Differential Effects of Fasting and Dehydration in the Pathogenesis of Diabetic Ketoacidosis

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Glycemia varies widely in patients with diabetic ketoacidosis (DKA), with plasma glucose concentrations between 10 to 50 mmol/L commonly encountered. The mechanism of this glycemic variability is uncertain. Our study examined the differential effects of fasting and dehydration on hyperglycemia induced by withdrawal of insulin in type 1 diabetes. To evaluate the respective roles of dehydration and fasting in the pathogenesis of DKA, 25 subjects with type 1 diabetes were studied during 5 hours of insulin withdrawal before (control) and after either 32 hours of fasting (n = 10) or dehydration of 4.1% ± 2.0% of baseline body weight (n = 15). Samples were obtained every 30 minutes during insulin withdrawal for substrate and counterregulatory hormone levels and rates of glucose production and disposal. Fasting resulted in reduced plasma glucose concentrations compared with the control study, while dehydration resulted in increased plasma glucose concentrations compared with the control study ($P < .001$). Glucose production and disposal were decreased during the fasting study and increased during the dehydration study compared with the control study. Glucagon concentrations and rates of development of ketosis and metabolic acidosis were increased during both fasting and dehydration compared with control. These data suggest that fasting and dehydration have differential effects on glycemia during insulin deficiency, with dehydration favoring the development of hyperglycemia and fasting resulting in reduced glucose concentrations. This finding is probably attributable to the differing effect of these conditions on endogenous glucose production, as well as to differences in substrate availability and counterregulatory hormone concentrations. The severity of pre-existing fasting and dehydration likely explains much of the variability in plasma glucose concentrations observed in DKA.

TYPE 1 DIABETIC PATIENTS presenting with diabetic ketoacidosis (DKA) display wide variation in the degree of hyperglycemia present at the time of diagnosis. The severity of presenting hyperglycemia correlates poorly with the severity of DKA and is an inaccurate indicator of the subsequent response to therapy.[1] Although the mechanism of glycemic variability in DKA is poorly understood, it most likely relates to the underlying cause of DKA in affected individuals. Known precipitating factors of DKA include either absolute or relative insulin deficiency in combination with fasting, infection, dehydration, alcohol intoxication, and/or stress.[2] These factors are frequently present in combination, making clarification of the hyperglycemic effect of any single precipitating factor difficult to assess.

We have previously shown that short-term fasting predisposes insulin-deficient patients with type 1 diabetes to the development of a relatively "euglycemic" ketoacidosis.[3] We subsequently hypothesized that pre-existent dehydration would have an opposite effect on glycemia during periods of insulin deficiency, resulting in hyperglycemia that is more severe than that observed in the fully hydrated state. Such enhanced hyperglycemia would presumably result from simple hemoconcentration of blood glucose, decreased renal glucose clearance, and possibly from enhanced counterregulatory hormone secretion in the dehydrated state. The purpose of this report is to compare the hyperglycemic effect of two common clinical conditions that occur in the setting of DKA: fasting and dehydration. Our results suggest that much of the variability in glycemia observed in patients with DKA can be explained by these two predisposing factors.

MATERIALS AND METHODS

Study Subjects

Twenty-five subjects with type 1 diabetes of at least 2 years duration were studied. Ten subjects were studied during 5 hours of insulin withdrawal before and after a 32-hour fast. The full substrate and hormonal response occurring in these 10 patients has been previously reported.[3] The remaining 15 subjects were studied under an identical protocol before and after dehydration of ≥3% of baseline body weight. The protocol was not randomized. Rather, the fasting arm of the protocol was completed first and the dehydration arm of the protocol was completed next using identical study inclusion and exclusion criteria. None of the subjects had advanced secondary complications of diabetes. All subjects were confirmed to be C-peptide negative on the basis of a Sustacal stimulation test, as previously described (stimulated C-peptide <0.17 nmol/L in all volunteers).[4] Baseline and descriptive characteristics of the study participants are summarized in Table 1.

Study Protocol

The protocol was approved by the University of New Mexico Human Research Review Committee, and all patients gave informed consent before enrollment. Briefly, all patients were admitted in the late afternoon to the University of New Mexico Clinical Research Center for a 48-hour hospital stay, at which time venous access was established in each arm. Venous access in one arm was used for administration of intravenous (IV) insulin and isotopic tracer, and venous catheterization of the contralateral forearm was used for repeated blood sampling. Line patency was maintained with a slow continuous infusion of heparinized 0.45% NaCl.

After establishing IV access, all patients received a continuous IV

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Table 1. Baseline and Descriptive Characteristics of Study Participants

Characteristic	Control Study (n = 25)	Fasting Study (n = 10)	Dehydration Study (n = 15)
Age (yr)	33 ± 8	38 ± 9	30 ± 6.5
Gender	13 M, 12 F	3 M, 7 F	10 M, 5 F
Duration of diabetes (yr)	17 ± 11	22 ± 13	14 ± 9
Body mass index (kg/m^2)	24.1 ± 2.9	24.8 ± 2.8	23.7 ± 3.0
Complications			
Eyes	3	1	2
Kidneys	5	3	2
Peripheral vascular	1	0	1
Neuropathy	2	1	1

NOTE. $P > .05$ for all comparisons.

infusion of regular human insulin mixed in heparinized 0.45% NaCl to a concentration of 0.1 IU/mL to establish and maintain euglycemia overnight, defined as a capillary blood glucose (CBG) level between 3.9 to 6.6 mmol/L (70 to 120 mg/dL). Patients were instructed to withhold all intermediate-acting insulin over the 24 hours before admission and all long-acting insulin over the week before admission. CBG was monitored hourly for the duration of the study with a One-Touch II (LifeScan, Milpitas, CA) glucose meter performed in duplicate, and the rate of insulin infusion was adjusted to maintain euglycemia during insulin infusion.

At midnight on the first day of hospitalization, all subjects were fed a standard 10 kcal/kg meal in accordance with the recommendations of the American Diabetes Association (ADA), and a small IV bolus of regular human insulin was administered to maintain glycemia. Food was subsequently withheld until completion of the first 5-hour insulin withdrawal study, which was performed at 8:00 AM the following morning (8 hours postprandial, the control study). All patients were allowed free access to water and noncaloric beverages during this arm of the study. On completion of the control study, the IV insulin infusion was resumed and normoglycemia was re-established.

For the 10 patients in the fasting group, an identical insulin withdrawal study was performed at 8:00 AM on the third hospital day after an additional 24 hours of fasting (32 hours postprandial, the fasting study). Fasting patients were allowed free access to water and noncaloric beverages throughout the study and were assumed to be fully hydrated.

After completion of the control study, the 15 subjects assigned to the dehydration arm of the protocol began a strict fluid restriction of 750 mL per 24 hours, and each received 5 mg of metolazone administered orally (Fisons Pharmaceuticals, Rochester, NY), as well as 40 mg of furosemide administered intravenously (Hoechst-Roussel Pharmaceuticals, Somerville, NJ) to induce a brisk diuresis. Patients enrolled in the dehydration arm of the protocol received a 10 kcal/kg ADA meal each day at 1:00 PM, 6:00 PM, and midnight. The goal of the dehydration protocol was to dehydrate patients of ≥3% of their baseline body weight. Nine of 15 patients received a second dose of 40 to 80 mg of IV furosemide at approximately midnight if the initial diuresis was inadequate. All patients received 40 mEq of oral potassium chloride (Abbott Laboratories, Birmingham, AL) with each dose of IV furosemide to prevent the development of hypokalemia. A second 5-hour insulin withdrawal study was performed at 8:00 AM the following morning (8 hours postprandial, the dehydration study). Patients were weighed every 6 hours on the same scale in hospital attire. Total body water was determined with bioelectrical impedance (RJL Systems, Clinton Township, MI) on admission and at 7:00 AM each morning during both the control and dehydration studies. On completion of all insulin withdrawal studies, euglycemia was re-established, and all patients were discharged home. Caffeinated beverages were not allowed during either the fasting or the dehydration studies.

Blood was sampled at −10 and 0 minutes for all variables, and these results were averaged to serve as the baseline. Blood was subsequently sampled every 30 minutes during each 5-hour insulin withdrawal study for determination of plasma glucose, glucose turnover, total ketones (acetoacetate plus β-hydroxybutyrate), nonesterified fatty acids (NEFA), polyethylene glycol (PEG)-treated (free) insulin, electrolytes, cortisol, glucagon, and growth hormone (GH). Samples were obtained hourly for plasma epinephrine.

Sample Analysis

Rates of glucose turnover were determined using primed continuous infusions of deuterated glucose during insulin withdrawal as previously described.[3] Briefly, D-2-glucose (Merck Isotopes, Montreal, Quebec, Canada) was infused at an average rate of 0.81 μmol/kg/min after a mean priming dose of 23.3 μmol/kg. Isotopic infusions were begun 2 hours before insulin withdrawal to assure attainment of isotopic equilibrium. Isotopic enrichment of glucose was determined using gas chromatography, mass spectrometry methods as previously described.[3,5] Rates of appearance (R_a) and disposal (R_d) were calculated using nonsteady state assumptions with the Steele equation.[5,6]

Plasma glucose concentrations during insulin withdrawal were determined using a Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, CA). Plasma acetoacetate and β-hydroxybutyrate concentrations were determined spectroscopically on the Cobas-Bio (Roche Analytical Instruments, Nutley, NJ) using the methods of Mellanby and Williamson.[7] Plasma NEFA levels were assayed enzymatically using the Wako Kit procedure (Wako Chemical, Dallas, TX) adapted to the Cobas-Bio. Serum-free insulin levels were determined after extraction with 25% polyethylene glycol using the Coat-a-Count radioimmunoassay (RIA) kit (Diagnostic Products, Los Angeles, CA).[8] C-peptide concentrations were determined by RIA (INCSTAR, Steelwater, MN), as were serum concentrations of cortisol and GH (Coat-a-Count RIA, Diagnostic Products). Serum glucagon levels were determined by the Washington University Core Laboratory (St Louis, MO) using radioimmunoassay.[9] Plasma epinephrine concentrations were determined radioenzymatically at the Washington University Core Laboratory, as previously described.[10]

Statistical Analysis

For clarity of presentation, data for all variables were reduced to 4 summary parameters for subsequent statistical analysis. These summary parameters are: (1) baseline concentration obtained before starting insulin withdrawal (mean of the −10 and 0 minute samples); (2) peak concentration during the 5-hour study; (3) nadir concentration during the 5-hour study; and (4) area under the curve (AUC) calculated according to the trapezoidal rule from baseline and incorporating data both above and below the baseline. In all cases, results for the baseline parameter are expressed as raw data, while results for all other parameters (ie, AUC, peak, and nadir) are reported after adjusting for baseline. Results are expressed as the mean ± standard deviation in text and tables and as mean ± the standard error in the figures.

Data from insulin withdrawal in the control studies were compared with those from the fasting and dehydration studies with respect to rates of metabolic decompensation and substrate turnover. Results were compared by analysis of variance for repeated measures in which the 2 arms of the study (ie, control + fasting; control + dehydration) were used as the grouping factor, and the interventions within each arm (ie, control *v* fasting, control *v* dehydration) served as the repeated factor. The control study was identical in the fasting and dehydration arms of the study.

RESULTS

Control Study Comparisons

For the sake of simplicity of presentation, results for the control studies for all variables have been combined (n = 25) in all figures and tables. To assure the validity of this combination, results were compared between the fasting control studies and the dehydration control studies by analysis of variance using the summary parameters previously described. Statistically significant differences were identified for only 2 parameters: baseline total ketone bodies (fasted control study = 314 ± 219 μmol/L, dehydrated control study = 128 ± 83 μmol/L, $P = .03$) and baseline plasma epinephrine (fasted control study = 289 ± 131 pmol/L, dehydrated control study = 164 ± 93 pmol/L, $P = .04$). Because all results are presented after baseline adjustment and because all subjects serve as their own controls in these paired analyses, these differences are deemed not to be clinically significant and not to effect the conclusions of the study.

Efficacy of the Dehydration Protocol

Subjects who participated in the dehydration protocol lost an average of 4.1% ± 2.0% of their baseline body weight during the protocol (control = 70.5 ± 11.3 kg *v* dehydrated = 68.9 ± 12.3 kg, $P < .001$). Total body water as determined by bioelectrical impedance was reduced from 43% ± 8% during the control study to 40% ± 7% during the dehydration study ($P < .001$). Hemodynamic parameters from subjects in the dehydration arm of the study were collected in the morning before the initiation of insulin withdrawal. Mean arterial pressure was 87 ± 7 mm Hg during the control study and 81 ± 12 mm Hg during the dehydration study ($P = .005$). Heart rate was 69 ± 15 beats per minute during the control study and 74 ± 15 beats per minute during the dehydration study ($P = .02$).

Plasma Glucose

Figure 1A depicts the development of hyperglycemia during insulin withdrawal in the control, fasted, and dehydrated states. Plasma glucose levels were comparable at the onset of insulin withdrawal, but the curves subsequently diverged, with glucose levels being reduced relative to control during the fasting study and increased relative to control during the dehydration study. As shown in Table 2, mean plasma glucose concentrations peaked at 12.32 ± 3.22 mmol/L above baseline in the control study compared with a peak of 6.94 ± 3.84 mmol/L above baseline in the fasting study ($P < .001$) and 17.93 ± 3.61 mmol/L above baseline in the dehydration study ($P < .001$). There were also statistically significant differences between the 2 interventions (fasting and dehydration) and between the interventions and the control study with respect to baseline adjusted glucose AUC.

Free Insulin

Figure 1B shows that serum-free insulin concentrations exhibited an initial steep decline after termination of the IV insulin infusion, followed by a plateau. Table 2 shows that total and nadir insulin concentrations were comparable between the 3 study conditions. Overall repeated measures analysis of variance showed no differences between the groups with respect to free insulin concentrations ($P = .34$).

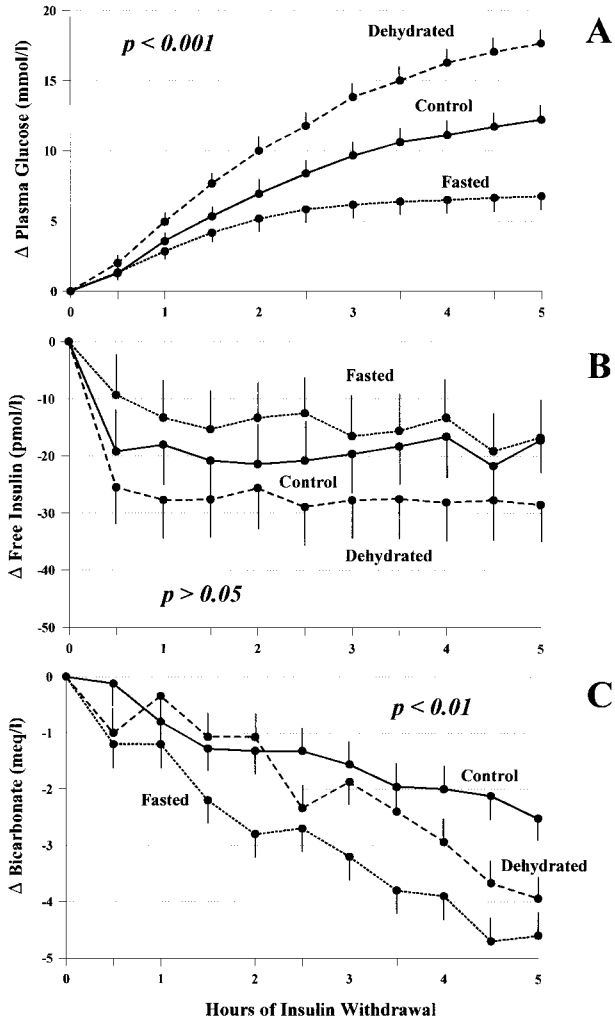

Fig 1. Change in (A) plasma glucose, (B) serum-free insulin, and (C) serum bicarbonate concentrations in type 1 diabetes patients during 5 hours of insulin withdrawal after 8 hours of fasting (solid line; n = 25), 32 hours of fasting (dotted line; n = 10), or dehydration of 4.1% ± 2.0% body weight (dashed line; n = 15). *P* values reflect results of the repeated measures analysis of variance.

Serum Bicarbonate

Serum bicarbonate concentrations declined steadily throughout all studies, reflecting a progressive development of metabolic acidosis during insulin withdrawal (Figure 1C). As shown in Table 2, rates of decline of serum bicarbonate were more rapid in the fasting and dehydration studies compared with the control studies. Similarly, nadir bicarbonate concentrations were reduced during the intervention studies compared with control, and bicarbonate AUC was reduced in the fasting study compared with the dehydration study.

Table 2. Results of Repeated Measures Analysis of Variance for all Study Variables

Variable	Parameter	Control (n = 25)	Fasting (n = 10)	Dehydration (n = 15)	Analysis Result
Glucose (mmol/L)	Baseline	6.00 ± 1.61	6.55 ± 1.67	5.88 ± 1.50	
	AUC	225 ± 68	144 ± 89	322 ± 76	c, i
	Peak	12.32 ± 3.22	6.94 ± 3.83	17.93 ± 3.61	c, i
Insulin (pmol/L)	Baseline	41 ± 36	56 ± 75	43 ± 27	
	AUC	−408 ± 522	−552 ± 930	−780 ± 756	
	Nadir	−22 ± 17	−31 ± 36	−31 ± 26	
Bicarbonate (mEq/L)	Baseline	21.5 ± 1.7	20.0 ± 2.3	23.1 ± 2.2	a, i
	AUC	−41 ± 38	−84 ± 30	−56 ± 32	a, e
	Nadir	−3.0 ± 1.7	−4.8 ± 1.5	−4.1 ± 1.3	e
TKB (μmol/L)	Baseline	202 ± 175	1,532 ± 1,002	187 ± 198	c, f, i
	AUC	27,329 ± 13,873	46,158 ± 17,211	34,969 ± 14,352	f
	Peak	1,692 ± 823	2,555 ± 930	2,342 ± 766	f
NEFA (mmol/L)	Baseline	0.71 ± 0.50	1.11 ± 0.67	0.47 ± 0.25	b
	AUC	14.75 ± 11.34	22.05 ± 17.16	21.71 ± 7.66	
	Peak	0.92 ± 0.40	1.28 ± 0.59	1.26 ± 0.42	e
Glucose R_a (mg/kg · min)	Baseline	2.10 ± 0.48	1.89 ± 0.66	2.00 ± 0.45	g
	AUC	15.6 ± 9.4	7.1 ± 9.9	21.7 ± 20.3	h
	Peak	0.74 ± 0.42	0.69 ± 0.99	0.95 ± 0.98	
Glucose R_d (mg/kg · min)	Baseline	1.79 ± 0.52	1.58 ± 0.47	1.50 ± 0.50	d
	AUG	16.1 ± 11.3	11.5 ± 16.4	25.3 ± 23.3	h
	Peak	0.97 ± 0.50	0.85 ± 1.11	1.49 ± 1.16	h
Glucagon (ng/L)	Baseline	58 ± 18	68 ± 21	66 ± 21	d, g
	AUC	174 ± 284	673 ± 925	509 ± 678	f
	Peak	17 ± 20	43 ± 47	43 ± 46	f
Epinephrine (pmol/L)	Baseline	213 ± 126	284 ± 147	273 ± 464	
	AUC	−186 ± 2674	1,010 ± 3,859	−2,516 ± 10,136	
	Peak	87 ± 98	1164 ± 120	98 ± 98	
Cortisol (nmol/L)	Baseline	384 ± 131	505 ± 119	497 ± 290	d
	AUC	−38,074 ± 83,736	−106,580 ± 106,580	15,230 ± 13,7012	a
	Peak	146 ± 138	88 ± 124	317 ± 237	a, g
GH (μg/L)	Baseline	2.3 ± 3.6	3.2 ± 3.7	3.0 ± 6.0	
	AUC	−8 ± 90	−43 ± 95	25 ± 146	
	Peak	5.6 ± 5.3	2.6 ± 2.8	8.6 ± 47.	a

NOTE. For each study variable, either the peak or the nadir is reported, depending on which of these summary parameters is more informative.
a = $P < .05$ for main effect of treatment (fasting or dehydration).
b = $P < .01$ for main effect of treatment (fasting or dehydration).
c = $P < .001$ for main effect of treatment (fasting or dehydration).
d = $P < .05$ for the main effect of control *v* intervention (fasting and dehydration).
e = $P < .01$ for the main effect of control *v* intervention (fasting and dehydration).
f = $P < .001$ for the main effect of control *v* intervention (fasting and dehydration).
g = $P < .05$ for the interaction term (fasting *v* dehydration).
h = $P < .01$ for the interaction term (fasting *v* dehydration).
i = $P < .001$ for the interaction term (fasting *v* dehydration).

Total Ketone Bodies

Figure 2A depicts the development of ketosis during insulin withdrawal in each of the 3 study conditions. Baseline concentrations of total ketone bodies (TKB) were significantly elevated in the fasting study compared with either the dehydration study or the control study. Nevertheless, the rate of development of ketosis and baseline-adjusted peak TKB concentrations were significantly elevated in the fasting and dehydration studies compared with the control studies during insulin withdrawal (Table 2, $P < .001$). Baseline adjusted TKB AUC levels were also increased after the intervention studies compared with their respective control studies ($P < .001$). Neither interven-

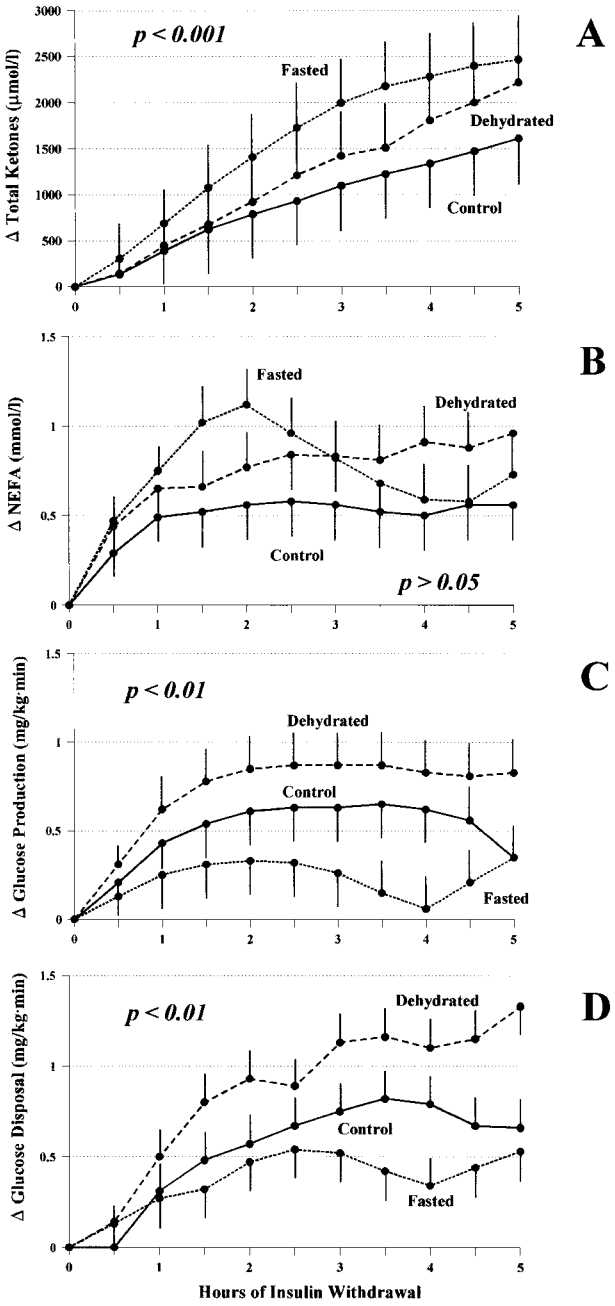

Fig 2. Change in (A) TKB concentrations, (B) NEFA concentrations, and rates of (C) glucose production and (D) glucose disposal in type 1 diabetes patients during 5 hours of insulin withdrawal after 8 hours of fasting (solid line; n = 25), 32 hours of fasting (dotted line; n = 10), or dehydration of 4.1% ± 2.0% body weight (dashed line; n = 15). *P* values reflect results of the repeated measures analysis of variance.

tion, however, was significantly more ketosis-inducing than the other.

NEFA

Baseline adjusted NEFA AUC concentrations were significantly elevated in the fasted and dehydration studies compared with the control studies (Table 2). Mean baseline adjusted NEFA concentrations exhibited a biphasic pattern during the fasting study (Fig 2B).

Glucose Turnover

Analysis of glucose turnover data showed significant differences in the effects of fasting and dehydration on rates of glucose production (R_a) and disposal (R_d). Specifically, glucose R_a AUC was significantly increased relative to control during the dehydration study and decreased relative to control in the fasting study (Table 2; Fig 3C). Similarly, peak glucose R_d and glucose R_d AUC were increased relative to control in the dehydrated state and decreased relative to control in the fasting state (Table 2; Fig 2C and D).

Counterregulatory Hormones

As shown in Fig 3, changes in counterregulatory hormone concentrations during the study were relatively modest. Nevertheless, baseline adjusted peak glucagon and glucagon AUC concentrations were significantly increased during the fasting and dehydration studies compared with the control studies (Table 2; Fig 3A). Epinephrine concentrations did not significantly differ according to study condition (Table 2; Fig 3B). Cortisol AUC concentrations were decreased in the fasting study relative to the control and dehydration studies, and peak cortisol concentrations were decreased in the fasting study and increased in the dehydration study relative to control (Table 2; Fig 3C). Finally, peak serum GH was decreased relative to control in the fasting study and increased relative to control in the dehydration study (Table 2; Fig 3D).

DISCUSSION

DKA is a common occurrence in type 1 diabetes, with an incidence of 5 to 8 episodes per year for every 1,000 patients with type 1 diabetes.[11] It is well established that glycemia can vary widely among persons with DKA and that short-term fasting predisposes patients to reduced blood glucose concentrations during insulin deficiency.[1,3,12] The current study further shows that a substantial portion of the glycemic variability observed in DKA may be attributable to variation in the nutritional and/or hydration status of patients before the onset of insulin deficiency. Furthermore, this study shows that preexistent fasting or dehydration accelerates the development of both ketosis and metabolic acidosis compared with control conditions in which neither of these factors is present.

The differential effects of fasting and dehydration on glycemia during insulin deficiency have not been previously demonstrated in a prospective study. Waldhausl et al[13] have previously shown that treatment of DKA with hypotonic fluid alone can reduce plasma glucose concentrations by up to 80% before the initiation of insulin therapy. Additionally, Owen et al[14] have shown that partial rehydration during insulin deficiency reduces plasma glucose concentrations mainly due to increased renal excretion of glucose. These same investigators further showed that partial rehydration results in decreased concentrations of glucagon and catecholamines, suggesting that dehydration may be a sufficient stimulus for secretion of these potent counterregulatory hormones.[14] The current study establishes

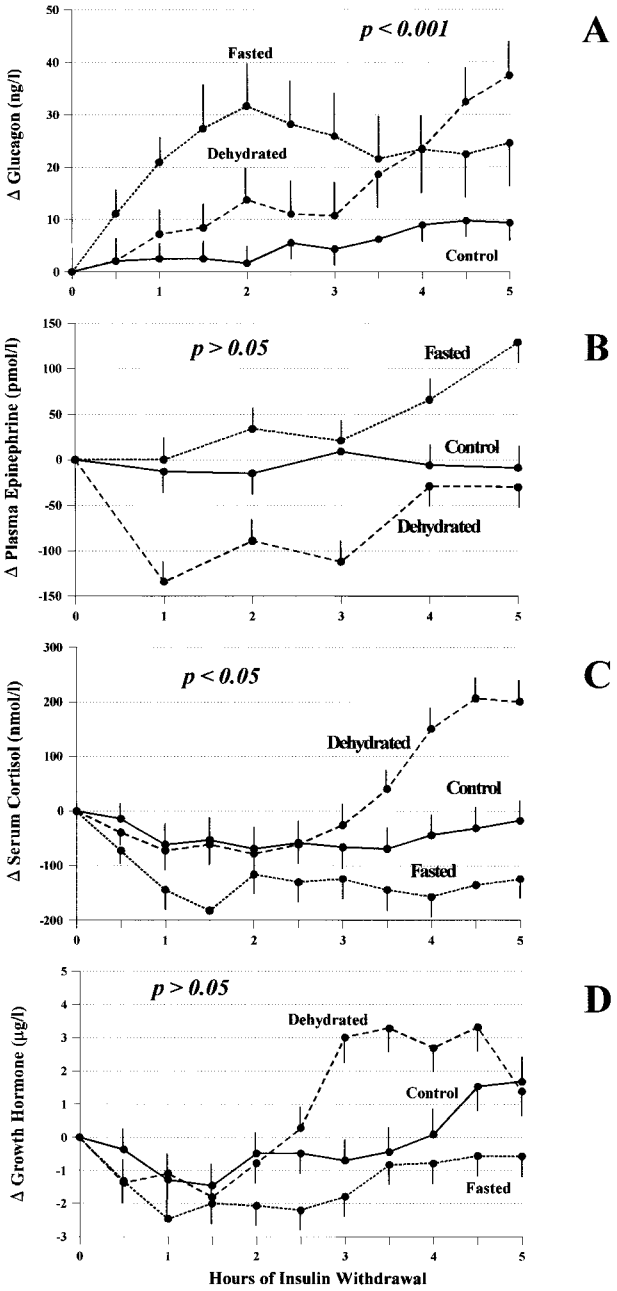

Fig 3. Change in (A) serum glucagon, (B) plasma epinephrine, (C) serum cortisol and, (D) serum GH concentrations in type 1 diabetes patients during 5 hours of insulin withdrawal after 8 hours of fasting (solid line; n = 25), 32 hours of fasting (dotted line; n = 10), or dehydration of 4.1% ± 2.0% body weight (dashed line; n = 15). *P* values reflect results of the repeated measures analysis of variance.

that pre-existent dehydration results in increased concentrations of glucagon, cortisol, and GH, but not epinephrine, during insulin deficiency. Conversely, fasting is associated only with increased concentrations of glucagon during insulin deficiency.

The mechanism for the observed divergence in plasma glucose concentration during fasting and dehydration appears to be related to increased glucose production in the dehydrated state and decreased glucose production in the fasting state relative to control conditions. The decreased glucose production observed during fasting is probably best explained by reduced hepatic glycogenolysis and gluconeogenesis.[15] Elevated rates of glucose disposal during dehydration compared with fasting are likely attributable to the mass action of glucose that occurs during hyperglycemia.[16,17] Unfortunately, urine was collected for total glucose excretion during insulin withdrawal from only 5 subjects during the dehydration study. Total glucose excretion during 5 hours of insulin withdrawal in these subjects was as follows: control study = 27.6 ± 9.8 g versus dehydration study = 13.9 ± 13.2 g (n = 5; $P = .08$).

The glucose production and disposal data deserve further comment and clarification. Although it may appear from Table 2 that rates of glucose disposal were greater than rates of glucose production in the face of increasing plasma glucose concentrations (a situation that is physiologically untenable), this perception is a by product of the depiction of the data as "change from baseline." When the data are analyzed in raw, unmanipulated form, mean rates of glucose production are consistently greater than mean rates of glucose disposal in all 3 study conditions. This finding is consistent with previous studies.[18] We chose to depict the data as change from baseline in an attempt to correct for baseline differences that occurred in our study and to more accurately reflect how the data were analyzed statistically.

Ethically mandated limitations of this study include the fact that the insulin withdrawal was relatively brief and that the DKA which developed, was relatively mild in most cases. Additionally, thiazide diuretics (such as metolazone) have been reported to cause insulin resistance and hyperglycemia in nondiabetic and type 2 diabetic patients.[18] This insulin resistance, however, is attributed to hypokalemia and is reported to occur after prolonged (weeks of) therapy. Moreover, this hyperglycemia can be prevented in both diabetic and nondiabetic subjects if hypokalemia is avoided during thiazide therapy.[19-21] Because potassium was aggressively and carefully replaced during the studies in which metolazone was administered in this study, hypokalemia did not occur (dehydration study: baseline $K^+ = 3.9 \pm 0.3$ *v* end of study $K^+ = 5.4 \pm 0.9$ mEq/L). Thus, it is unlikely that the limited, short-term administration of metolazone in this study contributed significantly to the severe hyperglycemia observed in the dehydration arm of the protocol independent of the dehydration it caused.

We conclude that short-term fasting and dehydration both accelerate the development of DKA during insulin deficiency, but that these 2 conditions have differential effects on glucose concentrations during insulin deficiency. Specifically, fasting slows the development of hyperglycemia during insulin deficiency while dehydration promotes the development hyperglycemia relative to control conditions in which subjects are both hydrated and fed. Given the common occurrence of both malnutrition and dehydration in patients who present with DKA, it is probable that heterogeneity in the severity of these 2 predisposing conditions, as well as in the severity of insulin deficiency and underlying illness, explains much of the glycemic variability observed in this condition.

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