EFFECT OF CARBOHYDRATE AND FAT IN THE DIET ON URIC ACID EXCRETION

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Apart from an early observation by Umeda (1) of a single case in which a diet high in fat and low in carbohydrate led to a diminution of uric acid output, little attention was devoted to this phase of the uric acid problem prior to the introduction of the ketogenic diet in the treatment of epilepsy. This stimulated the study of the uric acid elimination during fasting in epileptic children, normal persons being used as controls. All observers (2–6) reported that fasting resulted in decreased uric acid elimination in the urine. Leopold, Bernhard, and Jacobi (4) further showed that a high fat diet results in a marked decrease in the uric acid output. Their diet, used in children, was unusually low in carbohydrate, containing, daily, only 15 gm. of carbohydrate, 12 gm. of protein, and 110 gm. of fat. They also noted that a high carbohydrate, almost purine-free diet does not result in greater uric acid elimination than that observed on a diet with an equally low purine content, and moderate amounts of carbohydrate. Lennox (5), in a very comprehensive paper, showed that the feeding of a high fat diet does not relieve the uric acid retention resulting from prolonged fasting, but that the feeding of carbohydrate results in a prompt rise in uric acid excretion.

A state of acidosis and ketosis may be induced by a high fat, extremely low carbohydrate diet, as well as by prolonged fasting. The first may be considered an "exogenous" high fat diet, whereas the effect of fasting is essentially equivalent to an "endogenous" high fat diet. The diminished excretion of uric acid under both these conditions may therefore have been due to acidosis or ketosis. In fact, Lennox (5) demonstrated a fairly reciprocal relationship
between the blood uric acid and the plasma bicarbonate in the
course of his fasting experiments. To rule out acidosis as dis-
tinguished from ketosis, he added large amounts of sodium bi-
carbonate but there was no increase in the output of uric acid. He
also produced an acidosis, without ketosis, by administering
calcium chloride but caused no change in the uric acid excretion.
These observations excluded acidosis per se as the factor respon-
sible for the diminution in uric acid excretion during fasting or with
high fat diets. It was still to be determined whether the high fat
diet itself or the accompanying ketosis was responsible for the
diminution of uric acid excretion.

A review of the literature did not reveal any studies on uric acid
excretion that differentiated the effect of the high fat diet from
that of the accompanying ketosis in normal individuals. We
attempted to determine this by giving high fat diets which, how-
ever, included sufficient carbohydrates to prevent ketosis.

Procedure and Method

Seven patients were used as subjects. They were all afebrile
and well along in convalescence from various diseases, none of
which was related to uric acid metabolism. These subjects were
first placed on a diet of 150 gm. of carbohydrate, 80 gm. of protein,
and 100 gm. of fat (Diet I), to determine the average daily uric
acid excretion for each individual. This was followed by a diet
of 150 gm. of carbohydrate, 80 gm. of protein, and 250 gm. of fat
(Diet II). Diet II represented an increase of 150 gm. of fat over
that contained in Diet I, while the carbohydrate and protein
content remained unchanged. The subjects were then returned
to the basal diet of 150 gm. of carbohydrate, 80 gm. of protein,
and 100 gm. of fat (Diet III). Three of the subjects were subse-
sequently given a fourth diet (Diet IV) which contained 350 gm. of
carbohydrate in addition to the basal diet and was practically
equivalent in calories to Diet II. The actual caloric values of the
four types of diets were Diet I 1850, Diet II 3200, Diet III 1850,
and Diet IV 3250 calories.

Each day the total 24 hour urine was collected, with toluene as a
preservative, measured, and analyzed for its uric acid content.
The uric acid content was determined by Brown’s modification of
the Benedict method (7). With each change of diet, the uric acid
of the blood serum was determined by the method of Benedict. During administration of the high fat diet (Diet II) frequent tests for acetonuria were performed. Occasional determinations of the carbon dioxide-combining power of the blood were also made.

Results

Table I presents the uric acid excretion of one of the subjects on the varied diets administered. On the basal diet (Diet I), the daily uric acid excretion ranged between 505 and 567 mg., the average being 532 mg. On Diet II, which is rich in fat, the daily excretion varied from 300 to 480 mg., the average being 408 mg. This represented a 23 per cent reduction in uric acid excretion from that on the basal diet. A return to the basal diet, Diet III, resulted in a daily excretion ranging from 510 to 600 mg. of uric

### Table I

<table>
<thead>
<tr>
<th>Diet I, 150 gm. carbohydrate, 80 gm. protein, 100 gm. fat</th>
<th>Day</th>
<th>Urine Amount (cc.)</th>
<th>Uric acid (mg.)</th>
<th>Blood uric acid (mg. per cent)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>1490</td>
<td>552</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1120</td>
<td>515</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1200</td>
<td>567</td>
<td>1.9</td>
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<tr>
<td></td>
<td>4</td>
<td>1400</td>
<td>505</td>
<td></td>
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<tr>
<td>Diet II, 150 gm. carbohydrate, 80 gm. protein, 250 gm. fat</td>
<td>5</td>
<td>700</td>
<td>300</td>
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<tr>
<td></td>
<td>6</td>
<td>1350</td>
<td>450</td>
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<td>8</td>
<td>1400</td>
<td>480</td>
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<td></td>
<td>9</td>
<td>1480</td>
<td>382</td>
<td></td>
</tr>
<tr>
<td>Diet III, same as Diet I</td>
<td>10</td>
<td>1510</td>
<td>600</td>
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</tr>
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<td></td>
<td>11</td>
<td>1820</td>
<td>510</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>1540</td>
<td>568</td>
<td>1.8</td>
</tr>
<tr>
<td>Diet IV, 500 gm. carbohydrate, 80 gm. protein, 100 gm. fat</td>
<td>13</td>
<td>1600</td>
<td>550</td>
<td></td>
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<tr>
<td></td>
<td>14</td>
<td>1400</td>
<td>500</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>1500</td>
<td>600</td>
<td></td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>2400</td>
<td>658</td>
<td></td>
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</table>
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acid, the average being 559 mg., which is only slightly elevated as compared with the first period. On Diet IV, which is high in carbohydrates, and of approximately the same caloric content as the high fat diet (No. II), the uric acid excretion ranged from 500 to 658 mg., the average being 584 mg. This excretion is slightly greater than that observed with Diet III and is moderately elevated as compared with that of the original period on the basal diet (Diet I).

Table II presents the average amounts of uric acid excretion of all subjects during each diet period. The average daily uric acid excretion on Diet I varied from 495 to 717 mg., thus indicating a wide range for different individuals, but the daily excretion in each individual ranged within much narrower limits. During the period on Diet II (high fat) the average daily uric acid excretion decreased in each case from 11 to 28 per cent. The average decrease for all seven subjects was 21.3 per cent as compared with the basal diet (Diet I). A return to the low fat diet (Diet III) was followed in each of the cases, except one, by an increase in the daily uric acid excretion, the average value being moderately decreased as compared with the period of Diet I.

Only three of our subjects were put on Diet IV. On this diet the average daily uric acid excretion was 605 mg., while the average daily uric acid excretion of these three subjects on Diet I was

<table>
<thead>
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<th>Table II</th>
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<tbody>
<tr>
<td>Average Daily Excretion of Uric Acid in Each Diet Period</td>
</tr>
<tr>
<td>Case</td>
</tr>
<tr>
<td>Days</td>
</tr>
<tr>
<td>----</td>
</tr>
<tr>
<td>E. N.</td>
</tr>
<tr>
<td>M. U.</td>
</tr>
<tr>
<td>R. E.</td>
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<tr>
<td>C. S.</td>
</tr>
<tr>
<td>E. M.</td>
</tr>
<tr>
<td>L. M.</td>
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<tr>
<td>N. G.</td>
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</table>
590 mg., on Diet II 449 mg., and on Diet III 573 mg. While there was a very definite difference in uric acid excretion during the administration of the high carbohydrate and the high fat diet, a diminution of 25.8 per cent on the latter, there were only slight differences during the two periods on the basal diet and the carbohydrate diet.

The duration of each period varied from 1 to 9 days. In all cases frequent examinations of the urine for acetone during the period on Diet II failed to reveal the presence of acetone bodies. The occasional determinations of the blood carbon dioxide-combining power revealed normal values. At times there was a slight elevation of the blood uric acid during the administration of high fat diet, as in Table I. However, this was not consistent and usually varied within the range of error of the method used.

DISCUSSION

The classical treatment of gout by means of a diet low in proteins and purines is still the customary basis of therapy. However, recent investigations have revealed the importance of the relative amounts of carbohydrate and fat, as well as of protein, in the diet. Earlier investigations, as outlined above, indicated that a diet high in fat and low in carbohydrate caused a diminution in the excretion of uric acid in the urine, and that this diminution was not due to the acidosis developed. Our experiments have further shown that neither the ketosis nor the high caloric value of the diet is the cause, and that the result appears to depend directly on the high fat content.

The mechanism underlying these changes in the uric acid excretion is not determined. The observed diminution might be due to (1) diminished function of the kidney, (2) decreased absorption of purines from the diet due to a change in the amount of destruction in the intestines, (3) diminished "endogenous" production of purines, (4) disturbance of the function of the liver in formation of uric acid, or (5) increased retention in the tissues. The first was suggested by the earlier investigators, who considered the change as a "retention," but our data do not indicate a significant rise in blood uric acid. The second appears to us unlikely, in view of the low purine content of the diet. On the third, we have
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no information. The fourth (diminished formation by the liver) seems at least plausible, since the influence of high fat diet and high carbohydrate diet on some functions of the liver is well known and has received extensive therapeutic application (as, for example, in diseases of the liver parenchyma). The fifth possibility (increased retention by the tissues) cannot be excluded, especially in view of the clinical effect of a high fat diet in causing an exacerbation of symptoms in gouty individuals. This effect might also argue against the occurrence of decreased uric acid formation as the cause of diminished excretion, since it seems unlikely that a decrease in production would bring on the symptoms.

The effect of a high fat diet on patients with gout was studied by Lockie and Hubbard (8). Each of four gouty patients whose symptoms had subsided was placed on a very high fat, low carbohydrate diet. This was accompanied by a prompt return of symptoms, as well as by a reduction in the uric acid output and a rise in the blood uric acid. These patients were then put on a high carbohydrate, low fat diet, with a prompt relief in symptoms. Their studies are open to criticism, since their high fat diets were very low in carbohydrate, containing only 20 to 60 gm. However, the high carbohydrate diet which produced such beneficial effects varied in its content of fat and contained, in one instance, 130 gm: of fat per day. As soon as adequate clinical material has been obtained, we shall submit a report upon observations with similar diets on gouty patients.

This clinical observation plus our results may have a direct bearing on the therapy of the gouty diathesis which many clinicians believe to be more wide-spread than is commonly supposed. It would appear, therefore, that the diet in gouty patients should be low in purines to control the extrinsic factor, and low in fat content to control the intrinsic factors responsible for uric acid elimination. The resulting diet would therefore necessarily be high in carbohydrate content, with only moderate amounts of protein and fat. Mention may be made of the not infrequent association of gout and diabetes. The dietetic problem in these cases should now be greatly simplified, since our conclusions point to the value of a high carbohydrate diet in gout and the present tendency in diabetes is to employ a relatively high carbohydrate diet particularly with the use of insulin.
SUMMARY

1. A high fat diet diminishes the uric acid excretion in normal individuals.
2. Neither acidosis nor ketosis is of importance in this connection, since these factors were controlled by sufficient amounts of carbohydrate in the diet.
3. A high carbohydrate diet, calorically equivalent to the high fat diet, does not depress the uric acid elimination.
4. The factor responsible for the decrease in uric acid excretion in the urine of subjects on a high fat diet is not the increased caloric intake, but is the high fat content itself.
5. These observations support the use of a high carbohydrate, low fat, as well as a low purine diet in the treatment of the uric acid diathesis.

We are greatly indebted to Dr. Harry Sobotka under whose direction and supervision the urine and blood analyses were carried out.

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