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Diabetes, Prediabetes and Uricaemia

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Summary. Three diabetes surveys carried out at two yearly intervals on 10000 men aged 40 years and over have enabled us to compare four groups of subjects with regard to their serum uric acid level in relation to carbohydrate metabolism. Prediabetics, that is, persons who screened negative at previous surveys and subsequently developed diabetes, had a higher mean uric acid level than normals ($p < 0.001$). Their uric acid level was considerably higher than in diabetics, who had a mean value lower than normals (up to $p < 0.001$). Men, without diabetes, but having an abnormal GTT were found to have a mean value higher than the normals at each survey.

Key words: Diabetes, prediabetes, abnormal GTT, non-diabetic, uricaemia.

In a long term prospective diabetes survey carried out on 10000 men aged 40 years and over, it was found that men with diabetes had distinctly lower serum uric acid values than other men [Mean uric acid level for diabetics = 4.38 mg/100 ml versus 4.75 mg/100 ml for the total population ($p < 0.001$)] [1].

Our follow up studies have enabled us to examine the uric acid level in further groups of diabetics as well as to examine retrospectively the uric acid levels in 1963 of the diabetics discovered in the subsequent surveys [2, 3] over a five year period. Since these diabetics had screened negative for diabetes in 1963, their 1963 uric acid values were considered "prediabetic" values. In addition, in each of the examinations a group intermediate between the normal population and the diabetics, who showed only minor abnormalities of the GTT, was identified. Thus the uric acid values in four groups: the prediabetics, the abnormal GTT group, the diabetics and those who remained normal throughout the five years could be compared. This study has revealed a pattern of changes in the uric acid level which is related to the pathogenesis of diabetes and, after the disease develops, to the effects of diabetes itself.

Material and Methods

The observations are based on data from a diabetes prevalence survey [1] and two diabetes incidence surveys [2, 3]. These studies were carried out on 10059 men, aged 40 and over, at two yearly intervals as part of a prospective study of ischaemic heart disease in Israel [4]. The examinations of the subjects included, among others, a record of previous illnesses, a physical examination, E.C.G. and, amongst the biochemical tests, uric acid and a random blood glucose estimation.

The screening procedure for suspect diabetics included all those who were found to have a casual blood glucose value of 130 mg or over and/or who gave a history of diabetes. Further information was sought on all suspect diabetics to enable us to establish the diagnosis of diabetes. The details of the criteria for the diagnosis of diabetes and "abnormal GTT" are given in previous publications [1, 3]. Briefly, our criteria for diagnosis were based on a modification of the point system described by Remein and Wilkerson [5] for the glucose tolerance test. When data other than the GTT were used, the diagnosis of diabetes was usually based on 3 diabetic abnormalities – in the vast majority of such cases 3 fasting blood glucose levels of 130 mg. or over (Hagedorn-Jensen method). Serum uric acid determinations in the surveys were made by an adaptation of a method using phosphotungstic acid in the presence of cyanide and urea [6], manually in 1963, and by Autoanalyzer in 1965 and 1968.

The statistical comparison of different groups assumed a normal distribution of uric acid values (they are actually distributed log normally, e. g. with a slight

right hand asymmetry). An 'independent' t-test was used to assess significance. The test is robust against such deviations from normality as described above.

Results

The number of subjects (diabetic and non-suspect) given in the tables represents only those where full information in all the examinations was available. Those with an "abnormal GTT", that is, not sufficiently abnormal to be diagnosed diabetic, in one or more surveys, as well as the deceased, were also excluded from the non-suspect population.

Table 1 shows the *1968* mean uric acid values (+SD) for 8051 normals, 215 diabetics diagnosed in 1968 and the 585 diabetics diagnosed in 1963 and in 1965 combined. In parenthesis are shown also the values of the 412 diabetics diagnosed in 1963. All the diabetic groups have significantly lower mean uric acid values in 1968 compared with the normal subjects in the same year. The mean uric acid value of the 1968 diabetics is significantly lower than that of the non-suspect population of 1968 ($p < 0.02$). The mean uric acid level is progressively lower with increasing duration of the diabetes. The mean uric acid value of 1963 diabetics [M (+SD) = 4.68 (+1.32)] in the 1968 survey year was considerably lower than the mean uric acid value of the non-suspect population in the same year (5.29 + 1.06) ($p < 0.01$).

Table 1. 1968 uric acid values for non-diabetics and diabetics diagnosed in 1963, 1965 and 1968

	Total	Mean (mg/100 ml)	SD	Significance[a]
Normal				
Non-suspect	8051	5.29	1.06	
Diabetic (1968)	215	5.11	1.15	$p < 0.02$
Diabetics (1963 and 1965)	585	4.78	1.28	$p < 0.0001$
(Diabetics (1963 only)	412	4.68	1.32	$p < 0.001$)

[a] P values for the differences between the various groups and the normals. Non-suspects were free of diabetes from 1963 to 1968 inclusive.

The frequency distributions of serum uric acid values in these groups is shown in Fig. 1, which demonstrates a clear trend towards lower values in the diabetics, more especially in the diabetics of long standing. The differences between the diabetics and nondiabetics are statistically significant ($P < 0.01$, by the X^2 goodness of fit test). For 1968 diabetics there were approximately 3 times more diabetics observed than expected with values less than 3.0 mg per 100 ml and nearly twice as many as expected between 3.0 to 3.9 mg/100 ml. For the group with diabetes of longer standing, viz 1963 and 1965 diabetics, there were approximately 7½ times and 3 times more diabetics observed than expected for the corresponding low uric acid values.

Since the diabetics who were diagnosed in 1965 and in 1968 had screened negative for diabetes in the 1963 survey, it may be concluded that their 1963 uric acid values represent "prediabetic" levels.

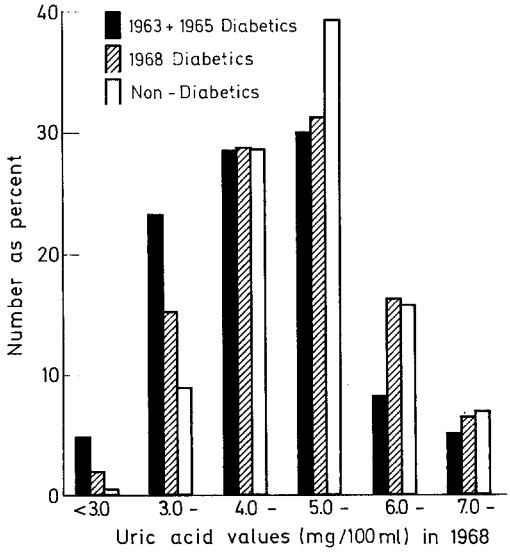

Fig. 1. A comparison of 1968 uric acid values in those diagnosed as diabetics in 1963 and 1965, in 1968, and non-diabetics throughout the 5 year period (1963 to 1968)

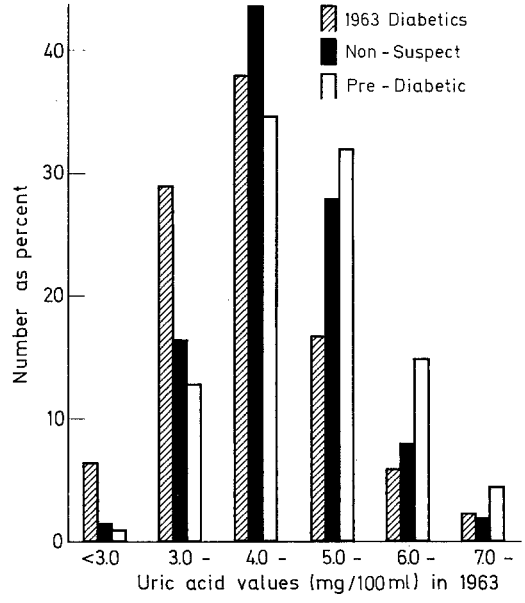

Fig. 2. The uric acid values in 1963 of those diagnosed as diabetics in 1963 compared to the non-diabetics (1963–1968) and prediabetics (i. e. Diabetes diagnosed in the 1968 survey after screening negative for diabetes in 1963 and 1965)

Table 2 shows a comparison of the mean uric acid level of the prediabetics in 1963 with the mean uric acid level of the non-diabetics and diabetics in the same year. Prediabetic uric acid levels, whether derived from a retrospective examination of the 1968 diabetics alone, or the 1965 and 1968 diabetics combined, are significantly higher than those of the non-diabetics. The mean uric acid level of the non-diabetics is again higher than that of the diabetics.

The percent distribution by their serum uric acid values in the same laboratory during 1963 is shown in Fig. 2 for 219 prediabetics (who screened negative twice, in 1963 and in 1965, and were diagnosed diabetic in 1968), for 8627 normals and 472 diabetics (diagnosed diabetic in the 1963 survey). In the histogram (See Fig. 2) which shows rising uric acid levels from left to right, the uric acid distribution is displaced to the left of the normal in the diabetics and to the right of the normal in the prediabetics, featuring the lower values in the diabetics and the higher values in the prediabetics.

The mean uric acid level of the non-suspect population in 1968 exceeded that of the non-suspect population in 1963 by as much as 0.54 mg/100 ml. Similar differences at repeat surveys, even where the same method was used, were observed in the Tecumseh [7] and other [8] surveys, and were considered to be due to technical factors in the performance of the tests. We have, therefore, avoided making direct comparisons of 1963 and 1968 uric acid data.

In our surveys, we have separated off a group with minor abnormalities of GTT ("Abnormal GTT group"). Their GTT criteria were intermediate between those for diabetics and the normals. It was decided to study them as a separate entity since they might have characteristics different from those of diabetics as well as from those of the normals. A high percentage of these subsequently develop diabetes [2]. In each of the 3 surveys their mean uric acid level was found to be slightly higher than the normals: in 1963, 73 had an abnormal GTT, Mean and SE = 4.90 ± 0.11 against that of the normals of 4.75 ± 0.01. In 1968 there were 171 with an abnormal GTT, the mean uric acid level being 5.39 ± 0.08 versus 5.29 ± 0.01 for the normals. Similar differences were seen in the 1965 abnormal GTT group (unpublished data). In this respect they behave like prediabetics, and indeed, are found to develop diabetes with the passage of time.

We have, therefore, observed a consistent trend in uric acid levels – higher than the normal in prediabetics, intermediate in abnormal GTT, and lower than normal in the diabetics. The longer the diabetes persists, the lower are uric acid levels.

Discussion

By standardizing the age and sex group, the uric acid changes relating to diabetes itself could more easily be discerned. Since the diabetics were of the maturity onset type, other factors known to influence the serum uric acid, such as ketosis in the young diabetic [9], could be excluded. In this older range, also, only minor fluctuations in uric acid were noted in the study population in various age groupings, a finding which is in keeping with other large population surveys [10]. An analysis of the uric acid data by six areas of birth ranging from Europe to the Middle East showed only insignificant deviations from the mean for the whole study population. The fluctuations with age and area of birth are too small to have a bearing on the findings.

Lower uric acid values in diabetics have been reported in other studies; one in a relatively small number of diabetics [11], and another [12] in a group of diabetic patients compared with groups of non-diabetic subjects studied by other investigators at other times and other places. Experiments in our biochemical laboratory showed that different concentrations of glucose, added to serum to simulate

Table 2. 1963 mean uric aid values according to diabetes status

	Total	Mean (mg/100 ml)	SD	Significance
Prediabetics derived from 1968 diabetics only	219	5.08	1.03	$p < 0.001$
Prediabetics derived from 1965 + 1968 diabetics	370	5.04	1.10	$p < 0.001$
Not suspect	8627	4.75	0.94	
Diabetic in 1963	472	4.38	1.08	$p < 0.001$

[a] P values for the difference between the mean uric acid values of the various groups and the non-suspect population.
Non-suspects were free of diabetes from 1963 to 1968 inclusive.

diabetic levels, did not influence the uric acid estimation as determined by a phosphotungstic acid method.

The finding of lower uric acid values in diabetics does not conflict with reports of a high incidence of diabetes in patients with gout [13, 14]. The reverse association, namely, the occurrence of gout in diabetes, has, however, been shown to be rare [15], and this would be in keeping with the lower uric acid level observed in diabetics.

The serum uric acid will depend upon the balance achieved between the rates of production and the rates of elimination of urate. Urate production is derived from exogenous (dietary) and endogenous sources. An analysis of the diet of the subjects did not suggest a smaller intake of uric acid precursors in the diabetics. In any case, neither diet nor treatment could be a likely explanation for lower uric acid values in newly diagnosed, previously unknown diabetics.

The possibility of a disturbance in endogenous uric acid production cannot be excluded, but there is at present no evidence of this in diabetics.

Polyuria could produce only a moderate increase in uric acid excretion [16, 17]. Markedly increased excretion of uric acid has, however, followed intravenous infusion of glucose [18]. We have reported an increased uric acid clearance in non-diabetic subjects during induced hyperglycaemia [19], confirming the findings of others [20]. This increase in uric acid clearance was not due to an increased glomerular filtration and occurred independently of the polyuria.

Under normal conditions uric acid is totally filtered in the renal glomeruli and probably totally reabsorbed in the proximal tubules. Some 5 to 10 percent is later secreted into the distal tubules and excreted in the urine [21]. In persons with hyperglycaemia and glycosuria there seems to be a competitive inhibition of uric acid reabsorption in the proximal tubules by glucose. The increased uric acid excretion arising in this way would cause a gradual decline in serum uric acid.

This might be what has occurred among the men with diabetes and is in keeping with our data which indicates that newly diagnosed diabetics had lower uric acid levels than non-diabetic men and that men with diabetes of longer duration had even lower levels than those newly discovered.

The finding of *higher* values in the pre-diabetics compared with the normals is unexpected; more so, since the values in diabetics are considerably lower than in prediabetics. Since diabetes surveys do not screen out all diabetics, it is reasonable to assume that amongst the "prediabetics" of 1963 some may already have been diabetic, but missed in the screening procedure. We would have expected therefore, a bias in favour of lower uric acid values in prediabetics.

Our finding of higher serum uric acid values in *prediabetics* and in persons with minor abnormalities of GTT throws a new light on the uric acid – diabetes relationship. To the best of our knowledge this relationship has not been reported prior to our studies [3, 22, 23], although a high incidence of diabetes in gout has been reported [13, 14], and an ethnic and genetic association of the two conditions has been noted [24]. These findings may serve to renew speculation of a connection between nucleo-protein metabolism and diabetes [25]. It has been suggested that uric acid [26] or a substance resembling uric acid might have an alloxan-like action on the B-cells of the islets and so produce diabetes [27]. However, others failed to confirm such a diabetogenic action for uric acid [28]. Alloxan, one of the best known diabetogenic agents [29], resembles uric acid structurally and may occur as a nucleo-protein breakdown product in man [30]. In the pigeon it has been shown to produce diabetes and an intense form of visceral gout [31]. More recently there have been several reports on a similar association of hyperglycaemia and hyperuricaemia resulting from the thiazide drugs in man [32].

We have found hyperuricaemia to precede the development of diabetes. Some of the factors bearing on the connection between hyperuricaemia and diabetes have been examined within the framework of this study. In our incidence studies [3, 22] no association was found between dietary factors, such as total calories, sugar, carbohydrate, protein (total and animal), and fat and the development of diabetes. Differences in dietary intake are, therefore, unlikely to account for the hyperuricaemia in the prediabetics.

A variety of blood dyscrasias in which there is accelerated nucleoprotein turnover [33] are accompanied by hyperuricaemia. However, there is no evidence to suggest that the prediabetic population is more prone to these disorders. Chronic renal diseases and hypertension [34] are associated with hyperuricaemia. Whilst chronic renal disease is not known to precede diabetes, an increased prevalence [35] as well as an increased incidence of diabetes in persons with hypertension has been reported [23]. The association between hypertension, hyperglycaemia and hyperuricaemia may be accentuated by treatment with the thiazides, previously mentioned [32].

Elevations of serum uric acid have been linked to hypercholesterolaemia in normotensive populations [36]. An interrelationship between gout, hyperlipidaemia and diabetes with hypertriglyceridaemia as the underlying common factor [37] has been described. Others [38] have found no significant increase in serum uric acid in those with the hypercholesterolaemic trait. Our study provides no information

relating to triglycerides. The well known association between diabetes and hypercholesterolaemia has been confirmed [1, 3, 23], but the association between hypercholesterolaemia and hyperuricaemia in these surveys still requires examination.

Clinically the relation of obesity to diabetes as well as to gout is well recognised. The association between obesity and diabetes has been confirmed in our prevalence [1] and incidence [3, 22, 23] surveys. Obesity may be the link between hyperuricaemia and diabetes and requires special consideration. Weight/height (W/H) indices used in the analyses of our survey data are discussed in a previous publication [39]. A preliminary analysis of the uric acid data of the prediabetics, the diabetics, the abnormal GTT group and the non-suspect population has been made in three weight/height groups – low, intermediate and high. It shows that, whilst the uric acid level rises with increase in W/H, the uric acid level in each W/H category is still lowest in the diabetics, intermediate in the normals and highest in the prediabetics, with that of the abnormal GTT group being similar to that of the prediabetics. In addition, we have shown recently in a five year diabetes incidence analysis [23] that *controlled for weight,* prediabetics still have higher serum uric acid than the normal population. Obesity in itself, therefore, does not account for the higher uric acid level in prediabetics.

It is possible that the hyperuricaemic tendency is part of a "constellation" of abnormalities found in the prediabetic state, namely: an obesity/hypertension/hypercholesterolaemia/hyperuricaemia syndrome and may serve to emphasize the close metabolic ties between these conditions and diabetes, rather than a causative connection between hyperuricaemia and the subsequent development of diabetes itself.

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References

1. Herman, J. B., Mount, F. W., Medalie, J. H., Groen, J. J., Dublin, T. D., Neufeld, N. H., Riss, E.: Diabetes prevalence and serum uric acid. Diabetes **16**, 858–868 (1967)
2. Herman, J.B., Medalie, J.H., Kahn, H.A., Neufeld, H.N., Riss, E., Perlstein, T.: Diabetes incidence. Diabetes **19**, 938–943 (1970)
3. Medalie, J.H., Papier, C., Herman, J.B., Goldbourt, U., Tamir, S., Neufeld, H.N., Riss, E.: Diabetes mellitus among 10000 adult men. Israel J. med. Sci. **10**, 681–697 (1974)
4. Groen, J.J., Medalie, J.H., Neufeld, H.N., Riss, E., Bachrach, C.A., Mount, F.W., Smith, H.: An epidemiologic investigation of hypertension and ischaemic heart disease within a defined segment of the adult male population of Israel. Israel J. med. Sci. **4**, 177–194 (1968)
5. Remein, Q., Wilkerson, H.: The efficiency of screening tests for diabetes. J. chron. Dis. **13**, 6–21 (1961)
6. Fister, H.J.: Manual of standardized procedure for spectrophotometric chemistry, Standard Scientific Supply Corp., 1950
7. Dodge, H.J., Mikkelsen, W.M.: Observations on the distribution of serum uric acid level in the participants of the Tecumseh, Michigan, Community Health Studies (a comparison of results of one method used at two different times and two methods used simultaneously). J. chron. Dis. **23**, 161–172 (1970)
8. Fessel, W.J.: Gout (a clinical comprehensive). (guest ed. A.B. Gutman), p. 57. North Carolina: Medcom 1971
9. Seegmiller, J.E., Laster, L., Howell, R.H.: Biochemistry of uric acid and its relation to gout. New Eng. J. Med. **268**, 821–827 (1963)
10. Zalokar, J., Lellouch, J., Claude, J.R., Kuntz, D.: Serum uric acid in 23923 men and gout in a subsample of 4257 men in France. J. chron. Dis. **25**, 305–312 (1972)
11. Mikkelsen, W.M.: The possible association of hyperuricaemia and/or gout with diabetes mellitus. Arthr. and Rheum. **8**, 853–859 (1965)
12. Beckett, A.G., Lewis, J.G.: Gout and serum uric acid in diabetes mellitus. Quart. J. Med. **29**, 443–458 (1960)
13. Weiss, T.E., Segaleff, A., Moore, C.: Gout and diabetes. Metabolism **6**, 103–106 (1957)
14. Herman, J.B.: Gout and diabetes. Metabolism **7**, 703–706 (1958)
15. Joslin, E.P.: Treatment of diabetes mellitus, ed. 9, p. 93. Philadelphia: Lea and Febiger 1952
16. Brochner-Mortensen, K.: Uric acid in blood and urine, Copenhagen: Levin and Munkegaard 1937
17. Bonsnes, R.W., Dill, L.V., Dana, E.S.: The effect of diodrast on the normal uric acid clearance. J. clin. Invest. **23**, 776–782 (1944)
18. Bonsnes, R.W., Dana, E.S.: On the increased uric acid clearance following the intravenous infusion of hypertonic glucose solution. J. clin. Invest. **25**, 386–388 (1946)
19. Herman, J.B., Keynan, A.: Hyperglycaemia and uric acid. Israel J. med. Sci. **5**, 1048–1052 (1969)
20. Christensen, P.J., Steenstrup, O.: Uric acid excretion with increasing plasma glucose concentration (pregnant and non-pregnant cases). Scand. J. clin. Lab. Invest. **10**, 182–185 (1958)
21. Gutman, A.B., Yu, T.F., Berger, L.: Tubular secretion of urate in man. J. clin. Invest. **38**, 1778–1781 (1959)
22. Kahn, H.A., Herman, J.B., Medalie, J.H., Neufeld, H.N., Riss, E., Goldbourt, U.: Factors related to diabetes incidence: A multivariate analysis of two years observation on 10000 men. J. chron. Dis. **23**, 617–629 (1971)
23. Medalie, J.H., Papier, C.M., Goldbourt, U., Herman, J.B.: Major factors in the development of diabetes mellitus in 10000 men. Arch. intern. Med. **135**, 811–817 (1975)
24. Prior, I.A.M., Rose, B.S., Harvey, H.P.B., Davidson, F.: Hyperuricaemia, gout and diabetic abnormality in Polynesian people. Lancet **1966 I**, 333–338
25. Lazarow, A.: Factors controlling the development and progression of diabetes. Physiol. Rev. **29**, 48–74 (1949)
26. Griffiths, M.: Uric acid diabetes. J. biol. Chem. **172**, 853–854 (1948)
27. Conn, J.W., Louis, L.H., Johnston, M.W.: Alleviation of experimental diabetes in man by administration of reduced glutathione. Science **109**, 279–280 (1949)
28. Grunert, R.R., Phillips, P.H.: Uric acid diabetes in the rat. Proc. Soc. exp. Biol. (N. Y.) **76**, 642–645 (1951)

29. Dunn, J.S., Kirkpatrick, J., McLetchie, N.G.B., Telfer, S.V.: Necrosis of islets of Langerhans produced experimentally. J. Path. Bact. **55**, 245–257 (1943)
30. Loubatières, A.: Experimental diabetes – A symposium. Oxford: Blackwell 1954
31. Goldner, M.G.: Alloxan diabetes. Its production and mechanism. Bull. N. Y. Acad. Med. **21**, 44–45 (1945)
32. Dollery, C.T., Pentecost, B.L., Samaan, N.A.: Drug-induced diabetes. Lancet **1962 II**, 735–737
33. Duncan, G.D.: Diseases of metabolism, p. 644. Philadelphia and London: W.B. Saunders Co. 1959
34. Cannon, P.J., Stason, W.B., Demartini, F.E., Sommers, S.C., Laragh, J.H.: Hyperuricaemia in primary and renal hypertension. New Eng. J. Med. **275**, 457–464 (1966)
35. Ostrander, L.D., Francis, T., Hayner, N.S., Kjelsberg, M.O., Epstein, F.H.: The relationship of cardiovascular disease to hyperglycaemia. Ann. intern. Med. **62**, 1188–1198 (1965)
36. Schrade, W., Boehle, E., Biegler, R.: Humoral changes in arteriosclerosis: Investigations on lipids, fatty acids, ketone bodies, pyruvic acid, lactic acid and glucose in blood. Lancet **1960 II**, 1409–1416
37. Berkowitz, D.: Gout, hyperlipidaemia and diabetes interrelationships. J. Amer. med. Ass. **197**, 77–80 (1966)
38. Jensen, J., Blankenhorn, D.H., Kornerup, V.: Blood uric acid levels in familial hypercholesterolaemia. Lancet **1966 I**, 298–300
39. Goldbourt, U., Medalie, J.H.: Weight – height indices. Brit. J. prev. soc. Med. **28**, 116–126 (1974)

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