Effect of 24 Hours of Starvation on Plasma Glucose and Insulin Concentrations in Subjects With Untreated Non–Insulin-Dependent Diabetes Mellitus

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Adherence to a low-calorie diet often results in a decrease in blood glucose concentration in persons with non–insulin-dependent diabetes mellitus (NIDDM). Whether this is due to the resultant weight loss or to a decrease in caloric intake has been uncertain. We have obtained data previously that indicated a very short-term reduction in caloric intake (5 hours) resulted in a significant decrease in plasma glucose concentration in subjects with NIDDM. The purpose of the present study was to determine if a further decrease in glucose would occur if the fast was extended from 5 to 24 hours. Seven male subjects with untreated NIDDM were studied after an 11-hour overnight fast. For the subsequent 24-hour period, subjects were given only water. Blood was obtained for glucose, insulin, C-peptide, triglycerides, nonesterified fatty acids (NEFA) alpha-amino acid nitrogen, urea nitrogen, and glucagon at hourly intervals for 24 hours beginning at 8 AM. The amount of glycogen degraded was calculated based on the potassium balance. Plasma glucose decreased from 158 mg/dL at 8 AM to a nadir of 104 mg/dL at 7 PM. It then increased by 30 mg/dL. Corresponding changes occurred in insulin and C-peptide. Serum glucagon remained unchanged. Serum alpha-amino acid nitrogen and urea nitrogen decreased. Triglycerides and NEFA increased. The calculated glycogen utilized over this period was approximately 167 g. This would provide approximately 700 kcal energy. The elevated blood glucose concentration in mild to moderately severe untreated NIDDM subjects was normalized following short-term fasting. Plasma insulin concentrations also decreased to within normal limits. These decreases were highly significant. Glycogenolysis is an important source of fuel during this period.

WE HAVE BEEN interested in glucose and insulin responses to test meals in people with non–insulin-dependent diabetes mellitus (NIDDM) fasted overnight. To compare results from one test meal with another, a method of quantifying the responses is necessary. Originally, we used the fasting value as a baseline and then calculated the net area above and below the fasting value. However, we observed that when subjects were given water only, plasma glucose concentration decreased, on average, 24 mg/dL during the 5-hour period of the study (a 17% decrease). In contrast, in normal subjects, plasma glucose decreased by only 5 mg/dL, or 6%, during a similar period. The data indicated that a very short-term reduction in caloric intake has a significant effect on plasma glucose concentration in subjects with NIDDM. The purpose of the present study was to determine if a further decrease in glucose concentration would occur following a more extended period of starvation in subjects with NIDDM. To our knowledge, this is the first report of the relationship between a 24-hour period of starvation and the changes in plasma glucose, insulin, and C-peptide concentrations in subjects with untreated NIDDM. Parts of these data have been published previously in abstract form.[1,2]

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SUBJECTS AND METHODS

Seven male subjects with mild untreated NIDDM were studied in the clinical research center. All subjects met National Diabetes Data Group criteria for the diagnosis of type II diabetes mellitus.[3] Thyroid, renal, and liver function tests were normal (data not shown). Patient characteristics are listed in Table 1. Written informed consent was obtained from all subjects, and the study was approved by the Department of Veterans Affairs Medical Center and the University of Minnesota Committee on Human Subjects. All subjects had ingested a diet containing at least 200 g carbohydrate per day with adequate food energy for 3 days before testing. None of the subjects were treated with oral hypoglycemic agents or insulin before the study.

Each subject was admitted to the Clinical Research Center on the evening prior to the study. An indwelling catheter was inserted into an antecubital vein and kept patent with intravenous saline. Following an overnight fast of 11 hours, subjects ingested 500 mL water at 8 AM. During the subsequent 24-hour period, they ingested only water ad libitum.

Blood was obtained at 7:30, 7:45, 8:00, 8:30, 9:00, 10:00, and 11:00 AM, 12:00 noon, 12:30, 1:00, 2:00, 3:00, 4:00, 5:00, 5:50, 6:00, 7:00, 8:00, 8:30, and 9:00 PM, and then hourly until 7:00 AM the following morning. Plasma or serum was assayed for glucose, insulin, C-peptide, urea nitrogen, triglyceride, non-esterified fatty acids (NEFA), alpha amino nitrogen, and glucagon. Urine was collected during four intervals over the 24-hour period, from 8:00 AM to 12:00 noon, 12:00 noon to 5:00 PM, 5:00 to 9:00 PM, and 9:00 PM to 8 AM. Urine was assayed for sodium, potassium, uric acid, glucose, urea nitrogen, and creatinine.

Plasma glucose concentration was determined by a glucose oxidase method using a Beckman glucose analyzer with an O_2 electrode (Beckman Instruments, Fullerton, CA). Serum immunoreactive insulin was measured using a standard double-antibody radioimmunoassay (RIA) method using kits produced by Incstar (Stillwater, MN). Glucagon

Table 1. Patient Characteristics

Patient No.	Age (yr)	Ht (m)	Wt (kg)	% IBW	BMI	Diabetes Duration	Glycosylated Hb (%)	Concomitant Disease
1	70	1.79	97	131	30.3	2 yr	6.7	Hypertension
2	57	1.75	102	146	33.6	3 yr	11.3	None
3	62	1.70	86	131	29.9	4 yr	11.4	CHD
4	67	1.83	105	138	31.4	1 mo	7.6	Degenerative joint disease
5	56	1.80	104	141	32.4	1 mo	11.3	Depressive disorder
6	75	1.78	89	124	28.2	13 yr	7.3	Hypertension, interstitial lung disease, chronic CHD
7	78	1.71	87	132	29.8	1 mo	6.5	CHD, pseudogout
x	66	1.77	96	135	30.8	18.5 yr	8.9	
SE	3	0.02	3.2	2.7	0.66	8.4 yr	0.9	

NOTE. % IBW determined using 1959 Metropolitan Life Insurance tables. Normal glycosylated hemoglobin = 4.2% to 6.2%.

Abbreviations: HT, height; WT, weight; IBW, ideal body weight; BMI, body mass index; Hb, hemoglobin; CHD, coronary heart disease.

was determined by RIA using 30K antiserum purchased from Health Science Center (Dallas, TX). C-peptide level was measured using a double-antibody RIA method with kits produced by Incstar. Alpha amino nitrogen was determined by the method of Goodwin.[4] Serum NEFA were determined enzymatically, using a kit purchased from Wako Chemicals (Dallas, TX). Triglycerides, urea nitrogen, sodium, potassium, and creatinine were determined using an EktaChem Analyzer (Eastman Kodak, Rochester, NY).

Statistics were determined by ANOVA, using the Statview 512+ program (Brain Power, Calabasas, CA) for the Macintosh computer (Apple Computer, Cupertino, CA). A P value less than .05 was the criterion for significance. Data are presented as the mean ± SEM.

RESULTS

Glucose concentration decreased from a mean of 158 mg/dL at 8:00 AM to a nadir of 104 mg/dL at 7:00 PM, ie, 11 hours later (Fig 1). At midnight, or 16 hours later, it was still 106 mg/dL. The concentration then began to increase until the final measurement at 7:00 the following morning, at which time the concentration was 130 mg/dL. Plasma insulin decreased from a mean of 29 μU/mL to a nadir of 14 μU/mL at 4:00 AM (20 hours later). Thus, insulin decreased more slowly than glucose. It then increased modestly. C-peptide decreased from approximately 1 pmol/mL at 8:00 AM to a nadir of 0.65 pmol/mL at 1:00 PM. It then increased slightly. Overall, the C-peptide curve paralleled that of insulin. Glucagon concentration remained stable and unchanged over the 24-hour period (Fig 1).

The alpha amino nitrogen concentration decreased slightly between 8:30 AM and 12:00 noon. It then remained stable for 12 hours. It increased slightly after 24 hours and remained stable from 1:00 until 7:00 AM (Fig 2). Plasma urea nitrogen decreased from 19 mg/dL to a nadir of 14 mg/dL at 8:00 PM. It was then remarkably stable. There was little change in the mean NEFA concentration for 5 hours

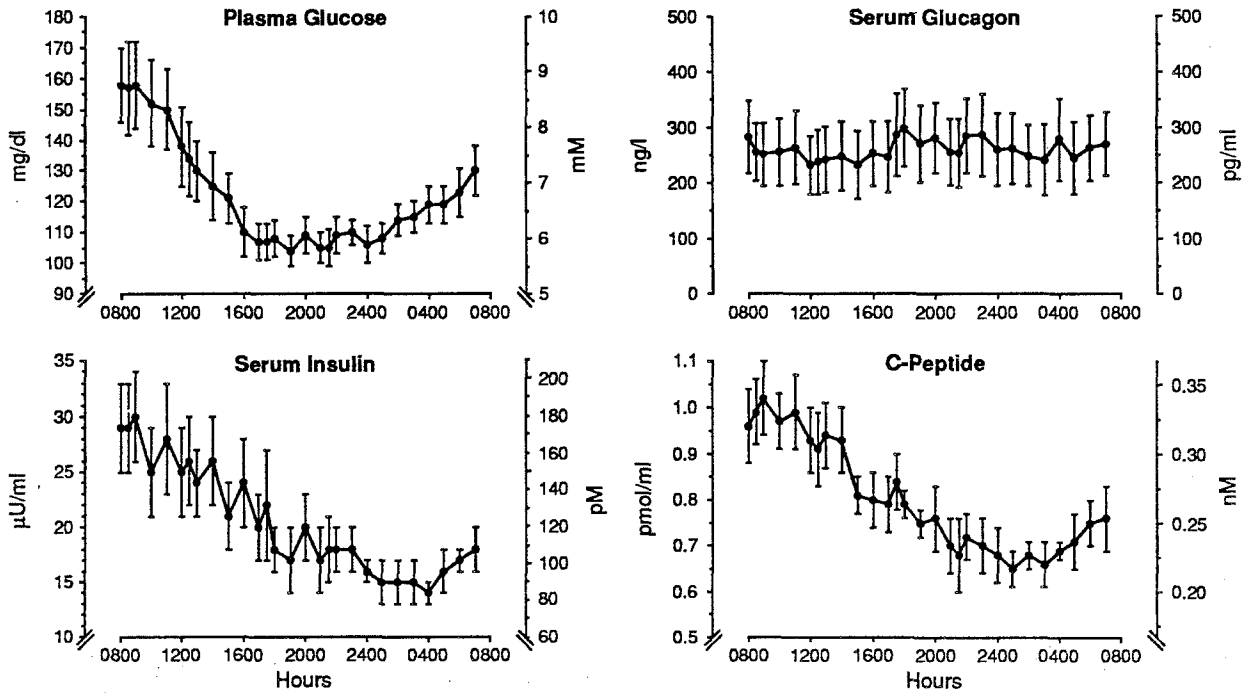

Fig 1. Plasma glucose, serum insulin, glucagon, and C-peptide response to starvation in 7 males with untreated NIDDM. The decrease in plasma glucose became significant at 1:00 PM and remained so for the duration of the experiment. Decreases in serum insulin and C-peptide became significant at 5:00 and 6:00 PM, respectively, and remained so for the duration of the experiment.

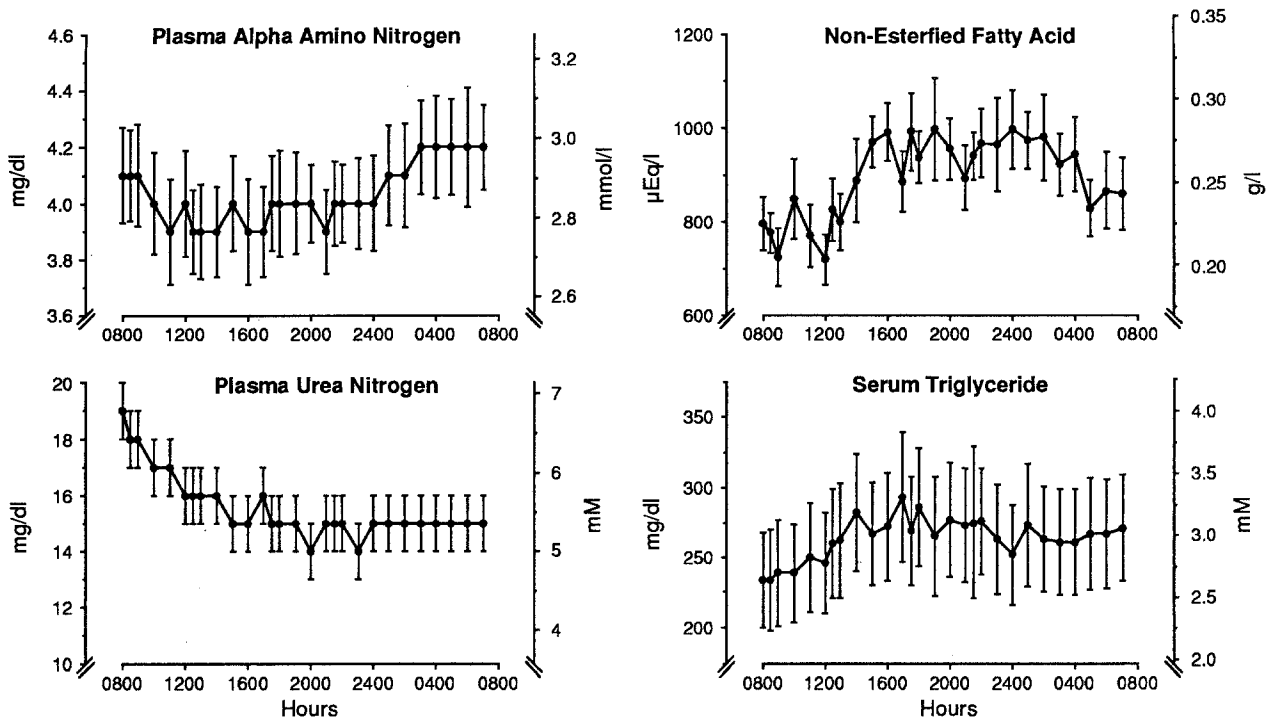

Fig 2. Plasma alpha amino nitrogen, urea nitrogen, NEFA, and triglyceride response to starvation in 7 males with untreated NIDDM. The decrease in plasma urea nitrogen became significant at 1:00 PM and remained so for the duration of the experiment. The increase in serum NEFA became significant at 3:00 PM and remained so until 4:00 AM.

(Fig 2). It then increased from approximately 800 μEq/L to approximately 950 μEq/L at 3:00 AM. The concentration then remained essentially stable until 2:00 PM. After 2:00 AM, NEFA decreased. The mean fasting triglyceride concentration at 8:00 AM was 234 ± 34 mg/dL. Individual values varied between 100 and 385 mg/dL. The mean was increased to approximately 270 mg/dL at 4:00 PM and remained stable thereafter. An increase occurred in all subjects except for the one whose initial triglyceride concentration was only 100 mg/dL.

The mean rate of urine creatinine excretion was 1.46 g/24 h. The mean total urine glucose excretion was less than 0.5 g/h. Urine sodium, potassium, urea nitrogen, and uric acid all decreased sequentially from the first collection (8:00 AM to 12:00 noon) to the last collection (9:00 PM to 8:00 AM; Table 2).

DISCUSSION

It has been known for many years that intermittent fasting, or a hypocaloric diet, decreases blood glucose in subjects with NIDDM.[5] The glucose-lowering effect of a hypocaloric diet clearly was demonstrated by Newburgh in 1942.[6] However, the relative contribution of a reduction in food energy versus a loss of weight in decreasing the circulating glucose concentration has not been clearly defined. Most commonly, when the patient returns to a weight-maintenance diet, the blood glucose concentration increases,[7-9] suggesting that the major factor is the reduction in food energy (particularly carbohydrates) rather than the loss of weight, as pointed out by Oakley et al.[10]

Few studies have determined the change in plasma glucose concentration in people with NIDDM following a short period of food energy deprivation, ie, when weight loss would be minimal. In most reports, the change in plasma glucose concentration over a 24-hour period was not the major focus of the study.

As early as 1924, MacLean[11] reported a decrease in glucose concentration from 158 to 88 mg/dL (44%) in one patient after a 2-day fast. Decades later, Faiman and Moorehouse[12] starved five subjects (three female and two

Table 2. Urinary Excretion of Metabolites and Electrolytes

	Creatinine		Glucose		Na		K		Urea N		Uric Acid	
Hours	mg/spec	mg/h	mg/spec	mg/h	m-atoms/spec	mmol/h	mm-atoms/spec	mmol/h	mg/spec	mg/h	mg/spec	mg/h
8:00 AM-12:00 noon	267 ± 26	67	222 ± 103	56	79 ± 17	19.8	42 ± 7	9.5	1,836 ± 192	459	26 ± 6	6.6
12:00 noon-5:00 PM	323 ± 19	65	87 ± 42	17	55 ± 15	10.9	31 ± 10	4.6	2,140 ± 104	428	21 ± 8	4.1
5:00 PM-9:00 PM	231 ± 10	58	38 ± 22	10	40 ± 7	10.0	29 ± 10	4.8	1,387 ± 102	347	20 ± 8	5.1
9:00 PM-8:00 AM	643 ± 50	58	88 ± 46	8	43 ± 8	3.9	41 ± 16	2.3	3,355 ± 257	305	19 ± 2	1.7
Total U/24 h	1,464		434		217		105		8,718		86	

Abbreviation: spec, specimen.

male) with untreated NIDDM for 3 days following a 14-hour overnight fast. Blood glucose decreased from a mean of approximately 190 to about 130 mg/dL (32%) after 24 hours. At the end of 3 days, the glucose concentration had decreased to approximately 115 mg/dL.

Jackson et al[13] starved seven obese female subjects with untreated NIDDM for 14 days.[13] The mean fasting plasma glucose concentration decreased from approximately 210 to 160 mg/dL (24%) following 1 day of starvation. After 14 days of starvation, the mean glucose concentration had decreased to approximately 80 mg/dL (62%).

Kalkhoff and Kim[14] starved six obese female subjects with NIDDM for 5 days. The mean glucose concentration decreased from 150 to 90 mg/dL (40%) after 5 days of total starvation.

Subsequently, Glauber et al[15] starved 14 subjects (13 males and one female) with untreated NIDDM, who were already fasted overnight, for an additional 10.5 hours. The mean plasma glucose concentration decreased from 234 to 152 mg/dL (33%).

Belfiore et al[16] starved seven obese subjects with NIDDM for 72 hours. The mean fasting glucose concentration decreased from 195 to 127 mg/dL (35%). Also, Féry et al[17] starved 21 obese subjects (10 female and 11 male) with NIDDM for 3 to 6 days. The fasting glucose concentration decreased from approximately 150 mg/dL to about 70 mg/dL (53%).

Clore et al[18] starved 19 obese subjects with NIDDM for 3 days. The mean fasting glucose concentration decreased from 265 mg/dL following an overnight fast to 185 mg/dL on the third day (30% decrease). Finally, we reported a decrease in fasting glucose concentration from 127 to 95 mg/dL (25%) during the 5 additional hours of starvation, following a 14-hour overnight fast in 10 male subjects with untreated NIDDM.[19] Subsequently, in a total of 35 male subjects with untreated NIDDM, glucose concentration decreased from 145 to 120 mg/dL (17%).[19-24] Groop et al[25] also reported similar data in seven subjects (four female and three male) with NIDDM starved for an additional 6 hours following an overnight fast. The mean glucose concentration decreased from 157 to 121 mg/dL (23%).

These studies are not directly comparable with regard to characteristics of patients, length of starvation, severity of diabetes, treatment of the disease, etc. However, from the data abstracted, it is clear that short-term starvation, ie, 6 to 72 hours following an overnight fast, resulted in a considerable decrease in glucose concentration. Interestingly, the decrement was generally in the range of 20% to 40% regardless of the initial fasting glucose concentration. Thus, in general, the higher the initial fasting glucose, the less likely the blood glucose will be normalized with a short period of starvation.

The short-term effects of a decreased–food-energy diet on the overnight fasting glucose concentration has only been determined in a few studies. Kelley et al[26] determined the glucose response to 7 days of an 800-kcal diet in seven obese subjects (five females and two males) with NIDDM. Plasma glucose decreased from 223 to 171 mg/dL. The subjects lost 2.2 kg during this time. Henry et al[7] studied 30 obese subjects (27 females and three males) with NIDDM. The subjects were placed on a 330-kcal diet for 30 to 40 days. The majority of the decrease in fasting plasma glucose occurred by 10 days, whereas the weight loss was continuous during the entire experimental period. Following 3 days on the 330-kcal/d diet, fasting plasma glucose decreased from 297 to approximately 230 mg/dL (23%). This was associated with a weight loss of less than 2 kg. After 10 days, at which time the subjects had lost 4.5 kg, the glucose concentration had decreased to 158 mg/dL (46%). Savage et al[27] studied one morbidly obese male with NIDDM. The fasting glucose concentration decreased from 220 mg/dL to "normal levels in 1 week" on a 500-cal diet.

In the present study, glucose concentration decreased from a mean of 158 to 104 mg/dL (34% decrease) 20 hours after the last meal. Associated with the decrease in glucose concentration were decreases in both insulin and C-peptide concentrations. The 52% decrease in insulin concentration we observed is greater than the 17%[12] and 24%[13] decreases following 1 day of starvation reported by others. It is similar to the 33%[12] and 44%[16] decreases reported following 3 days of starvation and the 50% decrease following 3 to 6 days of starvation.[17] C-peptide concentrations were not reported in these studies.

The nadir in insulin and C-peptide concentrations was delayed by 8 hours compared with the glucose concentration in the present study. A temporal dissociation between the decrease in glucose and insulin also was apparent in the data reported by Greenfield et al,[28] who starved 12 subjects with NIDDM for 10 days. The mean plasma glucose concentration reached a nadir at day six, whereas the mean plasma insulin concentration reached a nadir at day ten.

In the present study, plasma glucose gradually increased by 25% between 1:00 and 7:00 AM. This presumably was due to the expected nocturnal increase in growth hormone secretion and an induced insulin resistance.[29] However, growth hormone levels were not measured. It is unlikely that this increase was due to cortisol, since the peak in cortisol generally does not occur until 4:00 to 6:00 AM.[30] The increase in glucose concentration was not due to a decrease in insulin concentration or to an increase in glucagon concentration. Insulin concentration increased modestly, and glucagon concentration was stable. NEFA increased during the initial period of starvation, as expected.[7] However, NEFA then decreased during the period from 4:00 to 7:00 AM. This correlated with the increases in glucose and insulin concentrations. Thus, there was a reciprocal relationship between NEFA and glucose and insulin concentrations, suggesting a reciprocal relationship between oxidation of glucose and of free fatty acids.[31] Free fatty acids generally are oxidized in relation to their concentration. Therefore, presumably, there was an increased glucose production by the liver and/or the kidney between 4:00 and 7:00 AM.

Previous studies from our laboratory and others have demonstrated that digestion of ingested protein and metabolism of the resulting amino acids is a slow process: approximately 8 hours are required.[21,32-36] Metabolism of the amino acids results in an increase in urea distributed in total body

water. Excretion of this additional urea, ie, clearance from the total body water pool, also requires several hours. Thus, the decrease in plasma urea nitrogen noted is likely to have been due to the slow removal of urea nitrogen produced from previously ingested dietary protein. The last meal was ingested at 5:00 PM by our subjects. Plasma urea nitrogen reached a steady state at approximately 3:00 PM the following day. Thus, 22 hours were required to clear the urea produced from the meal and to produce a steady-state plasma urea concentration.

During the 24 hours of fasting, 8.7 g urea nitrogen were excreted in the urine. Correcting for the urea excreted before the plasma concentration was in a steady state, a net of 6.4 g urea nitrogen were lost during the fast. Since approximately 16% of animal protein is nitrogen, this represents 40 g protein catabolized. Lean body mass is approximately 80% water.[36] This then would represent a loss of 200 g lean body mass.

The total potassium excreted during 24 hours was 105 milliatoms (m-atoms) (Table 2). Since intracellular water contains approximately 150 m-atoms potassium/L,[37] 24 m-atoms potassium were lost in the urine due to the 160 mL water excreted after catabolism of 40 g protein.

Net urine potassium not due to protein catabolism was then 81 m-atoms. Potassium also can be lost due to extracellular fluid volume loss. This was estimated to be 6 m-atoms potassium, based on the urinary sodium loss and a concentration of 145 m-atoms sodium/L extracellular fluid.[37] The resulting 75 m-atoms potassium excreted then is not due to a loss of lean body mass or to a decrease in extracellular volume. It has been reported[38] and we have confirmed that 0.45 m-atoms potassium are lost per gram of glycogen degraded. The remaining 75 m-atoms potassium excreted would represent 167 g glycogen degraded during the fast. This amount of glycogen would provide approximately 700 kcal. The glycogen would contribute 188 g glucose added to the circulating glucose pool, if one accounts for the water lost during storage of glucose as glycogen. If this was released at a constant rate during the 24 hours of starvation, it would result in an addition of 1.36 mg glucose/kg body weight/min.

Hepatic glucose production results from both glycogenolysis and gluconeogenesis. The glucose production rate in postabsorptive subjects with various glucose concentrations has been reported.[38] There was a linear relationship between glucose concentration and glucose production rate, although there was considerable variability around the mean. At a glucose concentration of 158 mg/dL glucose production was approximately 2.3 mg/kg/min. At a glucose concentration of 104 mg/dL, it was approximately 1.8 mg/kg/min. These glucose values are the highest and lowest mean concentrations noted in the present study. Using these values, glycogen degradation could account for approximately 50% to 75% of the total production. This is similar to tracer data reported previously.[39]

In future studies, it will be interesting to directly determine the glucose production over a defined period and correlate this with the calculated amount of glycogen degraded in the same individuals during short-term starvation.

It is of interest that glucagon concentrations were not increased with fasting in these subjects. In normal subjects, glucagon has been reported both to increase[40] and to decrease[41,42] by 24 hours of starvation. In obese subjects, glucagon concentration was increased after 3 days of starvation. This was the first time point at which it was determined.[43] We are not aware of glucagon data in subjects with NIDDM fasted for 24 hours.

We were surprised to find an increase rather than a decrease in triglyceride concentration during the fast—the reason for this is unknown. We have been unable to find triglyceride data in short-term fasted subjects with NIDDM. However, an increased turnover has been described in normal subjects following a 3-day fast.[44]

In conclusion, our data clearly indicate that starvation has a rapid and profound effect on blood glucose concentration in subjects with NIDDM. This is associated with minimal weight loss. The calculated degradation of glycogen could account for at least 50% of glucose produced during the 24 hours of starvation.

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