

Hyperuricemia and Hypertriglyceridemia: Metabolic Basis for the Association

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Hypertriglyceridemia has been reported frequently in patients with hyperuricemia and gout. The current studies have evaluated this relationship. To examine whether hypertriglyceridemia leads to hyperuricemia, IV Intralipid was given to three gouty patients. Triglycerides increased from 169 to 700 mg/dl for three hours but caused no change in serum urate level or urine uric acid and oxypurine excretion. We next examined whether high carbohydrate intake increases serum urate and triglyceride levels. Four obese patients were placed on a 2000 kcal/d sucrose diet for seven days. The serum urate increased from 6.3 ± 1.7 to 7.9 ± 2.0 mg/dL. The percent uric acid clearance to creatinine clearance decreased from 5.9 ± 1.3 to the lowest mean value of 3.7 ± 1.2 , while serum triglycerides increased from 106 ± 33 to 252 ± 57 mg/dL and blood lactate from 607 ± 227 to 1167 ± 381 μ mol/L. A 3000 kcal/d glucose diet in four other obese subjects produced no change in serum urate levels but increased lactate and triglyceride levels. During an isocaloric sucrose diet in two normal men, the serum urate level increased from 5.3 and 4.0 to peak values of 9.5 and 7.4 mg/dL. The percent uric acid to creatinine clearance decreased from 5.6 and 6.6 to 2.9 and 3.3. The uric acid turnover did not increase. In three gouty patients the mean serum urate increased from 8.5 ± 1.5 to 10.6 ± 1.4 mg/dl following an isocaloric sucrose diet. The urine uric acid excretion increased from 0.30 and 0.25 to 0.37 and 0.38 mg/mg creatinine in two patients. The percent uric acid clearance to creatinine clearance decreased from 3.8 to 2.5 in one patient. The serum triglycerides were substantially elevated during the sucrose diet in the normal subjects and the gouty patients. Our studies show that a pure sucrose diet increases both the serum urate and triglyceride levels. The mechanism of the hyperuricemia is decreased renal clearance of uric acid in the obese normal controls and the normal subjects. Increased urate production and decreased uric acid clearance accounted for the hyperuricemia in the gouty patients. The contribution of excessive sucrose ingestion to clinically associated hyperuricemia and hypertriglyceridemia remains to be elucidated.

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HYPERTRIGLYCERIDEMIA is frequently associated with hyperuricemia and gout (reviewed in 1). Although the basis for this association is not established, the potential mechanisms include the following: hyperuricemia causes hypertriglyceridemia, hypertriglyceridemia causes hyperuricemia, or another alteration causes both hyperuricemia and hypertriglyceridemia. Previous experiments have examined some of these possibilities. Hyperuricemia itself does not increase plasma lipids.² The existence of a disorder, which causes both hyperuricemia and hypertriglyceridemia, is suggested by the observation of both abnormalities in two inborn errors of carbohydrate metabolism, glucose 6-phosphatase deficiency and fructose 1, 6-disphosphatase deficiency.³⁻⁶ In addition, administration of carbohydrate in the form of a fructose infusion or a high fructose diet increases uric acid synthesis and increases serum urate levels.⁷⁻¹¹ We have performed experiments to examine the possible metabolic basis for the association between hyperuricemia and hypertriglyceridemia.

MATERIALS AND METHODS

Uricase and xanthine oxidase were purchased from Sigma Chemical, St Louis. From New England Nuclear, Boston, we purchased [$2\text{-}^{14}\text{C}$]uric acid (57 mCi/mmol). Instagel was obtained from Packard Instruments, Downers Grove, Ill. In-line Cathivex filter units (0.22 and 0.45 μ m) were obtained from Millipore Corp, Bedford, Mass. All other reagents were of the highest quality commercially available.

Intralipid Infusion

Three gouty patients with normal renal function were admitted to the Wellesley Hospital (University of Toronto) Clinical Investiga-

tion Unit for studies with lipid infusions (Table 1). They were placed on an isocaloric purine-free diet and were off all medications known to alter uric acid synthesis or excretion. Colchicine 0.6 mg was given twice each day to prevent acute attacks of gout. Five days after admission the patients were given an intravenous (IV) infusion of intralipid. After an overnight fast, an IV line was inserted and 0.87 percent saline was run at the rate of 100 mL per hour. The following sequence was used to elevate plasma triglyceride levels: Two hour saline infusion; priming dose of 10% Intralipid (0.15 g/kg) given IV for five minutes; and one hour later this same dose of Intralipid was given followed by an infusion of 20 g of Intralipid (Kabi Vitrum, Berkeley, Calif) per hour for three hours. Blood samples were obtained at five to 60-minute intervals for levels of urate, creatinine, triglyceride, and cholesterol. Urine was collected at hourly intervals throughout the infusion period for measurement of creatinine, uric acid, and oxypurines.

Sucrose Diet

The influence of a 100% sucrose diet on uric acid metabolism was examined in studies involving four obese patients, two normal

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Table 1. Study Subjects

| Patient | Sex | Age (yr) | Weight (kg) | Serum Urate (mg/dL) | Urinary Uric Acid (g/d) | Diagnosis |
|----------------------------|-----|----------|-------------|---------------------|-------------------------|-----------|
| Intralipid Infusion | | | | | | |
| W.M. | M | 47 | 58.0 | 5.8 | 0.4 | Gout |
| A.M. | M | 55 | 78.3 | 6.7 | 0.4 | Gout |
| F | M | 64 | 104.5 | 8.1 | 0.5 | Gout |
| Sucrose Diet (g/kg) | | | | | | |
| R (5.2) | F | 42 | 94.5 | 3.8 | 0.5 | Obesity |
| N (3.9) | F | 40 | 126.5 | 7.3 | 1.0 | Obesity |
| B (4.5) | F | 39 | 110.1 | 6.8 | 0.8 | Obesity |
| L (3.1) | M | 42 | 159.5 | 7.4 | 0.8 | Obesity |
| W (9.2) | M | 22 | 68.8 | 4.0 | 0.3 | Normal |
| G (6.6) | M | 23 | 97.4 | 5.3 | 0.4 | Normal |
| G (5.7) | M | 54 | 120.0 | 10.2 | 0.3 | Gout |
| A (3.9) | M | 58 | 86.7 | 7.4 | 0.5 | Gout |
| K (6.0) | M | 73 | 87.9 | 7.9 | 0.4 | Gout |
| Glucose Diet (g/kg) | | | | | | |
| B (7.3) | M | 50 | 101.9 | 5.7 | 0.7 | Obesity |
| T (5.6) | F | 23 | 134.8 | 5.0 | 0.7 | Obesity |
| Cau | | | | | | |
| (6.9) | M | 47 | 108.3 | 8.1 | 0.6 | Obesity |
| Cat | | | | | | |
| (6.4) | F | 34 | 116.8 | 6.5 | 0.5 | Obesity |

subjects and three gouty patients (Table 1). All study subjects had normal renal function and discontinued use of any drugs known to alter uric acid metabolism or excretion ten days prior to admission. Colchicine (0.6 mg twice a day) was given to the gouty patients to prevent acute gouty arthritis. Urines were collected continuously on a 24-hour basis. Routine surveillance of vital signs and routine biochemistry assured the safety of the dietary alterations.

Three females and one male were admitted to the Clinical Investigation Unit of the Toronto General Hospital (University of Toronto). They were placed on a 2000 calorie sucrose diet (3.1 to 5.2 g/kg). The diet consisted of a flavored solution of sucrose divided up into four doses of equal amounts for seven days.

Three overweight patients with gouty arthritis and two normal controls with normal body weight were admitted twice to the Clinical Research Center at The University of Michigan Hospital. On one admission, patients were placed on a weight-maintenance, isocaloric, purine-free diet with 10% to 12% protein and 15% to 20% sucrose. On another admission these subjects were placed on an isocaloric diet containing 100% sucrose (gouty subjects, 3.9 to 6.0 g/kg; normal control subjects, 6.6 to 9.2 g/kg). Daily serum glucose, triglyceride, creatinine, uric acid and 24-hour urine collections for uric acid, creatinine, and oxypurines were obtained. Three times weekly venous samples for whole blood lactate were drawn.

The turnover of uric acid on and off a sucrose diet was examined in the two normal subjects. This approach allows the possibility of detecting increased synthesis of uric acid. Three to five days after hospital admission, 10 μ Ci of [14 C]uric acid contained in 0.88 mmol uric acid was administered IV through a 0.22 μ m Cathivex filter to the two normal subjects.¹² The filters were flushed with 40 mL of 0.87% sodium chloride to ensure delivery of the entire isotope dose. An aliquot consisting of 0.5 mL of each urine sample was added to 5 mL of Instagel and counted in a Packard model 3003 liquid scintillation spectrometer.

Analysis of the isotope study was performed according to the formula $A = a(I_i/I_0 - 1)$, where A is the miscible pool, a is the dose of uric acid injected, I_i is the concentration of the isotope injected, and I_0 is the concentration of the isotope at time 0.^{13,14} The natural logarithm of the isotope concentrations in the patients' urine are

plotted against days and the method of least squares is used to determine the intercept and slope of each straight line. The slope of the line provides a turnover rate expressed as pools replaced per day. The antilog of the intercept estimates the isotope concentration at time zero and allows the miscible pool size to be calculated.

Glucose Diet

Four additional obese subjects (two females and two males) were admitted to the Clinical Investigation Unit of the Toronto General Hospital for study during seven days of a 3000 kcal/d diet exclusively of glucose, in the form of a polymer (5.6 to 7.3 g/kg). As with sucrose, the flavored solution was taken in four equal doses, at mealtimes and bedtime.

Assays

The serum urate, urine uric acid, and urine oxypurines were measured by enzymatic spectrophotometric methods.^{15,16} Creatinine was quantified by autoanalyzer method.¹⁷ Lactate was determined by enzymatic spectrophotometric or fluorimetric techniques.^{18,19} Other measurements were performed by standard autoanalyzer techniques.

Statistical Analysis

Analysis of the data from the obese subjects during a sucrose and glucose diet was performed on CLINFO with a repeated measures analysis of variance using Dunnett's *t* statistic to compare the other time periods to time 0.²⁰ No analysis could be performed on the rest of the studies because of the smaller number of subjects.

RESULTS

Intralipid Infusion

Intralipid infusion increased plasma lipids fourfold by 90 minutes (Table 2). No substantial change is evident in serum urate values, urine uric acid and oxypurine excretion, and the uric acid clearance.

Sucrose Diet in Obesity

Four obese patients were placed on a 2000 calorie sucrose diet for seven days (Table 3). Overall, the most pronounced changes were evident on the fourth day. The serum urate increased from 6.3 ± 1.7 to 7.9 ± 2.0

Table 2. Intralipid Infusion

| | Baseline | Infusion* (90 minutes) |
|-----------------------|------------------|------------------------|
| Urate (mg/dL) | 6.7† (5.1–8.5)‡ | 6.9 (5.9–8.2) |
| Uur/Ucr§ (mg/mg) | 0.32 (0.24–0.42) | 0.35 (0.32–0.38) |
| Cur/Ccr (%) | 6.1 (4.2–9.2) | 6.3 (4.4–9.2) |
| Uoxy/Ucr¶ (umol/mg)¶¶ | 0.06 (0.01–0.12) | 0.09 (0.02–0.14) |
| Triglycerides (mg/dL) | 169 (106–234) | 671 (603–748) |

Three gouty patients were given an IV infusion of intralipid after an overnight fast. A marked elevation of plasma triglycerides is observed during intralipid infusion. No significant change in uric acid metabolism or excretion is evident.

*Urine collected from 60 to 120 minutes

†Mean; ‡Range

§Uur, filtered load of uric acid; Ucr, filtered load of creatinine

||Cur, clearance of uric acid; Ccr, clearance of creatinine.

¶¶Uoxy, filtered load of oxypurine, Ucr, filtered load of creatinine.

Table 3. Sucrose and Glucose Diets in Obese Patients

| Day | Serum Urate (mg/dL) | Serum Triglycerides (mg/dL)‡ | Blood Lactate (μmol/L) | Cur/Ccr† (%) |
|---------------------|---------------------|------------------------------|------------------------|--------------|
| Sucrose Diet | | | | |
| 0 | 6.3 ± 1.7* | 106 ± 33 | 607 ± 227 | 6.6 ± 1.9 |
| 2 | 7.0 ± 1.8 | 193 ± 53 | 1409 ± 495§ | 4.1 ± 0.6 |
| 4 | 7.9 ± 2.0 | 252 ± 57 | 1167 ± 381§ | 3.7 ± 1.2 |
| 7 | 8.2 ± 2.6 | 182 ± 119 | 1093 ± 325§ | 5.1 ± 3.7 |
| Glucose Diet | | | | |
| 0 | 6.3 ± 1.3 | 132 ± 24 | 898 ± 191 | 5.9 ± 1.2 |
| 2 | 6.5 ± 1.0 | 148 ± 56 | 1186 ± 709 | 4.3 ± 0.5 |
| 4 | 6.6 ± 0.5 | 212 ± 72 | 1710 ± 439 | 4.1 ± 2.5 |
| 7 | 6.6 ± 0.9 | 242 ± 116 | 1803 ± 460§ | 4.4 ± 2.7 |

Four obese nongouty subjects were placed on a 2000 kcal sucrose diet and four others on a 3000 kcal glucose diet for 7 days.

*Mean ± SD

†Abbreviations are the same as in Table 2.

‡No statistical analysis done because baseline value during the sucrose diet in one patient is missing.

§ $P < 0.01$; || $P < 0.05$

mg/dL on the seventh day. The percent uric acid clearance to the creatinine clearance decreased from 5.9 ± 1.3 to lowest mean value of 3.7 ± 1.2 , while serum triglycerides increased from 106 ± 33 to 252 ± 57 mg/dL and blood lactate from 607 ± 227 to 1167 ± 381 μmol/L. Serum creatinine did not change with values of 0.8 ± 0.1 and 0.8 ± 0.2 mg/dL before and during the study, respectively.

Glucose Diet in Obesity

The four subjects receiving this diet (Table 3) did not show increases in mean serum urate levels. There was a decrease in mean percent uric acid clearance to creatinine clearance from 5.9 ± 1.2 to the lowest mean value of 4.1 ± 2.5 . A doubling of blood lactate from

898 ± 191 to 1803 ± 460 mg/dL and a rise in mean serum triglycerides from 132 ± 24 to 242 ± 116 mg/dL were observed as well.

Sucrose Diet in Normal Subjects

During an isocaloric sucrose diet in two normal men (Table 4), the serum urate level increased from 5.3 and 4.0 to peak values of 9.5 and 7.4 mg/dL, while the urine uric acid excretion decreased from 0.25 and 0.24 to 0.20 and 0.18 mg/mg creatinine. The percent uric acid clearance to creatinine clearance decreased from 5.6 and 6.6 to 2.9 and 3.3, respectively. There was a rise in serum triglycerides and no consistent change in blood lactate levels.

During studies of urate metabolism using [14 C]uric acid, the urate pool sizes increased from baseline values of 925 and 1254 mg to 1248 and 1687 mg, respectively (Fig 1). No increase of uric acid turnover is evident. The baseline turnovers were 910 and 1083 mg/d as compared to 779 and 972 mg/d on sucrose, respectively.

Sucrose Diet in Gout

We next examined whether the influence of a sucrose diet on uric acid metabolism is the same in gouty patients as obese and normal subjects (Table 4). In gouty patients the mean serum urate increased from 8.5 ± 1.5 to 10.6 ± 1.4 mg/dL. The urine uric acid excretion increased from 0.25 and 0.30 to 0.37 and 0.38 mg/mg creatinine in two patients and decreased from 0.31 to 0.21 mg/mg creatinine in one patient. In one patient the renal clearance of uric acid decreased, while there was no change in the renal clearance of uric acid in two patients. There was a marked increase in

Table 4. Sucrose Diet in Normal Subjects and Gouty Patients

| | Serum | | | Urine | | |
|-----------------------|---------------|--------------------|----------------------|------------------|---------------------|--------------|
| | Urate (mg/dL) | Creatinine (mg/dL) | Triglyceride (mg/dL) | Uur/Ucr* (mg/mg) | Uoxy/Ucr* (μmol/mg) | Cur/Ccr* (%) |
| Normal Males | | | | | | |
| C.W. Baseline† | 4.0 | 1.0 | 67 | 0.24 | 0.08 | 6.6 |
| Sucrose | 7.4 | 1.2 | 125 | 0.18 | 0.08 | 3.3 |
| T.G. Baseline | 5.3 | 1.2 | 97 | 0.25 | 0.10 | 5.6 |
| Sucrose | 9.5 | 1.4 | 124 | 0.20 | 0.10 | 2.9 |
| Gouty Patients | | | | | | |
| L.G. Baseline | 10.2 | 1.1 | 310 | 0.30 | 0.16 | 3.3 |
| Sucrose | 11.6 | 1.1 | 737 | 0.37 | 0.15 | 3.5 |
| J.A. Baseline | 7.4 | 0.9 | — | 0.31 | 0.09 | 3.8 |
| Sucrose | 11.3 | 1.3 | — | 0.21 | 0.29 | 2.5 |
| W.K. Baseline | 7.9 | 1.6 | 184 | 0.25 | 0.08 | 5.0 |
| Sucrose | 9.0 | 1.4 | 413 | 0.38 | 0.58 | 6.0 |

Two normal male subjects and three gouty patients were studied during an isocaloric purine-free diet and isocaloric sucrose diet for an average of nine days. In the two normal men, the serum urate levels increase while the urine uric acid excretion and percent uric acid to creatinine clearance decrease. In the three gouty patients, the serum urate levels increase. In two of the gouty patients, the urine uric acid excretion increases and the uric acid to creatinine clearance increase. In the third patient, the urine uric acid excretion and urine uric acid to creatinine clearance decrease.

*Abbreviations are the same as for Table 2.

†Baseline refers to the values obtained during an isocaloric purine free diet.

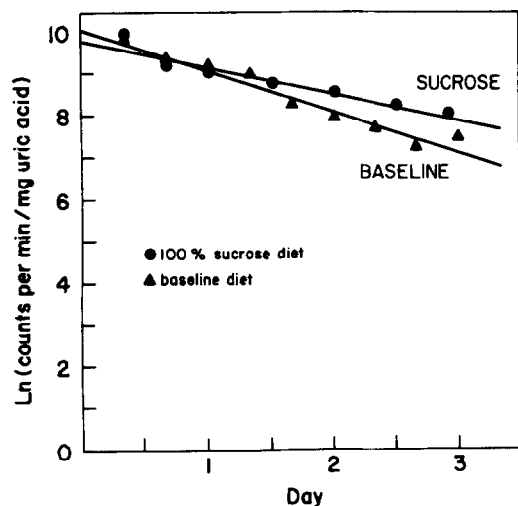


Fig 1. Increased Uric Acid Pool Size During a Pure Sucrose Diet. Two normal subjects were studied for changes in uric acid turnover during an isocaloric sucrose diet. This graph illustrates the representative results in one patient. It can be seen that the uric acid pool size increases during the sucrose diet from a baseline of 925 mg to 1248 mg. The number of pools turned over per day is decreased during the sucrose diet from a baseline of 0.98 to 0.62. The calculated uric acid turnover is not increased with a baseline value of 910 mg/d and 779 mg/d during the sucrose diet. Therefore, there is no rise in uric acid production.

plasma triglyceride levels, but no consistent change in blood lactate levels.

DISCUSSION

Hypertriglyceridemia occurs frequently in association with gout.^{1,21-25} The metabolic basis for the association between hyperuricemia and hypertriglyceridemia is unclear. One possibility that hyperuricemia itself increases plasma lipids is not supported by experiments performed.² Since lipid abnormalities are absent in first degree relatives of gouty subjects, they may reflect more the lifestyle of the patient than genetic factors.²⁶ This proposal is strengthened by the observations that obesity or excessive alcohol intake rather than the underlying hyperuricemia and gout account for the increased serum triglyceride.²⁷⁻²⁹

Our study examined two additional mechanisms which could possibly explain the association between hyperuricemia and hypertriglyceridemia. The data do not support the possibility that hypertriglyceridemia is the cause of hyperuricemia. Acute elevation of serum triglycerides did not modify uric acid synthesis or excretion in the current study or in a previous experiment.³⁰ However, these data are not conclusive since infused triglycerides have a different composition and metabolic origin than endogenous triglycerides. In addition, prolonged elevation might have effects not apparent from these acute experiments.

The possibility that excessive sucrose intake may

cause both hyperuricemia and hypertriglyceridemia was examined as well. The rationale for this approach is based upon the occurrence of both hyperuricemia and hypertriglyceridemia in patients with glucose 6-phosphatase deficiency^{3,4} and fructose 1,6-diphosphatase⁵ deficiency, inherited disorders of carbohydrate metabolism. In our study either a 2000 calorie sucrose diet or an isocaloric sucrose diet increased the serum urate level in obese patients, normal subjects, and gouty patients. Sucrose-induced elevations of serum urate levels have occurred in other studies as well.^{31,32} In addition, sucrose and glucose increased serum triglycerides in our obese and gouty patients and in subjects of previous reports.³²⁻³⁵ Direct, highly significant correlations between serum urate levels and triglyceride concentrations occurred during diets in which the sucrose content was varied from 3% to 33%.³²

The fructose moiety of sucrose may be the more important contributor to the hyperuricemia, since the pure glucose diet did not increase the serum urate level despite 50% more calories. The mechanism for the increased serum urate levels during sucrose intake could be related to increased synthesis of uric acid, decreased uric acid excretion, or both factors operating together. Both mechanisms account for the hyperuricemia of glucose 6-phosphatase deficiency.^{3,4,36} Increased degradation of hepatic ATP secondary to the fructose moiety of sucrose has been proposed to explain the association between sucrose intake and increased urate levels,³² since the latter results from IV fructose infusion.^{7-10,36} In contrast, no evidence for elevated uric acid synthesis is evident in the two normal subjects in our study despite the fact that these subjects had the largest quantity of sucrose ingestion. Our studies indicate that the primary mechanism of hyperuricemia during sucrose ingestion is a diminished renal clearance of urate in obese patients and normal subjects. In our obese subjects and in a previous study a sucrose load increased blood lactate levels,³⁷ but this is not a consistent observation in our experiments. Hyperlacticacidemia is a well-established factor which decreases uric acid clearance.³⁸

Pure sucrose intake increased uric acid synthesis in two gouty patients. This is indicated by the elevation of both serum urate levels and urine uric acid excretion. In one gouty patient there was both decreased clearance of uric acid and increased synthesis of the uric acid precursors hypoxanthine and xanthine. The basis for this heterogenous response of the three gouty patients is not clear. Although the gouty patients are obese, their response is distinct from the obese non-gouty subjects. However, studies of more gouty subjects will be necessary to confirm these observations.

The differences observed in obese, nonobese and gouty subjects may simply reflect the variation in the amount of fructose administered. Our data does not support this possibility (Table 1). The two normal subjects and the obese subjects had a similar quantity of sucrose intake. In addition, the normal subjects who ingested the largest quantity of sucrose, had no evidence for increased production of uric acid (Fig 1, Table 4). Thus, we cannot find evidence that the relative quantity of fructose determines the mechanism of hyperuricemia. On the basis of our data it appears that the gouty subjects may have some alteration in the metabolic handling of fructose such that there are different mechanisms for hyperuricemia.

Despite the relationship between high sucrose intake and increased serum urate levels, epidemiologic studies show no evidence for an association between glucose intolerance and gout^{39,40} or between serum urate and blood sugar levels.³⁹⁻⁴¹ In fact, hyperglycemia has uricosuric activity which lowers serum urate levels.^{39, 42-46} In this study, fasting plasma glucose actually dropped during both sucrose and glucose diets, and oral glucose tolerance improved in the obese subjects (EBM, unpublished data).

Our experiments support the concept that the excessive ingestion of sucrose is an etiological factor which increases both serum urate and serum triglyceride levels. However, the average American ingests sucrose equivalent to 15% to 20% of the daily caloric intake.⁴⁷ Therefore, our experiments represent an extreme variation in a short term study, although other studies have directly correlated serum urate levels with triglyceride concentrations during diets containing up to 33% sucrose.³² On the basis of the data available, it must be concluded that the contribution of excessive sucrose ingestion to clinically associated hyperuricemia and hypertriglyceridemia remains unclear. This will require extensive analysis of the dietary habits in the affected patients.

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