Elevated serum uric acid – a facet of hyperinsulinaemia

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Summary. In a representative sample of the adult Jewish population in Israel ($n=1016$) excluding known diabetic patients and individuals on antihypertensive medications, serum uric acid showed a positive association with plasma insulin response (sum of 1- and 2-hour post glucose load levels) in both males ($r=0.316$, $p<0.001$) and females ($r=0.236$, $p<0.001$). This association remained statistically significant in both sexes ($p<0.001$) after accounting by multiple regression analysis for age and major correlates of serum uric acid, i.e. body mass index, glucose response (sum of 1- and 2-hour post load levels), systolic blood pressure

and total plasma triglycerides. The net portion of the variance of serum uric acid attributable to insulin response was 12% in males and 8% in females, the total variance accountable by all these variables being 17% and 19% respectively. We conclude that elevated serum uric acid is a feature of hyperinsulinaemia/insulin resistance.

Key words: Serum uric acid, hyperinsulinaemia, Type 2 (non-insulin-dependent) diabetes, impaired glucose tolerance, hypertension, obesity, plasma triglycerides.

Large scale population studies have documented the elevation of serum uric acid levels that accompanies obesity and hypertension [1–9]. Alterations in serum uric acid levels associated with the full range of glucose intolerance are not uniform. While impaired glucose tolerance is accompanied by elevated serum uric acid [5, 8, 10], overt diabetes is reported to be associated with low levels in the absence of nephropathy [1–3, 5, 10]. Obesity and glucose intolerance are recognised states of insulin resistance reflected by hyperinsulinaemia [11–15]. We and others have recently shown that hypertension also is associated with hyperinsulinaemia independently of the effects of obesity, glucose intolerance and antihypertensive medication [15–19]. Elevated plasma triglycerides are another established marker of hyperinsulinaemia/insulin resistance [20–21]. They are also known to be associated with elevated serum uric acid [22, 23].

It therefore seemed likely that the alterations in serum uric acid levels in these conditions are an expression of the insulin resistant state. To test this hypothesis we studied a large representative sample of the adult Jewish population in Israel in order to evaluate the association of serum uric acid levels with hyperinsulinaemia, accounting for its known major correlates.

Subjects and methods

Participants and clinical procedures

The current report addresses a subgroup of the Israel Study of Glucose Intolerance, Obesity and Hypertension (The Israel GOH Study). This is an ongoing nationwide longitudinal study (started in 1969) of a sample of 5711 individuals (drawn from the Israel Central Population Registry) born between 1912 and 1941 [15, 24].

Between 1977 and 1982, 2769 participants – a representative group of the original sample [15, 24] – attended regional medical centers after having blood pressure and regular use of medications (verified by inspection of drug receptacles) recorded at home by specially trained nurses. Blood pressure (mmHg) was measured with a standard mercury sphygmomanometer in the sitting position, four measurements being obtained, two before and two after the interview. At the medical center weight, height, as well as fasting plasma glucose were determined, and, unless known to be diabetic, participants were asked to undergo a 100 g oral glucose tolerance test. From 1979 to 1982, determination of plasma insulin levels – fasting and in response to the oral glucose load, as well as of serum uric acid, serum creatinine and plasma triglycerides in the fasting sample were added to the protocol among other variables, and determined in the most recent series of participants, their age range being 37–70 years. The full set of data was available in 1211 participants who were not known diabetic patients. The detailed sampling procedure and design in both phases showing this group to be representative of the total sample in terms of demographic characteristics, body mass index and blood pressure, have been reported elsewhere [15, 24]. The analysis in this study relates to 1016 individuals of the 1211

- 558 males and 458 females, excluding 191 who were on antihypertensive medications, which are known to affect urate level [1-8] and 4 cases with extreme (≥ 5.6 mmol/l) triglyceride levels. Mean uric acid levels of 91 concurrently examined, previously known, treated, Type 2 (non-insulin-dependent) diabetic patients from our study were given for descriptive comparison, but were not included in the analysis, since insulin response was not measured in them. Informed consent was obtained from all participants, and the study was approved by the hospital ethical committee.

Laboratory procedures

Serum uric acid and creatinine ($\mu\text{mol/l}$), plasma glucose and triglyceride levels (mmol/l) were measured by routine automated Technicon Autoanalyzer II (Technicon Instruments Corporation, Tarrytown, NY, USA) glucose by potassium ferricyanide reduction, creatinine by the picric acid method, uric acid by the sodium tungstate method and triglycerides by conversion to fluorophore. Plasma insulin (mU/l) was determined in duplicate by Phadebas Radioimmunoassay kit (Pharmacia Diagnostics, Piscataway, NJ, USA), the within assay coefficient of variation being 4% and between assay 8%.

Classification of body mass index, blood pressure status and glucose tolerance

Body mass index (BMI: $\text{weight/height}^2 - \text{kg/m}^2$) was classified into three categories: normal or low - < 23 , intermediate - $23-26.9$ and high - ≥ 27 . Hypertension was defined as in our previous studies [15, 24] by at least two of the four measurements with either systolic > 145 or diastolic > 93 mm Hg, the remaining cases being categorised as normotensive. Glucose tolerance was classified according to the National Diabetes Data Group (NDDG) criteria [25]: normal glucose tolerance was defined by fasting level < 6.4 and 1 h level < 11.1 and 2 h level < 7.8 ; Type 2 diabetes was defined by fasting hyperglycaemia ≥ 7.8 or 1- and 2-h post load levels ≥ 11.1 ; cases with intermediate values between normal glucose tolerance and diabetes were defined as impaired glucose tolerance, which thus combined the NDDG non-diagnostic and impaired glucose tolerance categories. Classification of Type 2 diabetes by these criteria practically overlaps that by the WHO criteria, but the NDDG definition of normal glucose tolerance is more stringent [26]. The above definition of impaired glucose tolerance was adopted since unpublished data from our study indicate that the NDDG non-diagnostic group resembles impaired rather than normal glucose tolerance in levels of HbA_{1c} as well as of all biochemical variables analysed in the current report; this is true even for the subgroup defined as normal glucose tolerance by WHO. Part of the analysis was based on these categorical definitions and part on sum glucose (sum of 60 and 120 min post load glucose levels) as a continuous variable, representing the area under the glucose response curve.

Insulin response categories

Sum insulin, (sum of 60 and 120 min post load insulin levels) representing the area under the insulin response curve as a measure of insulin sensitivity [14] was divided into three categories. Cut-off points were defined as the values of the 50th (PN50) and 75th (PN75) percentiles (102.1 and 137.3 respectively) of the sum insulin distribution in the reference group, i.e. the 282 non-obese normotensive subjects with normal glucose tolerance. Hyperinsulinaemia was defined as sum insulin $\geq \text{PN75}$.

Statistical analysis

All statistical analyses were done separately for males and females.

Comparisons of serum uric acid and of sum insulin as dependent variables between categories of body mass index, blood pressure status and glucose tolerance as respective grouping factors, were done by analysis of covariance (BMDP Biomedical Computer Programs, University of California Press, Berkley, Los Angeles, London, Program 7D) adjusting for age as a covariate.

The univariate association of serum uric acid with all study variables was analysed by testing whether Pearson's correlation coefficients differed from zero.

The significance of the net association of uric acid as the dependent variable with sum insulin after accounting for all associated factors - age, glucose tolerance, total plasma triglycerides, mean systolic blood pressure and BMI, was analysed in three ways:

1. Comparing, by analysis of covariance, means of serum uric acid in three categories of sum insulin as a grouping factor - $< \text{PN50}$, PN50-PN74 and $\geq \text{PN75}$, adjusted for the following covariates - age, sum blood glucose, total plasma triglycerides, mean systolic blood pressure and BMI.
2. Comparing, by analysis of covariance, means of serum uric acid in two categories of sum insulin - $< \text{PN75}$ and $\geq \text{PN75}$, and the three categories of glucose tolerance (normal, impaired and diabetes) as grouping factors, adjusting for the remaining above variables as covariates.
3. The overall contribution of all the above variables in their continuous form, to the variance of serum uric acid was determined by multiple regression analysis (BMDP program 2R) using log transformed values to account for any skewness in the data. This analysis was repeated twice, once without sum insulin and again adding sum insulin to the equation.

Internal comparisons between adjusted means were based on error mean square of the analysis of covariance.

Results

Of the 1016 individuals studied, 286 (28.1%) were glucose intolerant comprising 226 with impaired glucose tolerance as well as 60 with newly found diabetes. Cases classified as hypertensive numbered 285 (28.1%). Hypertension was mild in the majority of cases, mean blood pressure being $147.7/91.5$ with only 6% having diastolic ≥ 100 . BMI ≥ 27.0 was found in 317 individuals (31.2%). At least one of these three conditions was present in 72.2%, at least two in 36.6% and all three in 9.2% of the study group. Mean serum creatinine was 89.1 exceeding 130 in 0.5%.

After adjustment for age, both serum uric acid and sum insulin increased consistently with increasing blood pressure and BMI level, differences between all categories being highly significant ($p < 0.001$) (Table 1). Impaired as compared to normal glucose tolerance

Table 1. Means of serum uric acid ($\mu\text{mol/l}$) and sum insulin (mU/l), adjusted for age, by sex, glucose tolerance, body mass index (BMI) and blood pressure status

	No. of cases		Serum uric acid		Sum insulin	
	M	F	M	F	M	F
Glucose tolerance						
Normal	368	362	341	265	141	134
Impaired	143	83	363	293	211	185
Diabetes-newly found	47	13	357	297	181	158
BMI						
< 23.0	108	108	329	263	116	119
$23.0-26.9$	284	199	341	268	151	141
≥ 27.0	166	151	373	286	212	165
Blood pressure status						
Normotensive	318	313	339	268	155	143
Hypertensive	240	145	359	279	171	146

Table 2. Simple correlation coefficients of all study variables in 558 males and 458 females

	Males	a	b	c	d	e	f	g	h	i	j	k	l	m	n
Females															
a) Serum uric acid															
plasma glucose			0.120	0.200	0.173	0.213	0.144	0.189	0.222	0.316	0.285	0.197	0.209	0.165	0.053)
b) fasting		0.218		0.463	0.379	0.483	0.122	(0.060)	0.167	0.203	0.136	0.098	(0.020)	(0.066)	(0.060)
c) 1 h		0.251	0.489		0.568	x	0.110	(-0.050)	0.291	0.406	0.133	0.226	0.140	0.091	0.157
d) 2 h		0.269	0.440	0.587		x	0.096	(0.038)	0.130	0.300	0.146	0.218	0.135	0.086	0.155
e) Sum 1 & 2 h		0.289	0.525	x	x		0.117	(-0.021)	0.259	0.410	0.154	0.249	0.154	0.100	0.175
Plasma insulin															
f) fasting		(0.083)	(0.069)	(0.070)	(0.038)	(0.064)		0.440	0.417	0.409	0.231	(0.062)	(0.057)	0.226	(-0.022)
g) 1 h		0.160	(-0.064)	(-0.050)	(-0.014)	(-0.039)	0.342		0.610	x	0.274	(0.080)	(0.072)	0.227	(-0.021)
h) 2 h		0.196	0.170	0.378	(0.068)	0.279	0.395	0.598		x	0.347	0.120	0.129	0.220	(0.024)
i) Sum 1 & 2 h		0.236	0.239	0.431	0.286	0.414	0.407	x	x		0.340	0.172	0.144	0.216	(0.082)
j) BMI		0.243	0.135	0.136	0.142	0.155	0.161	0.208	0.220	0.253		0.168	0.192	0.248	(0.019)
Blood pressure															
k) systolic		0.196	0.094	0.244	0.282	0.290	(0.073)	(0.069)	(0.037)	0.110	0.280		0.742	(0.060)	0.363
l) diastolic		0.165	(0.052)	0.178	0.190	0.205	(0.022)	(0.087)	(0.053)	(0.086)	0.282	0.823		0.113	0.144
m) Plasma triglycerides		0.167	(0.024)	(0.085)	0.136	0.118	0.180	0.232	0.175	0.212	0.141	0.131	(0.072)		(-0.047)
n) Age		0.238	0.153	0.201	0.230	0.239	0.100	(0.042)	(0.065)	0.140	0.198	0.420	0.229	(0.072)	

* Significance levels: $p < 0.05$ for $r = 0.083$ in males and 0.092 in females; $p < 0.01$ for $r = 0.109$ and 0.121 respectively; brackets denote non-significant correlations

Fig. 1. Mean serum uric acid ($\mu\text{mol/l}$) adjusted for age, sum glucose, blood pressure, BMI and plasma triglycerides, in males ($\diamond$) and females ($\blacksquare$) by sum insulin category (<PN 50, PN 50-74 and PN $\geq$ 75 denote ranges according to percentiles of the sum insulin distribution in non-obese normotensives with normal glucose tolerance)

was associated with significantly increased levels of sum insulin and serum urate ($p < 0.001$). Newly found diabetes as compared to impaired glucose tolerance was characterised by significantly decreased insulin levels ($p = 0.04$), while urate levels were unaffected. All these trends were similar in both sexes.

By and large all variables analysed were significantly correlated (Table 2). The correlation with the other study variables was stronger for sum insulin and for sum blood glucose as compared to their respective fasting levels or separate 1- and 2-h levels, and for systolic as compared to diastolic blood pressure. Consequently sum insulin, sum glucose and systolic pressure were chosen to represent plasma glucose, plasma insulin and blood pressure respectively in all further analyses. In both sexes there was a highly significant simple

correlation between serum uric acid and sum insulin, the correlation coefficients being 0.316 and 0.236 for males and females respectively ($p < 0.001$). These correlations were of the same order of magnitude as those between urate and its established correlates – BMI and blood pressure, as well as between sum insulin and its established correlates – sum glucose, triglycerides and BMI (Table 2).

Mean serum urate increased consistently in both sexes with increasing sum insulin after adjustment for all correlated variables – age, sum glucose, plasma triglycerides, mean systolic blood pressure and BMI (Fig. 1). The independent effect of sum insulin was significant in both males ($p < 0.01$) and females ($p = 0.04$). In males the adjusted means were 333 when sum insulin was in the range <PN50, 347 when it was between PN50 and PN74 and 357 in the range $\geq$ PN75, the respective values in women being 263, 265 and 278.

To evaluate the effect of glucose tolerance level on the association between serum uric acid and insulin response, mean uric acid levels were compared between normoinsulinaemic and hyperinsulinaemic individuals in normal and impaired glucose tolerance and in diabetes after adjustment for age, BMI, systolic blood pressure and triglycerides (Table 3). This analysis showed again an overall significant net association ($p < 0.01$ for males, $p = 0.03$ for females), of sum insulin and serum uric acid. The higher levels of uric acid in the presence of hyperinsulinaemia were observed in normal glucose tolerance ($p = 0.05$ in both males and females) as well as in individuals with impaired glucose tolerance and Type 2 diabetes ($p < 0.01$ for males and $p = 0.05$ for females). Furthermore, in normoinsulinaemic males and females, no significant differences were observed between the three levels of glucose tolerance. Only in hyperinsulinaemic individuals were uric acid levels significantly higher in impaired glucose tolerance and diabetes as compared to normal glucose tolerance in both males ($p = 0.03$) and females

Table 3. Mean serum uric acid in normo- and hyperinsulinaemic individuals adjusted for age, BMI, plasma triglycerides, systolic blood pressure and glucose tolerance level by sex

Glucose tolerance	Males				Females			
	Normoinsulinaemic		Hyperinsulinaemic		Normoinsulinaemic		Hyperinsulinaemic	
	No. cases	Mean urate	No. cases	Mean urate (p^a)	No. cases	Mean urate	No. cases	Mean urate (p^a)
Normal	214	338	154	351 (0.05)	219	261	142	273 (0.05)
Impaired	41	346	102	366 } (<0.01)	32	276	52	294 } (<0.05)
Diabetes-total	22	333	25	365 } (<0.01)	8	263	5	309 } (<0.05)
(p^b)		(NS)		(0.03)		(NS)		(0.01)
Diabetes by fasting plasma glucose								
<7.8	14	357	17	384	4	253	3	281
7.8–11.0	4	322	7	369	2	315	2	346
≥ 11.1	4	278	1	244	2	214	–	–

^a Significance of the difference between hyperinsulinaemic and normoinsulinaemic individuals; ^b significance of the difference between the glucose intolerant and normal categories

Table 4. Multiple regression analysis of the net effect of the study variables on serum uric acid by sex

Males			Females		
Variable	R ² increment	F	Variable	R ² increment	F
Sum insulin	0.118	72.9	Sum insulin	0.079	38.7
BMI	0.027	17.1	Age	0.049	25.5
Systolic b.p.	0.011	7.0	BMI	0.028	14.9
Triglycerides	0.011	6.9	Triglycerides	0.017	8.9
Age	<0.001	0.5	Sum glucose	0.013	7.0
Sum glucose	<0.001	0.2	Systolic b.p.	<0.001	0.3
Total	0.167			0.186	
Total without insulin	0.126			0.170	

($p=0.01$). As in normoinsulinaemic individuals, no significant difference between impaired glucose tolerance and diabetes was found. Further analysis revealed that among these newly found diabetic cases uric acid levels were similar to impaired glucose tolerance as long as fasting plasma glucose was less than 11.1. In the range ≥ 11.1 , uric acid levels decreased significantly ($p<0.01$) to levels below those found in normal glucose tolerance – 271 vs 343 in males, 214 vs 266 in females. The levels of uric acid in this range resembled the low levels in the 91 known, treated, diabetic patients – 244 in males and 256 in females (data not shown).

Multiple regression analysis indicated that when sum insulin was not entered into the equation the portion of serum uric acid variance explained by sum blood glucose, BMI, mean systolic blood pressure, total plasma triglycerides and age, amounted to 13% in males and 17% in females (Table 4). When sum insulin was added to the equation, the overall portion of the variance of uric acid explained by all variables increased to 17% in males and 19% in females. The independent increments in R² due to BMI and triglycerides were similar in males and females. However, females differed from males in that age and sum glucose were

independently correlated with urate and mean systolic blood pressure was not, while in males the reverse was true. The net increment in R² associated with insulin was highly significant and largest in both sexes – 12% in males and 8% in females ($p<0.001$).

Discussion

Our data, obtained in a large representative sample of an adult population, demonstrate a cross-sectional association between plasma insulin response to oral glucose load and serum uric acid in both sexes. This association was independent of age and other major factors shown in many studies as well as our own to be related to elevated serum uric acid on the one hand and to hyperinsulinaemia on the other. These factors include obesity [1–9, 11–15], untreated hypertension [1, 2, 4–7, 15–19, 27, 28], elevated triglycerides [20–23] and impaired glucose tolerance [1–3, 5, 8, 10–14].

In contrast to impaired glucose tolerance lower than normal levels of uric acid have been reported in treated diabetic patients [1–3, 5, 8, 10] and observed in our study as well. However, our findings indicate that in the majority of individuals with newly found, asymptomatic Type 2 diabetes, serum urate was as high as in impaired glucose tolerance. The elevation of serum uric acid associated with impaired glucose tolerance and newly found Type 2 diabetes seemed to occur only in the presence of hyperinsulinaemia. Serum urate in the diabetic individuals decreased below the level found in normal glucose tolerance only when fasting plasma glucose exceeded 11.1 mmol/l. This reduced level in severe fasting hyperglycaemia is in keeping with the known uricosuric effect of glycosuria, which is the prevailing explanation of the low serum uric acid among overt diabetic patients [2, 10, 29].

It is of interest that use of antihypertensive medications, including diuretics, which are associated with independently increased serum uric acid levels [1–8, 27, 30], is also known to lead in itself to impaired glucose

tolerance [31, 32] and by implication, to its attendant hyperinsulinaemia.

Another noteworthy finding, for which we have no explanation, is that age correlated significantly and independently of all other factors with serum uric acid and insulin response in females, while in males no such correlation was found.

The observed changes in serum uric acid associated with hyperinsulinaemia were small, and consisted of a subtle shift towards higher values within the normal range. Nevertheless, the association was present in both sexes and at all levels of glucose tolerance, independently of age and the major factors associated with increased uric acid levels and hyperinsulinaemia, despite the multicollinearity of all factors which would tend to obscure the association. Thus, while this is a cross sectional study which does not in itself enable inferences regarding direct causality, it appears as though the consistent trend of elevation of serum uric acid levels in the presence of hyperinsulinaemia could reflect a connection through common underlying pathophysiological processes. Several possibilities are suggested by current knowledge.

On the one hand are mechanisms implying decreased renal excretion of uric acid in the presence of hyperinsulinaemia. Decreased renal blood flow and excretion of uric acid have been described in hypertensive subjects with normal glomerular and tubular function [27, 33]. This has not been examined in impaired glucose tolerance or obesity. A second possibility relates to ketone bodies which are known to interfere with tubular secretion of uric acid [2]. While overt ketonaemia is not a feature of impaired glucose tolerance nor of uncomplicated obesity or hypertension, a subtle increase in keto acids in untreated obese Type 2 diabetes has recently been described [34] and could characterise insulin resistant states in general. A third possible mechanism is suggested by the effect of insulin on renal sodium reabsorption [35] and the implied association of increased sodium reabsorption with elevation of serum uric acid [36–38]. These putative mechanisms are consistent with the adequate renal function reflected by serum creatinine levels in our group.

On the other hand are mechanisms suggesting association of hyperinsulinaemia with increased uric acid production. Increased purine biosynthesis and turnover with its attendant elevation in serum uric acid levels due to increased activity of the hexose monophosphate shunt [39, 40] can be conceptually linked to disorders characterised by insulin resistance and/or hyperinsulinaemia. Increased flux of glucose-6-phosphate through the hexose monophosphate shunt due to impairment of the glycolytic pathway has been suggested as an explanation for the increased uric acid levels in impaired glucose tolerance [10] and may also be ascribed to excess carbohydrate and enhanced lipogenesis in the presence of excess insulin [36].

At this point it is impossible to say to what extent

these mechanisms or others account for this new epidemiologic observation of association of serum uric acid and insulin response. However, as hyperinsulinaemia is apparently a cause as well as a consequence of insulin resistance [11–14, 41], elucidation of the underlying processes might contribute to our understanding of the insulin resistant state.

Finally, it is of interest to reflect on the association of elevated serum uric acid and hyperinsulinaemia in connection with the recent hypothesis, based on epidemiological as well as experimental studies, that insulin is atherogenic [15, 42–47]. Not only glucose intolerance, obesity and hypertension, but disturbed lipoprotein profile as well, are characterised by hyperinsulinaemia [43, 44, 48–50], all being major risk factors for atherosclerosis [51–54]. Epidemiologic studies have also shown that an elevated serum uric acid level is associated with an increased risk for atherosclerotic heart disease but so far no pathophysiologic mechanism has been identified to explain this association [1–9]. Our findings suggest hyperinsulinaemia/insulin resistance as a possible link.

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