An 18-yr-old man with a classical history of hereditary fructose intolerance (HFI) developed typical biochemical changes following an oral fructose load: fructosemia, hypoglycemia, hypophosphatemia, hyperuricemia, and metabolic acidosis. Hypokalemia (3.1 meq/liter) was also noted. Three aspects of this case expand the published literature on this syndrome: (1) Metabolic acidosis was found to be due to both lactic acidosis and proximal renal tubular acidosis (RTA). We could quantitate the relative contribution of each, and found that urinary bicarbonate loss due to proximal RTA accounted for less than 10% of the fall in serum bicarbonate. The major cause of the metabolic acidosis was lactic acidosis. (2) Hypokalemia was found to be due to movement of potassium out of the extracellular space rather than to urinary loss. Potassium may have entered cells with phosphate or may have been sequestered in the gastrointestinal tract. (3) The coexistence of proximal RTA and acidemia made it possible to study the effect of acidemia on the urine-blood partial pressure of carbon dioxide (PCO$_2$) gradient in alkaline urine (U-B PCO$_2$). The U-B PCO$_2$ measured during acidemia was much higher at the same urine bicarbonate concentration than in normal controls during alkalemia, providing evidence in humans that acidemia stimulates distal nephron hydrogen-ion secretion.

FRUCTOSE INGESTION by patients with hereditary fructose intolerance (HFI) leads to a number of clinical and biochemical derangements that have been attributed to a specific enzyme defect: a deficiency of fructose-1-phosphate aldolase (E.C. 4.1.2.7.) in hepatic, renal cortical, and small intestinal cells. The clinical consequences of fructose ingestion in patients with HFI include a sensation of being acutely ill (gastrointestinal complaints including nausea, vomiting, and abdominal pain); the signs and symptoms of hypoglycemia (adrenergic and CNS symptoms); and other metabolic sequellae such as hyperuricemia, hypophosphatemia, and metabolic acidosis.

It may be difficult to evaluate the cause of metabolic acidosis in a patient with HFI who has ingested fructose, since lactic acidosis and both proximal and distal RTA may occur in this condition. In order to confirm the presence of proximal RTA, one should document reduced renal bicarbonate reabsorption, an increased fractional excretion of bicarbonate, and a failure to lower the urine pH during acidemia. However, to examine the fractional excretion of bicarbonate, administration of sodium bicarbonate may he required to bring the serum bicarbonate towards the normal range. Furthermore, the urine pH can be less than 5.3 if another form of metabolic acidosis coexists. The diagnosis of distal RTA may require the administration of ammonium chloride to a patient who is already acidemic and who may be producing hydrogen ions at an increased rate. The coexistence of lactic acidosis in this condition could further complicate the identification of RTA, especially if there is an enhanced loss of lactate in the urine.

We have recently studied a patient with HFI who developed metabolic acidosis within 3 hr of ingesting fructose. By applying a recently developed test of distal nephron hydrogen-ion secretion, the urine-blood PCO$_2$ gradient in alkaline urine (U-B PCO$_2$), we were able to simultaneously confirm the presence and quantitate the importance of proximal RTA, assess the contribution of lactic acidosis toward the severity of the acidemia, and rule out the diagnosis of distal RTA.

CASE REPORT

The patient was an 18 yr old white male who since childhood had complained of indigestion, vomiting, diarrhea, weakness, sweating, faintness, and drowsiness within half an hour of eating most sweet foods. As an infant, he developed vomiting and diarrhea after ingestion of both orange juice and sucrose-containing formulas, and his mother, with the help of a visiting nurse, eventually discovered that he thrived on glucose-containing formulas. She catered to his food likes and dislikes because of his obvious distress after certain foods and outright rejection of the same foods on re-exposure. Growth and development were normal. When older, he found he could not tolerate table sugar (sucrose), most fruits,
syrups, jellies, carrots, and sweet canned peas. The only
confection he could eat was one which contained dextrose as
the only carbohydrate (sweet tarts). There were no other
affected individuals in the family. There was no consanguin-
ity. His only sibling was healthy.

Physical examination was normal. Height was 167 cm,
weight 58 kg. He had almost perfect teeth, with only one
filling. A fructose tolerance test was performed to confirm
the clinical diagnosis of hereditary fructose intolerance.

MATERIALS AND METHODS
Following an overnight fast, 20 gm of reagent-grade
fructose in water was given orally. A venous blood sample
was drawn just prior to the fructose load and 15, 60, 120, and
180 min thereafter. Urine was collected by complete bladder
emptying at the same intervals.

Plasma glucose was measured using glucose oxidase in a
Beckman Glucose Analyzer (Beckman Instruments, Inc.,
Fullerton, Ca.); plasma fructose was measured by an enzy-
matic method,16 insulin by radioimmunoassay,17 plasma free
fatty acids by gas-liquid chromatography,18 and urinary
amino acids by thin-layer chromatography.19 Other blood
and urine determinations were done in the clinical biochem-
istry laboratory by routine methods.

RESULTS
Routine hematology, liver function tests, serum electrolytes, calcium, and phosphorus
were normal prior to the fructose tolerance test. Urinalysis was normal. A glucose tolerance test
done previously had been normal.

The results of the fructose tolerance test are
shown in Tables 1, 2, and 3. Thirty to 60 min
after fructose ingestion, the patient became
weak, sweaty, and drowsy. These symptoms
disappeared when an infusion of glucose was
administered. The typical biochemical features
of this disorder were seen: fructosemia, severe
hypoglycemia, hypophosphatemia, hyperuricemia,
and a rise in serum lactate. There was a rise
in SGOT from the baseline value of 20 U to 83 U
at 3 hr (normal < 40 U).

Table 1. Metabolic Changes Following Fructose in HFI:
Plasma Levels

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fructose (mg/dl)</td>
<td>1.1</td>
<td>14.2</td>
<td>7.6</td>
<td>1.8</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>88</td>
<td>50</td>
<td>24</td>
<td>22</td>
</tr>
<tr>
<td>Insulin (µU/ml)</td>
<td>20</td>
<td>10</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Free fatty acids (meq/liter)</td>
<td>0.93</td>
<td>0.82</td>
<td>2.19</td>
<td>1.96</td>
</tr>
</tbody>
</table>

Table 2. Acid-Base Studies and Serum Potassium Following Fructose in HFI

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pH</td>
<td>7.39</td>
<td>7.37</td>
<td>7.30</td>
<td>7.24</td>
</tr>
<tr>
<td>PCO₂ (mm Hg)</td>
<td>41</td>
<td>41</td>
<td>40</td>
<td>41</td>
</tr>
<tr>
<td>HCO₃⁻ (meq/liter)</td>
<td>2.7</td>
<td>2.3</td>
<td>1.9</td>
<td>1.7</td>
</tr>
<tr>
<td>K⁺ (meq/liter)</td>
<td>3.7</td>
<td>4.2</td>
<td>3.1</td>
<td>3.1</td>
</tr>
<tr>
<td>Anion gap (meq/liter)</td>
<td>18</td>
<td>14</td>
<td>2.1</td>
<td>2.3</td>
</tr>
<tr>
<td>Urine pH</td>
<td>6.09</td>
<td>7.65</td>
<td>7.51</td>
<td>6.16</td>
</tr>
<tr>
<td>HCO₃⁻ (meq/liter)</td>
<td>0</td>
<td>89</td>
<td>96</td>
<td>5</td>
</tr>
<tr>
<td>PCO₂ (mm Hg)</td>
<td>—</td>
<td>91</td>
<td>120</td>
<td>—</td>
</tr>
<tr>
<td>F. E. HCO₃⁻ (%)</td>
<td>0</td>
<td>8.8</td>
<td>7.5</td>
<td>0.2</td>
</tr>
<tr>
<td>TCO₂/GF (meq/liter)</td>
<td>24</td>
<td>22</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>Flow rate (ml/hr)</td>
<td>135</td>
<td>95</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>U-B PCO₂ (mm Hg)</td>
<td>—</td>
<td>50</td>
<td>50</td>
<td>—</td>
</tr>
</tbody>
</table>

*Fractional bicarbonate excretion.
†Tubular reabsorption of bicarbonate per litre glomerular filtrate.
‡See text for a discussion of normal data.
Acid-Base Measurements

The patient developed a moderately severe metabolic acidosis following fructose intake. The anion gap rose, as did the blood lactate concentration (Tables 2 and 3). Serum and urine ketones did not rise appreciably. Despite the acidemia, the urine pH was as high as 7.65, and the fractional excretion of bicarbonate was 8.8% when the serum bicarbonate concentration was 23 meq/liter. Bicarbonate reabsorption fell to 18 meq/liter glomerular filtration rate (GFR). The U-B PCO₂ was 80 mm Hg when the urine bicarbonate concentration was 96 meq/liter and the urine phosphate 8.7 was mM. This value for the U-B PCO₂ is well above the levels seen in patients with distal RTA (mean ± SEM 2.0 ± 2.1 mm Hg) and in normal controls (32.7 ± 3.1 mm Hg). Cumulative urine bicarbonate and lactate losses were only 19 and 9 meq respectively over the 3-hr period following fructose intake.

Potassium

The serum potassium concentration fell to a nadir of 3.1 meq/liter 2 hr after fructose infusion. Cumulative urine potassium excretion was only 32 meq over the 2-hr period.

Renal Tubular Function

Proteinuria and generalized aminoaciduria were evident by 1 hr. Fructosuria was suspected by the finding of a positive Clinitest (Ames Division, Mile Laboratory Ltd., Rexdale, Ontario) and negative Test-tape (Eli Lilly, Toronto, Canada) (glucose specific) at 1, 2, and 3 hr and was confirmed later by specific enzymatic assay. Phosphaturia, uricosuria, and lactaturia were present (Table 3). The fractional excretion of urate fell somewhat, coincident with a rise in blood lactate, but still remained at a higher level than might be expected.¹⁴

DISCUSSION

Acidosis in HFI could occur by at least four mechanisms: lactic acidosis, proximal RTA, distal RTA, and loss of sodium bicarbonate into the gastrointestinal tract.

Lactic acidosis. Lactic acidosis occurs regularly following fructose administration in patients with HFI, and the blood lactate concentration may approach 7 meq/liter.⁴ Lactic acidosis also occurs in normal individuals given fructose.⁵ In normals, lactate is probably derived directly from fructose entry into the glycolytic pathway below the regulatory enzyme phosphofructokinase.⁶ The fructose-induced reduction in liver-cell ATP levels may also contribute to lactate accumulation by favoring anaerobic glycolysis.⁷ The mechanism for lactate accumulation in HFI is not known precisely, however, it is unlikely to be due simply to direct metabolism of fructose-1-phosphate (F-1-P), since the activity of the enzyme F-1-P aldolase is markedly reduced. It may be due to the inhibition of gluconeogenesis by F-1-P and the presence of low insulin levels.³ In the patient presented here, blood lactate rose approximately 4 meq/liter and could explain most of the fall in serum bicarbonate (7 meq/liter) and rise in anion gap (5 meq/liter). Excretion of lactate anion in the urine may lead to a fall in the serum bicarbonate without a commensurate rise in the unmeasured anion gap,¹⁷ however, lactate excretion was very small in this patient.

Proximal RTA. Proximal RTA was first described in patients with HFI by Morris in association with a “Fanconi type” syndrome.⁵ He showed that, on a fructose free diet, patients with HFI had normal renal bicarbonate reabsorption, but after fructose administration and during bicarbonate infusion to maintain serum bicarbonate near normal, the tubular reabsorption of bicarbonate fell 20%–30%, so that bicarbonate reabsorption was approximately 19 meq/liter GFR. The fractional bicarbonate excretion rate was 38% at normal serum bicarbonate levels.³ Distal RTA was unlikely in these patients because they could reduce their urine pH when the serum bicarbonate level fell below its renal threshold (16 meq/liter). Our patient clearly had proximal RTA, based on a bicarbonate reabsorption rate of 18 meq/liter GFR, as well as other manifestations of a proximal tubular lesion including proteinuria, aminoaciduria, fructosuria, uricosuria, phosphaturia, and lactaturia. The fractional bicarbonate excretion (9%) was less than the level usually considered diagnostic for proximal RTA (15%).¹⁹ however, the latter figure applies only when serum bicarbonate is in the normal range. In our patient, the serum bicarbonate fall was primarily due to the
concomitant lactic acidosis. The urinary loss of bicarbonate (19 meq), if its distributional space had been one-half of body weight,<sup>20</sup> would account for a fall in serum bicarbonate of less than 1 meq/liter.

**Distal RTA.** Distal RTA appears to have been present in one previously described patient with HFI who also had nephrocalcinosis.<sup>6,7</sup> That patient had a urine pH of 6.5 when the arterial bicarbonate concentration was 10 meq/liter, strongly suggesting distal RTA. However, no data were presented to establish whether proximal RTA was present with fructose administration. The relationship between distal RTA and HFI is not clear, since it has been described in only one patient and since distal RTA has not been found in other patients with HFI in whom this lesion has been specifically looked for.<sup>5,21</sup>

Distal RTA of the secretory-limit type<sup>*</sup> was ruled out in our patient by the finding of a high value for the U-B PCO₂ in the alkaline urine that developed during the fructose tolerance test.<sup>*</sup> Inspection of the data on patient L.R., study 4, described by Morris<sup>7</sup> reveals that this patient too had a normal U-B PCO₂ (59 mm Hg, urine bicarbonate 105 meq/liter) at a time when there was obvious proximal RTA (bicarbonate reabsorption, 21 meq/liter GFR).

The U-B PCO₂ of 80 mm Hg seen in our case at 2 hr is well above the levels obtained in normal controls at the same urine bicarbonate concentration.<sup>9</sup> The normal range was established by bicarbonate infusions and was measured during alkalemia.<sup>8</sup> This patient offered the opportunity to measure the U-B PCO₂ in alkaline urine that developed during the fructose tolerance test.<sup>8</sup> The very high U-B PCO₂ suggests that acidemia stimulated distal nephron hydrogen-ion secretion. A similar finding has recently been documented experimentally in dogs with proximal RTA induced by lysine.<sup>23</sup> In these dogs, it was found that the U-B PCO₂, when corrected for urine bicarbonate concentration, was directly related to blood [H⁺]. Our patient and the patient described by Morris had similar urine bicarbonate values (96 and 105 meq/liter respectively), however, our patient had a higher U-B PCO₂ (80 versus 59 mm Hg) and also a higher blood [H⁺] (50 versus 34 nM). These data suggest that the relationship between distal nephron hydrogen secretion and blood [H⁺] is also present in man. In summary, this protocol allowed us to confirm the diagnosis of proximal RTA and excluded diagnosis of secretory limited distal RTA by simultaneous measurement of bicarbonate reabsorption and the U-B PCO₂.

**Bicarbonate loss into the gastrointestinal tract.** Patients with HFI often develop symptoms of abdominal pain, nausea, and vomiting following fructose ingestion, which have been attributed to the deficiency of fructose-1-phosphate aldolase in small intestinal cells.<sup>2</sup> It would not be surprising, therefore, if sequestration of fluid and electrolytes, including bicarbonate, occurred in the bowel lumen. Such “third-space” loss of bicarbonate theoretically could contribute to the genesis of metabolic acidosis unassociated with a change in the anion gap. Clinical and radiographic manifestations of ileus were not specifically looked for in our patient, nor, to our knowledge, have they been noted in previously reported patients. Nevertheless, gastrointestinal sequestration of bicarbonate could have accounted for part of the acidemia not explained by accumulation of lactic acid or loss of bicarbonate in the urine.

**Potassium**

The serum potassium fell to 3.1 meq/liter following fructose, a finding that has been documented in several previous cases.<sup>5,6,21,24</sup> It is of interest that Froesch stated in a review article that “serum potassium levels often fall after administration of fructose to patients with HFI, but this is not a regular finding and should not be used for the diagnosis”.<sup>1</sup> Nevertheless, hypokalemia does occur in many patients with HFI, and this requires an explanation. Urinary loss of potassium is probably not the cause of the fall in serum potassium. In our patient, urinary potassium loss was 32 meq, and in a patient described by Morris, the urinary potassium loss was 8 meq,<sup>2</sup> while serum potassium fell by 0.6 and 1.5 meq/liter, respectively. It has been estimated that, in the absence of changes in potassium distribution, total-body potassium deficits of 100–200 meq must occur to account for a fall in

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<sup>*</sup>The other experimentally-defined variant of distal RTA, characterized by increased back-diffusion of hydrogen ions, typified by the lesion induced by amphotericin B, cannot be ruled out by this test.<sup>22</sup>
serum potassium of 1 meq/liter. Therefore, it appears most likely that the fall in serum potassium was due to a shift of potassium out of the extracellular space. A shift of potassium into the intestinal tract might be anticipated in patients with HFI, as the enzyme is deficient in intestinal cells and these patients do develop abdominal pathology. Potassium may also shift into the intracellular space, but the mechanism cannot be either a rise in insulin levels or alkalemia in this patient, since insulin levels fell and the patient became acidemic (Tables 1 and 2). Possible explanations include either a catecholamine-induced potassium entry into cells or potassium entry into the intracellular space along with inorganic phosphate to maintain electrical neutrality when F-1-P accumulated in hepatic, renal, and intestinal cells. Why the serum potassium remained low while the serum phosphate showed a late rise (at 2 and 3 hr) in this patient is not clear, but similar observations have been made previously. Possibly, catecholamine levels fell, gastrointestinal absorption of potassium increased, or phosphate was released from bone or membrane phospholipids that were not associated with intracellular potassium stores.

Uric Acid Metabolism

At least three different processes could have affected uric acid metabolism in this patient. First, the serum uric acid rose following fructose ingestion, a response that occurs both in normals and, to a greater extent, in patients with HFI. The hyperuricemia is believed to result from increased conversion of adenine nucleotides to urate, presumably reflecting the fall in intracellular inorganic phosphate, which activates adenosine deaminase. Second, the elevation of the fractional excretion of uric acid above the normal range would be expected as part of the Fanconi-like syndrome induced by fructose. Fractional uric acid excretion fell from 22% at 1 hr to 12% at 2 and 3 hr, while another index of proximal tubular function, fractional phosphate excretion, was increasing, suggesting that an additional factor may have been affecting renal urate handling—possibly the effect of the elevated blood lactate concentration inhibiting uric acid secretion. In summary, overproduction of urate should be expected in patients with HFI who have ingested fructose. Renal excretion should increase due to the Fanconi-like lesion and decrease because of the elevated blood lactate concentration. The net result on the blood urate concentration will depend on the relative magnitude of these three processes.

SUMMARY

This patient with HFI developed metabolic acidosis, due mainly to lactic acidosis, following fructose administration. Proximal RTA was demonstrated by a reduced rate of bicarbonate reabsorption, and distal RTA was ruled out by U-B PCO₂ measurements. Hypokalemia developed simultaneously despite systemic acidosis and appears to be a feature of this condition. Hypokalemia is attributed to a shift of potassium from the extracellular space.

ACKNOWLEDGMENT

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REFERENCES


