diastolic blood pressure >100 mmHg), which was treated at the time of the study with nondiuretic hypotensive drugs. Two patients gave a history of renal calculi. None had previously acknowledged renal disease. Control subjects were either hospital personnel or patients with miscellaneous noninflammatory musculoskeletal disorders. None had hypertension or a history of kidney disorder. Where possible, control subjects received no drugs during the investigation period, but some continued to take occasional analgesics. Oral permission was obtained for the studies, which were conducted on both inpatients and outpatients.

Blood urea and creatinine were estimated by a standard AutoAnalyzer technique and glomerular filtration rate (GFR) was determined after a single intravenous injection of ^{51}Cr edetic acid.[9] Urine concentrating ability was assessed by measuring urine osmolality after 15 hours fluid deprivation. On the fourth day of a low purine diet a 24-hour urine sample was obtained, each voided specimen being

collected separately under toluene and paraffin for pH estimation. Pooled specimens were evaluated for 24-hour excretion of uric acid, protein, ammonium, and titratable acid. Urine and simultaneous blood uric acid levels were measured by the method of Simmonds,[10] titratable acid and ammonium concentration by the method of Chan.[11] Midstream specimens of urine from gout patients were examined for cells, casts, and infection. Fasting serum cholesterol and triglyceride were estimated respectively by the methods of Searcy and Bergquist[12] and Wahlefeld.[13] Fourteen gouty patients and 11 normouricaemic controls, matched for age, were given a weight-related dose of ammonium chloride in divided doses over 1 hour as described by Wrong and Davies[14] in their acid load test. Urine pH, ammonium and titratable acid excretion were estimated before and at regular intervals for 8 hours after the acid load.

Results were compared statistically by Student's *t* test and the chi-squared test where appropriate.

Results

Gouty subjects and their controls were well matched for age and sex. Those with a history of gout had a significantly greater body weight and were more obese as reflected by a significantly lower ponderal index (height in inches divided by cubed root of weight in pounds). Regular alcohol consumption was significantly more frequent among the gouty. Blood uric acid and uric acid excretion were both significantly greater in those with gout (Table 1).

The mean levels of blood urea and creatinine of the gouty were higher than those of controls, but the differences were not significant. Glomerular filtration rate and urine osmolatily after fluid deprivation were significantly reduced in the gout patients (Table 2). There was a significant inverse correlation between GFR and age for hyperuricaemic subjects ($r = -0{\cdot}54$; $P<0{\cdot}001$) and normouricaemic subjects ($r = -0{\cdot}4$; $P<0{\cdot}01$). The disparity between GFR values of gout and controls was more evident in

Table 1 *Some clinical and laboratory features (mean ± SD) of gout and age-matched normouricaemic control subjects*

	Gout	*Controls*	*Number of Paired Observations*	*t*	*P*
Numbers of subjects	51	51	—	—	—
Sex	50M 1F	49M 2F	—	—	—
Age ± SD	48 ± 11·7	47 ± 11·6	51	1·83	NS
Regular alcohol (>2 pints beer/day)	37 (72%)	14 (27%)	—	$\chi^2 = 20{\cdot}7$	<0·0005
Body wt. ± SD (kg)	81 ± 11·8	74·8 ± 11·3	51	2·97	<0·005
Ponderal index ± SD	12·2 ± 0·58	12·46 ± 0·55	51	2·35	<0·025
Blood uric acid ± SD (mmol/l)	0·39 ± 0·06	0·22 ± 0·08	51	11·2	<0·001
Uric acid ± excretion SD (mmol/24 h)	3·14 ± 0·97	2·76 ± 0·73	49	2·68	<0·02
Serum triglyceride ± SD (mmol/l)	2·97 ± 1·17	2·03 ± 0·85	42	4·3	<0·001
Serum cholesterol ± SD (mmol/l)	6·52 ± 1·51	6·2 ± 1·25	42	1·15	NS

Conversion SI to traditional units: serum uric acid × 16·8; urine uric acid × 168; serum triglyceride × 88·5; serum cholesterol × 38·7.

Table 2 *Renal function tests (mean ± SD) in gouty and normouricaemic subjects*

	Gout	*Controls*	*Number of paired observations*	*t*	*P*
Blood urea ± SD (mmol/l)	5·85 ± 1·24	5·6 ± 1·2	51	1·04	NS
Blood creatinine ± SD (μmol/l)	90·80 ± 20	83·3 ± 15·7	51	1·9	NS
GFR ± SD (ml/min/1·73m²)	96 ± 20	106 ± 23	51	2·97	<0·005
Urine concentration ± SD (mosm/kg)	807 ± 134	869 ± 135	44	3·15	<0·005
Excluding hypertensive patients: GFR ± SD (ml/min/1·73m²)	98 ± 19·5	107 ± 24	39	2·46	<0·02
Urine concentration ± SD (mosm/kg)	831 ± 127	877 ± 126	32	2·17	<0·05
No. patients with proteinuria (mean g/24h)	16 (0·53)	5 (0·34)	—	$\chi^2 = 7{\cdot}25$	<0·005

Conversion SI to traditional units: Urea × 6·0; creatinine × 0·0113.

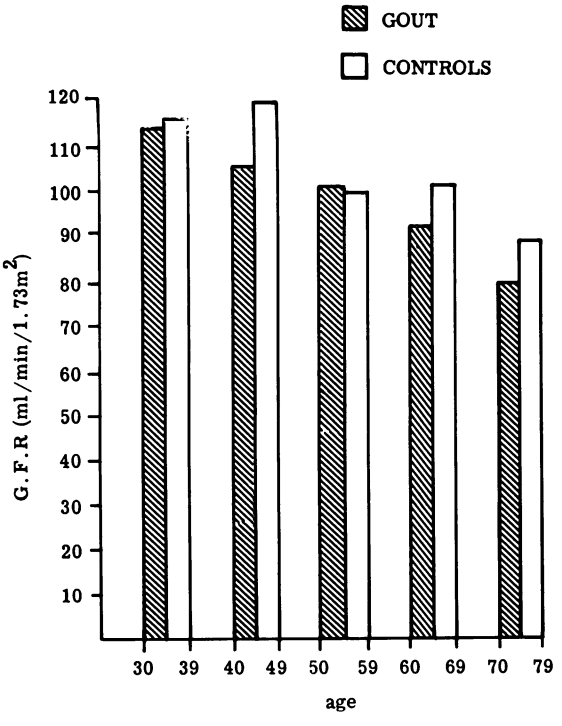

Fig. 1 *Mean GFR of gout and control subjects showing progressive decline with each decade.*

the elderly (Fig. 1). A positive correlation was obtained between the GFR and urine osmolality values of the gouty ($r = 0{\cdot}56$; $P<0{\cdot}001$) and control groups ($r = 0{\cdot}54$; $P<0{\cdot}001$). Significant differences between GFR and urine osmolality of the gout and control subjects were still apparent after exclusion of the 12 hypertensive gouty patients from the comparison (Table 2). Eighteen patients (35%) had a family history of gout. Their mean GFR and urine osmolality were lower than that of age-matched gouty subjects without family histories of gout. The difference between the osmolality values was significant (Table 3). Tophi were observed in 8 (16%) of the gouty subjects. These had mean GFR and osmolality values which were lower than those of 8 age-matched gouty patients without tophi, but the differences were not significant. Renal function of 12 patients excreting more than 3·5 mmol uric acid/24 h (588 mg/24 h) was similar to that of age-matched patients excreting significantly less uric acid (Table 3).

The average duration of gout was 6 years (range 1–26 years) and there was a weak inverse correlation between the length of history and GFR ($r = -0{\cdot}33$; $P<0{\cdot}05$). There was no correlation between GFR and the number of acute gouty episodes ($r = 0{\cdot}07$, NS). Fasting serum triglyceride levels were significantly higher in the patients with gout (Table 1). Twenty-eight (55%) gouty subjects had hypertriglyceridaemia (>2·2 mmol/l). Renal function of these patients was not significantly different from that of patients with normal serum triglyceride values (Table 3). Regular alcohol consumption (more than 2 pints (1·1 l) beer daily) was significantly more common among the gouty than among controls (Table 1). Hypertension occurred in 8 (21%) of the regular drinkers and 4 (28%) of the more abstemious gout patients. Alcohol abuse did not appear to be associated with more pronounced impairment of renal function (Table 3). Proteinuria in excess of 0·1 g/24 h was significantly more

Table 3 *Renal function in gouty patients with and without the following: (a) a family history of gout;* (b) *tophi;* (c) *urate excretion >3·5 mmol/24 h;* (d) *hypertriglyceridaemia;* (e) *regular alcohol consumption*

	No. gout patients	*Mean age ± SD*	*No. with hypertension*	*GFR ± SD (ml/min/1·73)²*	*Urine concentration ± SD (mosm/kg)*
Family history of gout	18	46 ± 13	6	89 ± 25	751 ± 126*
No family history	18	47 ± 12	4	97 ± 22	862 ± 116*
Tophi	10	54 ± 10	1	85 ± 25	743 ± 127
No tophi	10	53 ± 10	2	93 ± 16	815 ± 102
Uric acid excretion 3·5 mmol/24 h	12	39 ± 11	1	101 ± 18·7	846 ± 89
Uric acid excretion <3·5 mmol/24 h	12	48 ± 11	2	98·5 ± 18·7	815 ± 86
Hypertriglyceridaemia (>2·2 mmol/l)	28	46 ± 11	9	98 ± 16	793 ± 136
Normal serum triglyceride	23	50 ± 12	3	94 ± 23	813 ± 147
Regular alcohol (> 2pints beer/day)	37	47 ± 12	8	97 ± 20	808 ± 125
None or occasional alcohol	14	52 ± 10	4	95 ± 20	806 ± 160

*$t = 2{\cdot}98$; $P<0{\cdot}01$. Conversion SI to traditional units: urine uric acid × 168; serum triglyceride × 88·5.

frequent among the gouty patients (Table 2). Examination of midstream urine specimens revealed no evidence of infection amongst the gouty, but 9 (17%) had microscopic haematuria (6–200 red cells/μl).

The diurnal pattern of urine pH revealed that the gout subjects maintained relatively acid urine throughout the day (Fig. 2). and excreted daily volumes of urine with a significantly lower pH (Table 4). However, the range between minimum and maximum pH values over 24 h was not significantly different from that of controls (Table 4). Net acid excretion was similar in both groups, but gouty patients excreted significantly more titratable acid and significantly less ammonium when expressed as a percentage of net acid (Table 4). The percentage of net acid excreted as ammonium by the gout patients did not correlate with either GFR ($r = 0{\cdot}13$) or urine osmolality ($r = 0{\cdot}23$). Acid loading with ammonium chloride induced a similar fall of urine pH in gout and normouricaemic subjects but, the rate of ammonium excretion was consistently lower in the gouty patients. (Fig. 3).

Urate clearance, even when corrected for GFR was significantly lower for the gout patients (Table 4).

Discussion

Our results have shown that in a gouty population several aspects of kidney function may be

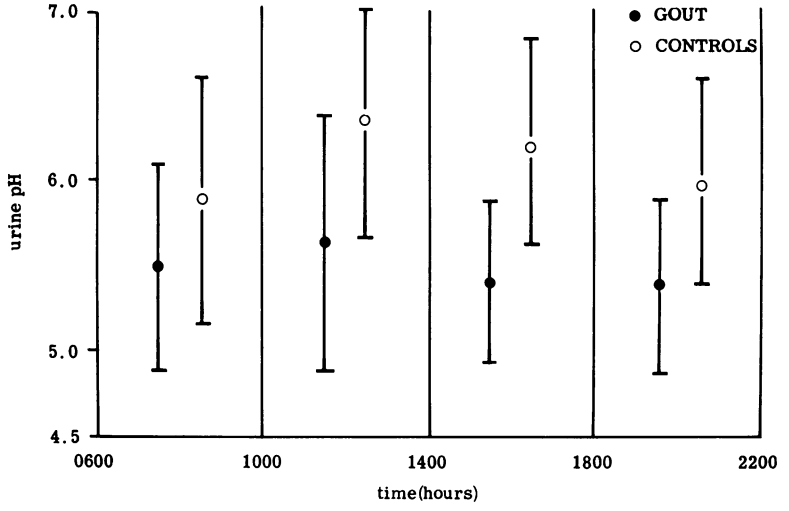

Fig. 2 *Mean ± SD of urine pH values throughout the day in gout and control subjects.*

Table 4 *Renal excretion of hydrogen ion and urate clearance in gout and control subjects*

	Gout	*Controls*	*Number of paired observations*	*t*	*P*
pH 24h Urine ± SD	5·60 ± 0·43	5·90 ± 0·56	48	2·7	<0·001
Daily range urine pH ± SD	0·93 ± 0·53	1·14 ± 0·55	47	1·87	NS
Ammonium excretion ± SD (mmol/24 h)	32·4 ± 11·0	35·3 ± 16·1	42	0·91	NS
Titratable acid excretion ± SD (nmol/24 h)	23·3 ± 11·3	16·3 ± 12·0	42	2·94	<0·01
Net acid excretion ± SD (mmol/24 h)	55·7 ± 19·3	51·6 ± 24	42	1·04	NS
% Net acid excreted as ammonium ± SD	59 ± 13·3	70 ± 16·2	42	3·75	<0·001
% Net acid excreted as titratable acid ± SD	41 ± 13·3	30 ± 16·2	42	3·75	<0·001
Urate clearance ± SD (ml/min/1·73m²)	5·03 ± 1·4	8·3 ± 3·0	50	7·4	<0·001
$\frac{\text{Cur}}{\text{GFR}} \times 100 \pm \text{SD}(\%)$	5·4 ± 1·7	8·1 ± 3·2	49	5·44	<0·001

Cur = Corrected urate clearance.

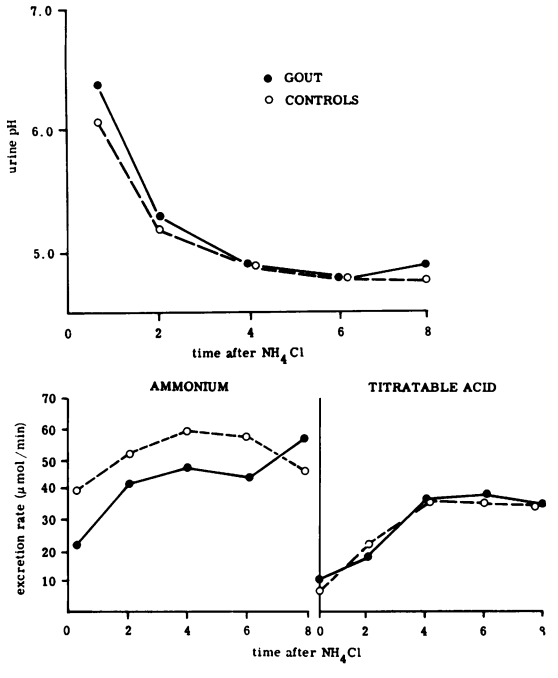

Fig. 3 *Results of acid load test in 14 gout and 11 control subjects showing mean values of pH and hydrogen ion excretion rates during 8 hours after anmomium chloride ingestion. The mean age of gout patients was 52 ± 10 yr and of controls 50 ± 9 yr; mean GFR was 88 ± 23 for gout and 103 ± 21 ml/min/1·73m² for controls; mean urine concentration was 807 ± 143 for gout and 848 ± 125 mosm/kg for controls.*

significantly impaired. A preliminary report of the same study predicted that differences between the renal function of gouty and normouricaemic subjects might become more evident with the inclusion of older patients.[8] Glomerular filtration rates declined with age in both gouty and control subjects, but this aging phenomenon appeared to be accentuated in the gouty. This is consistent with a slowly progressive renal disorder and is in accord with the previously reported prevalence of uraemia in older patients with gout.[15] Urine osmolality paralled GFR values, and there was no evidence of a disproportionate decline of urine concentrating ability. Renal tubular dysfunction has been considered an early feature of kidney involvement in gout,[16] but this has been disputed.[17]

Hypertension did not appear to be the cause of the renal impairment in our gout patients, since significant differences were still apparent when those with hypertension were excluded from the analysis. However, the disparity between gout and control subjects was less striking when those with high blood pressure were omitted. Hypertension in gout is certainly associated with more obvious renal impairment.[18]

Those with a family history of gout had less efficient urine concentrating ability, but it is doubtful whether these patients represented an entity. None was a member of a family which exhibited juvenile gout or severe renal disease. Several such families have now been reported,[19] but the relationship between their gout and kidney failure is uncertain and may not be one of cause and effect as originally suggested.[20]

The duration of gout correlated with the decline of GFR, but this partly reflected the natural effect of aging. There was no relationship between GFR and the number of gouty attacks. Patients with tophi had worse renal function, although the difference was statistically insignificant. There was no obvious relationship between impaired GFR and the amount of uric acid excreted, an observation which conflicts with an earlier report.[21]

Obesity, alcohol excess, and hypertriglyceridaemia are acknowledged features of gout[22] and were confirmed in this study. Obesity may have contributed to the hypertension which was observed in 12 (23%) of our gout patients, thereby influencing renal function.[17] Heavy alcohol consumption has been incriminated in hypertension[23] and provides a putative link between gout and raised blood pressure.[24] In our study excessive alcohol consumption was not more frequent among those with hypertension, nor was renal dysfunction more pronounced among regular drinkers. Some reports have emphasised that premature arteriosclerosis of renal vessels is a histopathological feature of gout.[17 25] Hypertriglyceridaemia might conceivably predispose to this finding, but we could not demonstrate that its presence exerted an adverse effect on kidney function.

The relatively acid urine excreted by gouty subjects has been documented repeatedly[26 27] and was confirmed in the current study. Pak Poy[28] suggested that attenuation of the normal diurnal rhythm of urine pH may be an early feature of renal disease in gout. The range of urine pH in our gout patients was not significantly less than that of the controls, but despite wide fluctuations the pH levels were generally lower throughout the day. This pattern was associated with an increased excretion of hydrogen ion as titratable acid and a reduction in the proportion excreted as ammonium. Hitherto this phenomenon has been attributed to a preferential buffering of tubular hydrogen ion by titratable acid precursors due to a reduced capability of ammonium production. The response to acid

loading in gout and control subjects supported this contention by demonstrating a relatively impaired excretion rate of ammonium in the gouty patients. A similar pattern of hydrogen ion excretion after acid loading can be discerned in patients with renal failure caused by miscellaneous diseases.[14]

It would therefore be reasonable to assume that in gout, impaired ammonium excretion reflects overall kidney dysfunction. Indeed, the gouty patients subjected to an acid load had lower GFR and urine concentration tests than their age-matched controls, though the differences were not significant. If this were the only factor involved, an inverse correlation might to expected between daily ammonium excretion and other measurements of renal function. There was not the least evidence that such a relationship pertained. It is likely that, although kidney disease contributes to the impaired excretion of ammonium in some patients with gout, there is an additional and more complex association. This is supported by our previous demonstration of a reciprocal relationship between ammonium and uric acid excretion following a prolonged acid load.[29]

Controversy has surrounded the pathogenetic role of reduced urate clearance in gout, and the data have been variously interpreted. Gutman *et al.* [30] maintained that renal elimination of uric acid was not specifically impaired in gout, whereas Nugent[31] reached the opposite conclusion. The total evidence argues strongly in favour of a relative defect of urate clearance in the majority of patients with gout.[32] The reduced clearance of uric acid apparent in many of the gouty patients examined by us is consistent with this view and similar to the findings of a previous study conducted in the United Kingdom.[33]

The major finding of our survey is the confirmation of impaired kidney function in gout. In no patient was this sufficient to cause clinically significant nitrogen retention, and the evidence suggested a slowly progressive disorder in the majority of patients. Our study has not provided a clear indication of the mechanism involved except by inference. Weineman[34] has reviewed the topic at length and concluded that, although the evidence is not compelling, there is a strong suspicion that uric acid is of itself deleterious. This suspicion has been reinforced by the finding that allopurinol treatment appears to retard the progression of renal dysfunction.[35]

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