GOUT, HYPERURICAEMIA AND CARBOHYDRATE METABOLISM

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The best-known experimental diabetogen is alloxan which is structurally related to uric acid. Griffiths[13,14] has demonstrated experimentally that under certain conditions uric acid is diabetogenic. Patterson[34] showed that alloxan and dehydroascorbic acid form addition compounds with glutathione and act synergistically in producing an insulin-dependent diabetic state in laboratory animals.

Beckett and Lewis[2] reviewed the relationship between gout and diabetes. Weiss *et al.*[44] showed that persons with gout have a high incidence of impaired carbohydrate tolerance, and this observation was confirmed by Herman.[17] These workers did not take familial incidence of diabetes into account in their studies. Jackson[20] states that gout is a prediabetic condition, and Ibrahim[18] mentions the possibility that altered uric acid metabolism may be related to disturbed carbohydrate metabolism with destruction or inhibition of pancreatic β cells and the development of diabetes.

In view of the known relationship between gout and abnormal carbohydrate metabolism in Europeans, the following investigation was conducted in Natal Indian subjects among whom this relationship has not yet been studied. The objectives were to assess whether or not gout or hyperuricaemia were associated with a high incidence of abnormal carbohydrate metabolism in a diabetes-prone population, and to evaluate the nature of any abnormalities found.

CLINICAL MATERIAL AND METHODS

Three groups of patients were studied:

A. Patients with gout (typical podagra or arthritis with or without tophus formation, responding to colchicine, and associated with raised serum uric acid levels, according to the criteria of Lockie[26] and Seegmiller[39]).

B. Patients with hyperuricaemia discovered during the investigation of other diseases, e.g. hypertension, diabetes, arthritis, etc.

C. A miscellaneous group of patients in whom serial studies were performed.

Serum uric acid was determined by the method of Brown,[5] serum cholesterol by the method of Lepännen,[25] and the blood 'true' glucose and blood urea by the methods of King.[22] The majority of glucose-tolerance tests were performed with 100 G. of glucose,[24,36] although in the early stages of the investigation several patients had 50 G.-tests performed. An abnormal test was regarded as being present if the fasting blood-glucose level exceeded 120 mg. per 100 ml. or if the blood glucose exceeded 140 mg. per 100 ml. 2 hours after administration of the test dose of glucose.

A preliminary study of serum uric-acid levels in 40 non-glycosuric Indians revealed that the normal values were 4·9±2·5 mg. per 100 ml. and 3·7±0·5 mg. per 100 ml. for males and females respectively. Serum uric-acid values above 6 mg. per 100 ml. are generally regarded as abnormal irrespective of age.[11,15,42] Serum cholesterol values up to 350 mg. per 100 ml. were regarded as within normal limits. Practically all tests were performed with the patient in the fasting state.

RESULTS

A. Patients with Gout (Table I)

Thirty-six patients, all males, were studied—35 Indians and 1 Bantu. Ages ranged from 28-75 years (average 49·8 years), the duration of gout varying from 1 month to 20 years. Three patients had a family history of the disease.

Abnormal carbohydrate metabolism was found in 20 patients—3 raised fasting values, 17 abnormal tolerance tests. Of these, 5 patients had a family history of diabetes and were therefore possibly prediabetics or latent diabetics. One patient with no family history of diabetes was receiving oral thiazide diuretic therapy, and 1 patient with a family history of diabetes was being similarly treated. Therefore, 14 patients with no family history of diabetes or oral diuretic therapy had abnormal carbohydrate metabolism (46·6%). In the whole group hypertension was not associated with significant alteration in carbohydrate metabolism. Four of the 16 hypertensive patients had evidence of renal failure, and of these 3 had abnormal carbohydrate tolerance. Two normotensive patients had raised blood-urea levels, but both had normal glucose tolerance. In 3 out of 6 patients albuminuria was associated with abnormal glucose tolerance.

There were insufficient numbers to attempt a correlation between the degree of elevation of serum uric-acid levels and abnormal carbohydrate metabolism. The figures do, however, suggest that serum uric-acid levels above 8 mg. per 100 ml. in patients without a diabetic family history were less commonly associated with abnormal carbohydrate tolerance. Seven patients with gout had blood-sugar levels above 180 mg. per 100 ml. without associated glycosuria, and of these patients only 1 had a family history of diabetes. No patients had raised serum cholesterol levels.

B. Patients with Hyperuricaemia (Table I)

There were 12 patients in this group, all Indians—10 males and 2 females. Their ages ranged from 26 to 62 years (average 42·9 years). Five patients had hypertension, 1 diabetes, 1 diabetes with hypertension, 2 rheumatoid arthritis, 1 polyarthritis with pulmonary stenosis, 1 myocardial infarction, and in 1 coronary artery disease was suspected. There was a family history of diabetes in 2 patients, and gout in 1.

Eight patients had abnormal glucose-tolerance tests, and 1 had elevation of the fasting blood glucose. One of these patients had a family history of diabetes, and this patient and one other were on oral diuretics. All 6 patients with hypertension had abnormal carbohydrate tolerance, whereas this association was present in only 3 of the 6 normotensive patients. Two patients had albuminuria and abnormal carbohydrate tolerance. No patients were uraemic. Four patients had raised renal glucose threshold values in the absence of a family history of diabetes.

One patient with myocardial infarction had a serum uric acid of 10·6 mg. per 100 ml., which fell later to 7·6 mg. per 100 ml. Serum cholesterol values were 445, 485 and 530 mg. per 100 ml. on successive occasions. Glucose tolerance was abnormal. His son, aged 17 years, had a serum uric acid of 5 mg. per 100 ml. and a serum chol-

TABLE I. GLUCOSE TOLERANCE IN PATIENTS WITH GOUT OR HYPERURICAEMIA

		Family history of diabetes	*On treatment with oral diuretics*	*Fasting blood sugar over 120 mg./100 ml.*	*Abnormal glucose-tolerance test*	*No family history. No diuretics. Abnormal tolerance*	*% Abnormal glucose tolerance*	*Blood sugar above 180 mg./100 ml. without glycosuria*	*No family history of diabetes*
A. Gout	36	5	1 (+ 1)	3	17	14/30	46·6	7	6
B. Hyperuricaemia	12	2	1 (+ 1)	1	8	7/9	77·7	4	4
Totals	48	9		4	25	21/39	53·8		
Indians only ..	47	9		28		20/38	52·6		

esterol of 330 mg. per 100 ml. Further family studies were not possible, but it was thought that the patient was an example of the hyperuricaemic hypercholesterolaemia syndrome described by Harris-Jones.[15]

When all 39 patients with gout or hyperuricaemia are considered together, it is noted that 21 (53·8%) had abnormal carbohydrate metabolism in the absence of a family history of diabetes or medication with oral diuretics. Ten of these patients with hyperuricaemia (48%) had raised renal glucose threshold values in the absence of a family history of diabetes.

C. Miscellaneous Group

The 12 patients in this group were those in whom serial studies were undertaken, and some of the cases were drawn from groups A and B. In 6 there appeared to be an inconstant correlation between serum uric-acid levels and impaired glucose tolerance (Table II). In this small series it is impossible to ascertain a correlation between the degree of renal failure present, hyperuricaemia, and glucose tolerance. Three of the 6 patients with abnormal carbohydrate tolerance had a family history of diabetes.

DISCUSSION

Hyperuricaemia, hypercholesterolaemia and early coronary artery disease may be associated with hypertension and diabetes, and it is suggested that a fundamental biochemical abnormality may underlie these conditions.[28] In Europeans with gout and hyperuricaemia, Herman[17] found abnormal carbohydrate tolerance in 21%, while Weiss *et al.*[44] observed this abnormality in 28% of subjects. From the results presented in this paper (excluding the only Bantu in the series), abnormal glucose tolerance was found in 52·6%[20,38] of Natal Indians with gout or hyperuricaemia in the absence of a family history of diabetes mellitus or medication with thiazide diuretics.[3,21] If Indians with a family history of diabetes are included (and Weiss *et al.*[44] and Herman[17] do not report having excluded such patients), the association of hyperuricaemia and abnormal carbohydrate metabolism is 59·6%,[28,47] which is striking. The number of patients studied in this series is too small to draw any valid conclusions regarding the relationship of hypertension to this syndrome, but hypertension and hyperuricaemia tend to be associated with a higher incidence of abnormal glucose tolerance, particularly if significant albuminuria is present.

Beckett and Lewis[2] studied uric-acid levels in a group of diabetic patients, and a similar study has been made on Natal Indians.[29] Natal Indians are largely insulin-independent[6] and are possibly largely diabetic owing to adrenocortical hyperfunction.[20] In view of this it is interesting to note that serum uric-acid levels are generally higher in Indians than those found by Beckett and Lewis[2] in Europeans, and that in Indians there is no significant difference between diabetics and controls.

Eidlitz[11] states that serum uric-acid levels are higher at all ages in persons with arteriosclerosis than in non-arteriosclerotic controls, and that a metabolic relationship exists between uric acid and lipids. The incidence of diabetic vascular complications is higher in Natal Indians than Europeans or Bantu,[9,16,40] but the present study failed to reveal any relationship between uric-acid and cholesterol levels. Beckett and Lewis[2] found no statistical relationship between uric-acid levels and occlusive vascular disease, but it appears possible that the association of hyperuricaemia, hypertension, abnormal carbohydrate tolerance and/or diabetes may be related to the higher incidence of vascular disease in Indians, and further studies along these lines are indicated. Vascular disease does not appear to be related to serum cholesterol values in Indian diabetics.[36]

The significance of glucose-tolerance tests is at present under review[4,27] and some authors believe that abnormal glucose tolerance does not necessarily indicate the presence of diabetes.[8,21] There is however evidence that suggests that abnormal glucose tolerance indicates significantly higher likelihood of clinical diabetes developing.[8,22,36,37] For this reason, in the present study the 2-hour blood 'true' glucose level in excess of 140 mg. per 100 ml. in Natal Indians may be of great importance in the management and prognosis of these patients. The true incidence of dia-

TABLE II. SERIAL STUDIES ON HYPERURICAEMIC INDIANS

Age and sex	*Family history*	*Blood Urea**	*Serum uric urea**	*Fasting sugar*		*2-hour sugar*		*Hypertension*	*Diagnosis*	*Oral diuretic*
				*Blood**	*Urine*	*Blood**	*Urine*			
45–M	D + G	N	5·6	64	—	129	—	No	Gout	Yes
		N	9·1	139	—	205	—			No
50–M	(D)	N	6·1	76	—	85	—	No	Gout	No
		N	10·1	90	—	124	—			No
66–M	Nil	71	8·0	93	—	210	—	Yes	Gout + C.C.F.	No
		47	6·3	95	—	140	—			No
38–M	Nil	N	10·1	180	—	260	—	Yes	HPT + C.C.F.	Yes
			8·5	131	—	235	—		(Albuminuria ++)	Yes
			4·7	100	—	200	—			Yes
23–F	Nil	N	4·8	81	—	94	—	Yes	Pre-eclampsia	No
			5·4	74	—	126	—		(1 week later)	No
			2·9	—	—	—	—		(Postpartum)	No
38–M	D + G	N	8·7	61	—	69	—	Yes	Gout	No
		N	7·7	112	—	266	—			No
46–M	Nil	47	7·7	91	—	103	—	Yes	Gout	No
		N	9·0	96	—	85	—			No

*=mg. per 100 ml.

betes in Natal Indians is not known, but from a preliminary study of 36 patients in whom there was no known family history of diabetes, abnormal glucose tolerance was present in 50% of adults attending this hospital. There was also evidence of raised renal glucose threshold in this group in 50% of those with abnormal tests. (The highest blood-glucose values found in the absence of glycosuria were 280 and 350 mg. per 100 ml.) In view of these findings it is possible that the frequent finding of abnormal carbohydrate tolerance in patients with hyperuricaemia may merely reflect the high incidence of abnormal glucose tolerance in Indians, but this is not believed to be the likely explanation in view of the findings on serial study in the present series. Furthermore, the abnormal glucose tolerance and raised renal threshold values in hyperuricaemic patients may not be related to hyperuricaemia *per se* as suggested by Violle,[43] but may be a feature of the diabetic syndrome found in Natal Indians. Campbell[6] reported abnormal glucose tolerance in about 36% of otherwise healthy male Indian insurance proponents, and the difference between his figures and those briefly reported above may be due to age differences[37] or selection of patients from a 'sick' population, i.e. a selected group of patients who were present at hospital because they were ill, and in whom a glucose-tolerance test was done because diabetes was suspected.

Perkoff *et al.*[35] reported an association between uraemia and altered carbohydrate tolerance, but this was only noted in 1 patient in the present series. Notelowitz[32] is studying carbohydrate metabolism in patients with pre-eclampsia and associated hyperuricaemia in order to assess whether or not the hyperuricaemia is related to the recognized association between pre-eclampsia and diabetes, or represents a prediabetic state.

Beckett and Lewis[2] state that if serum uric-acid levels are to be correlated with diabetogenicity, then one must reconcile this fact with the lower serum uric-acid levels found in diabetes. Padova and Bindersky[33] do not agree with the findings of Beckett and Lewis, and have found that high serum uric-acid levels are present in diabetic keto-acidosis. As keto-acidosis and insulin-dependence are uncommon in Natal Indian diabetics, it is difficult to define 'severity' of diabetes or correlate 'severity' with uric-acid values. Ibrahim[18] believes that uric acid may be of significance, but Weiss *et al.*[44] think that the hyperuricaemia of gout has an ameliorating effect on the clinical expression of the familial tendency to diabetes. The results of the present study support Ibrahim's view, but it should be noted that gout is uncommon in Natal Indian diabetics, and that no examples of insulin-dependent diabetes were found in association with hyperuricaemia.

Shapiro *et al.*[41] showed that in hypertensive patients, with a family history of diabetes, use of thiazide diuretics could unmask a latent diabetic state, but did not relate this to the known effect of these compounds on serum uric-acid levels.[1,3,10,21,45] Experience at the hypertension clinic at this hospital does not support the findings of Shapiro *et al.* (Seedat[38]). This aspect of the relationship between uric acid and carbohydrate metabolism will have to be studied further in Indian patients with hypertension and secondary hyperuricaemia.[12,45]

If one is to accept that hyperuricaemia and gout are possibly associated with the later emergence of diabetes, the corollary is that these patients are potential diabetics (prediabetic) and that they should possibly receive prophylactic oral sulphonylurea therapy as suggested by Jackson.[19] Young[46] has stated that 'oversecretion of growth hormone during a short period of time may be one cause of human diabetes mellitus'. It appears from the evidence of the present study, and that of other workers, that hyperuricaemia may occupy the same position.

SUMMARY

The relationship between gout and hyperuricaemia and glucose tolerance has been studied in 47 Natal Indians. The incidence of abnormal glucose tolerance was found to be 59·6%. If patients with a family history of diabetes or use of oral diuretic drugs are excluded, the association between hyperuricaemia and abnormal glucose tolerance was found in 52·6%.

The significance of these results has been discussed, and it is concluded that abnormal uric-acid metabolism is a manifestation of prediabetes.

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