Serum Uric Acid as a Harbinger of Metabolic Outcome in Subjects With Impaired Glucose Tolerance

The Finnish Diabetes Prevention Study

Leo Niskanen, MD, PhD1
David E. Laaksonen, MD, PhD, MPH1
Jaana Lindström, MS, PhD2
Johan G. Eriksson, MD, PhD2
Sirkka Keinänen-Kiukaanniemi, MD, PhD3
Pirjo Ilanne-Parikka, MD4

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erum uric acid is the major product of
purine metabolism (1). In cross-
sectional studies, uric acid corre-
lates with components of the metabolic
syndrome: hypertension, obesity, low
HDL cholesterol, hypertriglyceridemia,
hyperinsulinemia, and insulin resistance
(2–4). Although determination of uric
acid is widely available and inexpensive, it
has been overlooked as a marker of dis-
turbed glucose metabolism. We studied
its role in predicting changes in glucose
tolerance and insulin levels and in the de-
development of type 2 diabetes in the Finn-
ish Diabetes Prevention Study.

RESEARCH DESIGN AND
METHODS — The design of the Finn-
ish Diabetes Prevention Study has been
previously described in detail (5). Briefly,
40- to 65-year-old overweight or obese
individuals with impaired glucose toler-
ance were eligible. Impaired glucose tol-
erance was defined as a 2-h plasma
glucose of 7.8–11.0 mmol/l after oral glu-
cose (75 g) with a fasting glucose
≤7.8 mmol/l (6). The protocol was approved
by the ethics committee of the National
Public Health Institute (Helsinki, Fin-
land). All participants gave written in-
formed consent.

In all, 522 individuals from five study
centers were randomly assigned to the in-
tervention (n = 265) or control (n = 257)
groups. Serum uric acid concentrations
were measured at baseline and at least
during the follow-up in 475 of the
522 participants, and these 475 are in-
cluded in the present study. The original
trial ended after an average follow-up of
3.2 years. In this study, follow-up was ex-
tended to 4.1 years (range 1–6). In all,
103 of the 475 participants for whom re-
peated measurements of uric acid were
carried out developed diabetes during the
4.1-year follow-up.

Details on the intervention and as-
sessments of leisure-time physical activity
(LTPA) and nutrient intakes as well as the
changes in dietary factors and body
weight have been previously reported (7–
8). Uric acid was determined photomet-
ically by the hydroxylamine method (9).
Diabetes was defined by the 1985 World
Health Organization criteria as fasting
plasma glucose concentrations ≥7.8 or
2-h concentrations ≥11.1 mmol/l (6). A
general linear model was used to assess
the association of clinical, biochemical,
LTPA, and dietary variables at baseline ac-
cording to baseline uric acid categorized
into thirds. The changes in variables de-
note baseline levels subtracted from the
average follow-up levels. A general linear
model was also used to assess the associ-
ation of uric acid and its changes with
changes in plasma glucose and insulin
concentrations after adjustment for co-
variates. The association of baseline uric
acid concentrations and its changes dur-
ing the follow-up with the risk of type 2
diabetes was assessed with Cox propor-
tional hazards models. Statistical signifi-
cance was P < 0.05. Analyses were
performed with SPSS 11.0 for Windows
(Chicago, IL).

RESULTS — At baseline, women had
lower uric acid than men (327 ± 74 vs.
393 ± 76 μmol/l, P < 0.001). BMI and
plasma glucose and insulin concentra-
tions increased across uric acid tertiles
(Table 1). The increase in body weight
and waist circumference across uric acid
tertiles was partly influenced by sex but
remained highly significant when ad-
justed for sex (not shown).

Concentrations of uric acid decreased
by 4.7 μmol/l in the control group and by
7.7 μmol/l in the intervention group (P =
0.44, ANCOVA model with adjustment
for sex, age, and baseline uric levels). Fe-
male sex (P = 0.001), lower BMI (P =
0.008), and a decrease in BMI (P < 0.001)
were each independently associated with
a decrease in uric acid in a model where
the change of uric acid was a continuous
dependent variable and sex, age, random-
ization group, baseline uric acid, BMI and
its changes, energy-adjusted dietary fiber
intake and its changes, and moderate-to-
vigorous LTPA and its changes were used
as explanatory variables. Baseline energy-
adjusted fiber intake (P = 0.090) and its
changes (P = 0.089) also tended to pre-
dict the changes in uric acid in this model.

Baseline uric acid levels (Table 1)
**Uric acid in impaired glucose tolerance**

Table 1—Baseline characteristics of the Finnish Diabetes Prevention Study participants according to tertiles of baseline serum uric acid and its changes

<table>
<thead>
<tr>
<th>Baseline serum uric acid</th>
<th>Serum uric acid concentrations (μmol/l)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>272 (99–310)</td>
<td>346 (311–380)</td>
</tr>
<tr>
<td>n</td>
<td>158</td>
<td>159</td>
</tr>
<tr>
<td>Age (years)</td>
<td>55.0 ± 7.2</td>
<td>55.6 ± 6.9</td>
</tr>
<tr>
<td>Sex (men/women)</td>
<td>18/140</td>
<td>58/101</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>Blood pressure medication (%)</td>
<td>22</td>
<td>25</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30.4 ± 4.4</td>
<td>31.4 ± 4.5</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>100.9 ± 11.7</td>
<td>98.8 ± 11.4</td>
</tr>
<tr>
<td>Men</td>
<td>103.0 ± 10.9</td>
<td>102.6 ± 8.9</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/l)</td>
<td>6.1 ± 0.7</td>
<td>6.3 ± 0.8</td>
</tr>
<tr>
<td>2-h plasma glucose (mmol/l)</td>
<td>8.8 ± 1.4</td>
<td>9.0 ± 1.5</td>
</tr>
<tr>
<td>Fasting serum insulin (pmol/l)</td>
<td>11.0 (8.0–15.0)</td>
<td>14.0 (11.0–18.0)</td>
</tr>
<tr>
<td>2-h serum insulin (pmol/l)</td>
<td>69 (41–101)</td>
<td>88 (61–131)</td>
</tr>
<tr>
<td>Creatinine (μmol/l)</td>
<td>78 ± 11</td>
<td>83 ± 12</td>
</tr>
<tr>
<td>Moderate-to-vigorous LTPA (h/week)</td>
<td>1.5 (0.4–3.7)</td>
<td>2.3 (0.7–4.0)</td>
</tr>
<tr>
<td>Dietary energy intake (kcal/day)</td>
<td>1,692 ± 517</td>
<td>1,742 ± 505</td>
</tr>
<tr>
<td>Total fat (g) (energy adjusted)</td>
<td>71.0 ± 13.1</td>
<td>72.6 ± 11.4</td>
</tr>
<tr>
<td>Fiber intake (g) (energy adjusted)</td>
<td>20.6 ± 7.2</td>
<td>20.3 ± 6.4</td>
</tr>
<tr>
<td>Changes in fasting glucose (mmol/l)</td>
<td>−0.09 ± 0.05</td>
<td>0.06 ± 0.04</td>
</tr>
<tr>
<td>Changes in 2-h glucose (mmol/l)</td>
<td>−0.52 ± 0.16*</td>
<td>−0.02 ± 0.14</td>
</tr>
<tr>
<td>Changes in fasting insulin (pmol/l)</td>
<td>−2.2 ± 0.5*</td>
<td>−0.7 ± 0.5</td>
</tr>
<tr>
<td>Changes in 2-h insulin (pmol/l)</td>
<td>−32 ± 5*</td>
<td>−22 ± 4</td>
</tr>
<tr>
<td>Development of diabetes</td>
<td>28 (18)</td>
<td>36 (23)</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>1 ref</td>
<td>1.48 (0.88–2.47)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Changes in serum uric acid</th>
<th>Serum uric acid concentrations (μmol/l)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>−57 (−224 to −28)</td>
<td>−9 (−28 to 9)</td>
<td>42 (10–310)</td>
</tr>
<tr>
<td>Changes in fasting glucose (mmol/l)</td>
<td>−0.09 ± 0.05†</td>
<td>0.01 ± 0.04</td>
</tr>
<tr>
<td>Changes in 2-h glucose (mmol/l)</td>
<td>−0.65 ± 0.16†</td>
<td>−0.19 ± 0.14</td>
</tr>
<tr>
<td>Changes in fasting insulin</td>
<td>−1.9 ± 0.6†</td>
<td>−1.2 ± 0.6</td>
</tr>
<tr>
<td>Changes in 2-h insulin</td>
<td>−26 ± 5†</td>
<td>−27 ± 4</td>
</tr>
<tr>
<td>Development of diabetes</td>
<td>30 (19)</td>
<td>33 (21)</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>1 ref</td>
<td>1.40 (0.82–2.39)</td>
</tr>
</tbody>
</table>

Data are means ± SD, tertiles, median (interquartile range), and n (%) unless otherwise indicated; changes are expressed as means ± SE. Data are for those participants in whom serum uric acid concentrations were measured at baseline and at least once during the follow-up. For continuous baseline variables, the P value for the trend across tertiles of baseline serum uric acid concentrations was assessed with linear regression with the variable as the dependent variable and uric acid as the explanatory variable; categorized uric acid was entered in the model as a continuous variable. For categorical baseline variables, the P value was correspondingly assessed with logistic regression. For the changes in insulin and glucose, the trend across tertiles was assessed with a general linear model. Changes were adjusted for age, sex, and randomization group and baseline fasting or 2-h glucose or insulin concentrations, respectively. For baseline levels of uric acid, adjustment was also made for the change in uric acid levels during follow-up. For the change in uric acid levels, adjustment was also made for baseline uric acid levels. The trend across tertiles for the development of diabetes was assessed with Cox proportional hazards with adjustment as described above.*P < 0.05, †P < 0.01 for the trend across thirds.

were associated with the increase in fasting and 2-h plasma glucose concentrations during the follow-up but not after including baseline BMI and its changes in the model (not shown). Baseline uric acid levels were associated with the changes in insulin levels after adjustment for changes in insulin acid during follow-up (Table 1) and for 2-h insulin, even in a model including age, sex, group, blood pressure medication, and baseline creatinine, systolic blood pressure, triglycerides, BMI, levels of daily energy intake, intakes of poly-, monounsaturated, and saturated fat and fiber, and LTPA and their changes during the follow-up (model 2) (P = 0.001). The changes in uric acid levels were associated with changes in fasting and 2-h glucose and insulin concentrations during the follow-up after adjustment for baseline uric acid (Table 1). These associations persisted in model 2, described above for fasting and 2-h glucose (P = 0.040 and 0.011) but not for insulin.

Individuals with changes in uric acid levels in the upper third were nearly twice as likely to develop diabetes during the follow-up (Table 1). Baseline uric acid predicted diabetes (P = 0.037) even after adjustment for variables in model 2, but after extensive adjustment, the changes in uric acid concentrations were not associated with incident diabetes (P = 0.30).

We checked whether the associations with metabolic outcome were modified by sex, intervention, BMI at baseline, or weight loss during the trial. Uric acid and its changes seemed to be more strongly associated with metabolic outcome in...
women, the control group, and individuals with a BMI above the median, but the interactions were not significant ($P = 0.11–0.81$).

CONCLUSIONS — In this lifestyle intervention study in high-risk middle-aged subjects with impaired glucose tolerance, baseline uric acid and its changes predicted a twofold increase in the likelihood of developing type 2 diabetes. Furthermore, uric acid and its changes during follow-up were related to corresponding changes in fasting and postload glucose and insulin levels. Although hyperuricemia and hyperinsulinemia are closely linked, the mechanisms behind this association remain obscure. The most conceivable hypothesis is that this occurs at the renal level: renal tubular function is influenced by hyperinsulinemia, and urinary uric acid clearance decreases with decreasing insulin-mediated glucose disposal. Thus, decreased uric acid excretion leads to hyperuricemia (3). Hyperuricemia has been an independent risk factor for progression to hyperinsulinemia and thereby preceded hyperinsulinemia in the 11-year follow-up of nondiabetic participants of Atherosclerosis Risk in Communities Study (10). However, hyperglycemia may lead to increased urinary excretion of uric acid (11), which could partly explain the nonsignificant difference in the decrease of uric acid between intervention and control groups.

References