Metabolic effect of a LoBAG<sub>30</sub> diet in men with type 2 diabetes

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We have recently reported that a diet composed of 30% protein, 50% fat, and only 20% carbohydrate dramatically decreased the percentage of total glycohemoglobin (%tGHb; from 9.8 to 7.6%, Δ = 2.2%) without inducing ketosis in people with type 2 diabetes (4). This was the result of a decrease in both overnight fasting and postprandial glucose concentrations. A 5-wk crossover design was used, and the subjects were weight stable. We referred to this diet as the low biologically available glucose-30 diet; high-protein diet; glycemic index; diabetes; thyroid hormone; protein balance

WE HAVE RECENTLY REPORTED that a diet composed of 30% protein, 50% fat, and only 20% carbohydrate dramatically decreased the percentage of total glycohemoglobin (%tGHb; from 9.8 to 7.6%, Δ = 2.2%) without inducing ketosis in people with type 2 diabetes (4). This was the result of a decrease in both overnight fasting and postprandial glucose concentrations. A 5-wk crossover design was used, and the subjects were weight stable. We referred to this diet as the low biologically available glucose-30 diet; high-protein diet; glycemic index; diabetes; thyroid hormone; protein balance

In the present publication, the same hormones, effectors, metabolic substrates, and products as those determined in the LoBAG<sub>30</sub> diet study were determined. The results are discussed in relation to those obtained previously.

Although the study was a controlled crossover design, only the results obtained at the beginning and the end of the LoBAG<sub>30</sub> diet are presented here for brevity. The data obtained when the subjects consumed the control diet are available on request. In general the results remained stable.

RESEARCH DESIGN AND METHODS

Eight men with mild, untreated type 2 diabetes were studied in a special diagnostic and treatment unit (SDTU), similar to a clinical research center. All participants met the National Diabetes Data Group criteria for the diagnosis of type 2 diabetes (1). Three subjects were not being treated with oral hypoglycemic agents or insulin. The five subjects who were being treated with oral hypoglycemic agents discontinued their medication for ≥6 wk before starting the study, at which time the %tGHb had stabilized. None of the subjects had been treated with insulin. Three of the subjects had participated in the LoBAG<sub>20</sub> study. Participant characteristics will be reported (unpublished observations). The study was approved by the Department of Veterans Affairs Medical Center and the University of Minnesota Committees on Human Subjects. All participants gave written informed consent prior to enrollment in the study. Exclusion criteria included hematological abnormalities, kidney disease, liver disease, macroalbuminuria (>300 mg/24 h), congestive heart failure, or untreated thyroid disease. Before the study, participants were interviewed to determine their physical activity level and any food aversions. The study process and commitment was explained in detail. Participants confirmed that they had been weight stable for ≥3 mo. They were instructed to maintain their current activity level throughout the study. Two weeks before beginning the study, the participants completed a 3-day food questionnaire, with one of the days being a Saturday or a Sunday. This information was used to calculate the total food energy necessary to maintain body weight.

The study diet was designed to consist of 30% carbohydrate, 30% protein, and 40% fat. The saturated fatty acid content of the diet was ~10% of total food energy; thus the majority of the fat was mono- and polyunsaturated. The diet composition will be published separately. Each patient was on a 6-day menu rotation for a total of 5 wk.

Participants were admitted to the SDTU on the evening before the study. The next day in the SDTU, standardized meals again were completed a 3-day food questionnaire, with one of the days being a Saturday or a Sunday. This information was used to calculate the total food energy necessary to maintain body weight. On the second day in the SDTU, standardized meals again were given. In addition to the meals at 0800, 1200, and 1800, a snack was given at 2000. Fasting blood was obtained at 0730, 0745, and 0800. Samples were collected every 15 min for the first hour after meals, every 30 min for the next 2 h, and then hourly until the next meal. Blood was drawn at a total of 46 time points. After this 24-h data
accumulation period, the participants were sent home with all of the necessary food for the next 2–3 days.

Participants returned to the SDTU every 2–3 days to pick up food and meet with the study dietitian and study coordinator. At that time, they provided a urine specimen for analysis of creatinine and urea to determine dietary compliance. They also were weighed and had blood pressure, tGHB, and blood glucose measured. If their body weight decreased or increased on two successive occasions, the total food energy of the meals was increased or decreased as appropriate to attempt to maintain stable weight throughout the study. In addition, participants were interviewed regarding dietary compliance during each visit. At the end of the 5-wk period, the participants again were admitted to the SDTU and blood was drawn as described above. At that time, meals (breakfast, lunch, dinner, and snacks) were given as appropriate for the day in the menu rotation.

The plasma and urine creatinine, plasma urea nitrogen, and uric acid were measured with an automated method on an Ortho-Clinical Diagnostics Vitros 950 analyzer (Raritan, NJ). NEFAs were measured enzymically using a kit manufactured by Wako Chemicals (Richmond, VA); total α-amino nitrogen concentration by the method of Goodwin, which is a measure of the total amino acids; plasma TSH (Abbott Architect, Abbott Park, IL), growth hormone (GH; Quest, New Brighton, MN), B12, and folate (Diagnostic Products, Los Angeles, CA) by chemiluminescence; total triiodothyronine (T3) and free thyroxine (T4) by Chemiflex (Abbott Architect); IGF-I by RIA (Quest); homocysteine by HPLC (Hewlett-Packard, Palo Alto, CA); microalbumin using a Beckman-Coulter array 360 analyzer (Fullerton, CA); urinary free cortisol in the laboratory of Dr. B. Pearson-Murphy (McGill University, QC, Canada), using an HPLC purification step followed by a cortisol-binding assay; urinary aldosterone by RIA (Diagnostic Products); urinary calcium and magnesium colorimetrically on a J&J Vitros Instrument (J&J Engineering, Poulsbo, WA); and qualitative urinary ketones with a Ketostix (Bayer, Elkhart, IN).

The total amount of protein oxidized was determined by quantifying the urine urea nitrogen excreted over the 24 h of the study, adjusted for a change in the amount of urea nitrogen retained endogenously. The latter was calculated by determining the change in plasma urea nitrogen concentration between the fasting baseline and at the end of the 24-h study period and by correcting for plasma water by dividing by 0.94. In this calculation, it is assumed that there is a relatively rapid and complete equilibration of urea in total body water. Total body water as a percentage of body weight was calculated using the equation of Watson et al. (Watson et al. 1980). The overall assumption is that a change in plasma urea concentration is indicative of a corresponding change in total body water urea concentration. In this 24-h study, the beginning and ending urea nitrogen concentrations were essentially identical, indicating no retention of urea. The sum of total urea nitrogen in urine and body water was divided by 0.86 to account for 14% lost to metabolism in the gut (Hamberg and Vilstrup 1994).

Net integrated 24-h area response was calculated using the fasting value as baseline. Total integrated 24-h area response was calculated using zero as baseline. Both area calculations were done using a computer program based on the trapezoid rule. Statistics were determined using Student’s t-test for paired variates, with the StatView program (Brain Power, Calabasas, CA) for the Macintosh computer (Apple Computer, Cupertino, CA). Significance was represented by a P value of <0.05. Data are presented as means ± SE.

RESULTS

The mean fasting NEFA concentration decreased from 691 ± 74.6 μeq/l before starting the LoBAG30 diet to 622 ± 54.8 μeq/l at the end of 5 wk (Fig. 1, top). This was not statistically significant (P > 0.05). The net and total 24-h NEFA area responses were essentially unchanged.

The mean fasting α-amino acid nitrogen concentration was 4.01 ± 0.1 mg/dl before the diet and remained unchanged after 5 wk on the diet. The net and total 24-h area responses were significantly increased after 5 wk on the LoBAG30 diet. Inset: net and total 24-h integrated NEFA area response pre- and post-5 wk on the LoBAG30 diet.

The mean fasting uric acid concentration increased from 4.7 ± 0.4 mg/dl before the diet to 5.5 ± 0.4 mg/dl after 5 wk on the diet (P = 0.002; Fig. 2, top). The net 24-h area was unchanged after 5 wk on the diet (P = 0.9; Fig. 2 top inset). However, the total 24-h area significantly increased from...
The mean fasting plasma urea nitrogen concentration increased from 15 ± 1 mg/dl before the diet to 19 ± 1.8 mg/dl after 5 wk on the diet (P < 0.05; Fig. 2, bottom). The net 24-h area response increased from −4 ± 7.1 to 28 ± 11.7 mg·h·dl⁻¹; however, this was not significant (P = 0.09; Fig. 2, bottom inset). The 24-h total area increased from 346 ± 22 to 479 ± 42 mg·h·dl⁻¹ (P = 0.004; Fig. 2, bottom inset).

The calculated total amount of protein ingested during the 24-h study periods at the beginning and at the end of the 5 wk was compared with the total protein metabolized.

At the beginning of the study, during the first 24 h while subjects were ingesting the control (15% protein) meals, 105 g of protein were calculated to have been ingested, and 88 g were calculated to have been metabolized (84%; Fig. 3). During the last 24 h at the end of the LoBAG₃₀ diet, 214 g of protein were calculated to have been ingested, and 144 g were calculated to have been metabolized (68%). The difference in percent metabolized approached statistical significance (P = 0.064).

Serum GH concentrations at the beginning and end of the study were not significantly different (Table 1). However, the serum IGF-I concentration increased significantly from a mean of 118 ± 23 to 158 ± 51 ng/ml (P = 0.006).

The mean fasting plasma creatinine levels were identical (0.9 mg/dl) before and at the end of the diet period, respectively (Table 1). Both the net (0.3 ± 0.3 vs. 1.7 ± 0.5 mg·h·dl⁻¹) and total 24-h creatinine responses (22.2 ± 1.5 vs. 23.9 ± 1.9 mg·h·dl⁻¹) increased after 5 wk on the diet, but only the total was statistically significant (P = 0.04, data not shown).

Plasma renin activity at the end of 5 wk on the LoBAG₃₀ diet was unchanged (Table 1), as was the mean 24-h urinary aldosterone excretion (Table 2). The mean urinary free cortisol increased by 57% (P = 0.045).

Neither the serum TSH nor the free T₄ were significantly affected by ingestion of the LoBAG₃₀ diet. The total T₃ was significantly decreased (P = 0.041; Table 1). Blood pressure, serum homocysteine, folate, and B₁₂ did not change at the end of 5 wk on the LoBAG₃₀ diet (Table 1). The urinary pH, creatinine clearance, and sodium excretion also did not change (Table 2). The mean microalbumin excretion decreased by 50%; however, this did not reach statistical significance (P = 0.089).

The 24-h urinary urea nitrogen increased, as expected, when the subjects ingested the LoBAG₃₀ diet (P = 0.006). The mean increase was only ~54%, and not twofold as would be expected with a doubling of the protein content of the diet.

**DISCUSSION**

In the first study in this series (unpublished observations), we will report that the LoBAG₃₀ diet resulted in a major
A high-protein, low-carbohydrate diet results in a highly significant decrease in plasma glucose and in %tGHb, as has clearly been demonstrated in this (30% carbohydrate) and in our previous study (4), in which the carbohydrate content was 20% (LoBAG20). The diet is not ketogenic. Plasma lipids were unchanged with the exception of a small but significant decrease in total cholesterol and an approximately 40% decrease in triglycerides.

Because a relative change in carbohydrate and fat in the diet could have other metabolic consequences, we determined a small but significant decrease in %tGHb without a change in serum insulin. Thus a decrease in fasting and postprandial glucose concentration and in the %tGHb without a change in serum insulin. Thus a high-protein, low-carbohydrate diet results in a highly significant decrease in plasma glucose and in %tGHb, as has clearly been demonstrated in this (30% carbohydrate) and in our previous study (4), in which the carbohydrate content was 20% (LoBAG20). The diet is not ketogenic. Plasma lipids were unchanged with the exception of a small but significant decrease in total cholesterol and an approximately 40% decrease in triglycerides.

Because a relative change in carbohydrate and fat in the diet could have other metabolic consequences, we determined a number of other factors in the present study by using the same protocol and compared the results with those obtained with the 20% carbohydrate diet (LoBAG20) (15). Comparisons were made between the results obtained at the beginning and end of the 5-wk intervention period for the LoBAG20 and LoBAG30 diets.

An elevated homocysteine concentration is considered to be an independent risk factor for cardiovascular disease (Smulders et al. 1999). It, as well as determinants of the homocysteine concentration, folate, and B12 were unchanged. This was also true when subjects ingested the LoBAG20 diet.

The mean microalbumin excretion was decreased by 50%, as indicated earlier. Two of the subjects met the criteria for microalbuminuria at the beginning of the study. In one subject, the microalbumin decreased from 185 to 61 mg; in the other subject the initial microalbumin was 41 mg and this remained unchanged. Interestingly, this latter subject continued on the diet for a total of 10 wk. At the end of the 10 wk, the microalbumin excretion was 14 mg. Thus there is at least a suggestion that the LoBAG30 diet may result in an improvement in microalbuminuria.

We obtained evidence in previous studies (14, 15) that increasing the protein content of the diet resulted in an increase in IGF-I concentration. The current data provide additional support. Increasing the protein content of the diet from 15 to 30% resulted in an ~35% increase in IGF-I regardless of whether the carbohydrate content was 40% (14), 20% (Nuttall and Gannon 2005), or 30% as in the present study. Thus the dietary protein-induced increase in IGF-I is independent of the amount of dietary carbohydrate and fat. GH is known to increase in triglycerides.

### Table 1. Hormone and metabolite data

<table>
<thead>
<tr>
<th></th>
<th>30% LoBAG/Pre</th>
<th>30% LoBAG/Post</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Common SI</td>
<td>Common SI</td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>3.8±0.1 g/dl</td>
<td>38±1 g/l</td>
<td>4.3±0.2 g/dl</td>
</tr>
<tr>
<td>Prealbumin</td>
<td>21.3±1.2 mg/dl</td>
<td>21.3±1.2 mg/dl</td>
<td>21.3±1.7 mg/dl</td>
</tr>
<tr>
<td>TSH</td>
<td>1.76±0.35 μU/ml</td>
<td>1.76±0.35 μU/ml</td>
<td>1.43±0.27 μU/ml</td>
</tr>
<tr>
<td>Total T3</td>
<td>97.1±4.99 ng/ml</td>
<td>97.1±4.99 ng/ml</td>
<td>86.3±4.02 ng/ml</td>
</tr>
<tr>
<td>Free T4</td>
<td>1.04±0.07 ng/ml</td>
<td>1.04±0.07 ng/ml</td>
<td>1.03±0.04 ng/ml</td>
</tr>
<tr>
<td>B12</td>
<td>495±9.2 pg/ml</td>
<td>495±9.2 pg/ml</td>
<td>487±116 pg/ml</td>
</tr>
<tr>
<td>Folate</td>
<td>19.1±1.9 ng/ml</td>
<td>19.1±1.9 ng/ml</td>
<td>20.2±1.1 ng/ml</td>
</tr>
<tr>
<td>Homocysteine</td>
<td>104±12.8 μg/dl</td>
<td>7.7±0.9 μg/dl</td>
<td>109±11.8 μg/dl</td>
</tr>
<tr>
<td>Uric acid</td>
<td>4.7±0.4 mg/dl</td>
<td>282±24 μmol/l</td>
<td>5.0±0.4 mg/dl</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.9±0.1 mg/dl</td>
<td>79.6±8.84 μmol/l</td>
<td>0.9±0.1 mg/dl</td>
</tr>
<tr>
<td>Growth hormone</td>
<td>0.2±0.04 ng/ml</td>
<td>0.2±0.04 μg/l</td>
<td>5.5±0.2 ng/ml</td>
</tr>
<tr>
<td>IGF-I</td>
<td>118±22.9 ng/ml</td>
<td>118±22.9 ng/ml</td>
<td>158±50.6 ng/ml</td>
</tr>
<tr>
<td>Renin</td>
<td>0.37±0.8 ng/ml</td>
<td>0.37±0.8 ng/ml</td>
<td>0.78±0.25 ng/ml</td>
</tr>
<tr>
<td>Blood pressure (s)</td>
<td>138±8.8 mmHg</td>
<td>138±8.8 mmHg</td>
<td>132±5 mmHg</td>
</tr>
<tr>
<td>Blood pressure (d)</td>
<td>71±5.5 mmHg</td>
<td>71±5.5 mmHg</td>
<td>70±3 mmHg</td>
</tr>
</tbody>
</table>

Values are means ± SE. Common, common units; SI, Système International; s, systolic; d, diastolic. *Statistically significantly different from low biologically available glucose (LoBAG)/pre data.

### Table 2. Twenty-four-hour urine data

<table>
<thead>
<tr>
<th></th>
<th>30% LoBAG/Pre</th>
<th>30% LoBAG/Post</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Common SI</td>
<td>Common SI</td>
<td></td>
</tr>
<tr>
<td>Volume</td>
<td>3733±479 ml</td>
<td>3733±479 ml</td>
<td>3661±573 ml</td>
</tr>
<tr>
<td>pH</td>
<td>6.2±0.2</td>
<td>6.2±0.2</td>
<td>6.2±0.2</td>
</tr>
<tr>
<td>Sodium</td>
<td>5382±575 mg</td>
<td>234±25 mmol</td>
<td>5980±483 mg</td>
</tr>
<tr>
<td>Potassium</td>
<td>3783±164 mg</td>
<td>97±42 mmol</td>
<td>3705±386 mg</td>
</tr>
<tr>
<td>Calcium</td>
<td>388±73 mg</td>
<td>9.9±19 mmol</td>
<td>262±62 mg</td>
</tr>
<tr>
<td>Glucose</td>
<td>81260±14571 mg</td>
<td>451±81 mmol</td>
<td>3176±1347 mg</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1681±137 mg</td>
<td>14±1.2 mmol</td>
<td>1948±157 mg</td>
</tr>
<tr>
<td>Urea</td>
<td>13±0.6 g</td>
<td>0.2±0.01 mol</td>
<td>20±2 g</td>
</tr>
<tr>
<td>Uric acid</td>
<td>814±48 mg</td>
<td>4.9±0.3 mmol</td>
<td>1009±67 mg</td>
</tr>
<tr>
<td>α-Albumin</td>
<td>38±21 mg</td>
<td>38±21 mg</td>
<td>19±7 mg</td>
</tr>
<tr>
<td>Aldosterone</td>
<td>12.5±1.3 μg</td>
<td>0.03±0.004 μg</td>
<td>11.2±1.5 μg</td>
</tr>
<tr>
<td>Free cortisol</td>
<td>32.0±5.5 μg</td>
<td>0.08±0.01 μmol</td>
<td>50.2±6.6 μg</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>128±13 ml/min</td>
<td>128±13 ml/min</td>
<td>144±17.4 ml/min</td>
</tr>
</tbody>
</table>

Values are means ± SE. *Statistically significantly different from LoBAG/pre data.
stimulate IGF-I production. The fasting GH concentration was not significantly increased in any of the studies. However, the fact that a single fasting GH concentration did not increase does not necessarily mean that an increase in dietary protein did not stimulate GH secretion at some time during a 24-h period. Most of the GH is secreted during sleep (5). This issue is being addressed in current studies in our laboratory.

Some years ago, we (19) reported that, in normal, young subjects, high-protein meals (40% of food energy) resulted in increased postprandial serum cortisol and ACTH concentrations. In the present studies, we measured urinary free cortisol as an index of integrated cortisol secretion. The urinary free cortisol was increased 43% (P < 0.05; Table 2). In our previous study (LoBAG20; Ref. 15), also with a protein content of 30%, the urinary free cortisol was increased 57% (P < 0.05). Thus, regardless of the carbohydrate content of the diet, an increase in protein results in a statistically significant increase in urinary free cortisol excretion.

It has been reported by others that protein stimulates an increase in renin and aldosterone (2). However, in our subjects fed the LoBAG20 diet, we did not observe an increase in either. This was also true in the present LoBAG30 study. Thus, in people with type 2 diabetes it is unlikely that a high-protein diet stimulates renin and aldosterone production.

Serum TSH and free T3 remained unchanged after the LoBAG30 diet. This was also the case in our previous LoBAG20 diet study. However, the total T3 decreased significantly from a mean of 97.1 to 85.9 ng/dl after 5 wk on the diet (P = 0.041). After 5 wk on the LoBAG20 diet, the total T3 decreased from a mean of 85.9 ng/dl to 81.9 ng/dl. Although that decrease was small, it was statistically significantly different (P < 0.01). The decreases in total T3 are what might be expected with a decreased carbohydrate content of the diet (3, 9).

The calculated protein intake was nearly identical in the two studies (LoBAG30 214 g; LoBAG20 212 g). The calculated protein balance also was positive and identical in both studies (70 ± 5.6 and 70 ± 17.3 g/day for the previous and present study, respectively).

The mean urine urea nitrogen excreted was 12.9 g before and 20.4 g after 5 wk on the LoBAG30 diet and was essentially identical to that in our previous study (12.8 vs. 20.6 g, respectively) (15).

Glucagon has been reported to stimulate urea synthesis in human subjects independently of amino acid availability (6, 8). The total integrated glucagon area was increased modestly in both the LoBAG30 and LoBAG20 diets. Thus, if glucagon is playing a role in the regulation of urea synthesis, the effect was similar in both studies.

A positive nitrogen balance could be due to an increase in protein synthesis, a decrease in protein degradation, or a combination of the two. It also could be due to a greater loss of nitrogen in the stool than that calculated or to an increased loss as urine ammonia, or from the skin, or from bodily secretions, or a combination of these.

Nevertheless, the large calculated positive nitrogen balance (Fig. 3) is a problem. Clearly, it is greater than could be explained by an increase in lean body mass. This is a problem noted in other studies and remains unexplained even when stool, skin, and secretion losses have been included in the analysis (17).

An elevation in amino acids, particularly leucine, is known to stimulate protein synthesis (13). Branched-chain amino acids also are known to inhibit protein degradation (11). Although we did not determine individual amino acids after 5 wk on either the LoBAG30 or the LoBAG20 diet, the net 24-h integrated postprandial plasma amino acid area was markedly increased in both studies without an increase in insulin. This suggests that branched-chain amino acids were also increased in both studies. Overall, the increased amino acid concentration should have contributed to the increased positive nitrogen balance.

Interestingly, even though the net amino acid area responses were two- to threefold greater when the control (15% protein), the amino acid concentration still returned back to the fasting value at 24 h; i.e., an accelerated removal rate was present. Thus the removal mechanism was not saturable at these dietary protein amounts.

IGF-I has been reported to stimulate protein synthesis. IGF-I increased by ~35% in all studies in which dietary protein was increased from 15 to 30% (14, 15). Thus IGF-I could have contributed to a positive nitrogen balance (12).

Insulin apparently has little effect on protein synthesis or degradation in the splanchnic bed (13). However, insulin is known to inhibit proteolysis in skeletal muscle, although the mechanism is less well understood. A role for ATP-dependent ubiquitin-proteasome proteolysis has been suggested (18). Increased mRNAs for ubiquitin and proteasome subunits have been reported in insulin-deficient rats (10, 12). Insulin may also have a direct inhibitory effect on proteasomal peptidase activity (see Ref. 12 for review).

The total integrated insulin area did not change with the LoBAG30 diet (483 before and 470 μU·h·ml⁻¹ after 5 wk). It decreased significantly with the LoBAG20 diet (789 before and 589 μU·h·ml⁻¹ after 5 wk, P < 0.05). The nearly identical positive protein balance in the two studies, even though the insulin concentrations were different, suggests that insulin is not playing a major role mechanistically.

As to potential limitations of the study, we note the following. First, only males were studied. Second, as indicated in the first paper in the series (unpublished observations), the study was powered to show a change in %tGHb. Because we intended to perform multiple analyses, the calculated n required to show a significant change in %tGHb was increased approximately threelfold. However, a power calculation was not done for each of the elements measured. Therefore, it is possible that a type II error could be present (i.e., failure to identify differences) for the data presented other than for the %tGHb results.

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GRANTS

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REFERENCES


