Severe Hyperglycemia: Effects of Rehydration on Endocrine Derangements and Blood Glucose Concentration

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SUMMARY

Diabetic ketoacidosis is associated with an excess secretion of counterregulatory hormones. The effect of rehydration on these endocrine derangements before insulin administration is unknown. Therefore, we measured the effect of rehydration with hypoosmolal fluid (220 mosmol/kg) on blood glucose (BG), immunoreactive insulin (IRI), immunoreactive C-peptide (IRCP), immunoreactive glucagon (IRG), human pancreatic polypeptide (hPP), growth hormone (GH), prolactin (PRL), cortisol, aldosterone, renin (PRC), epinephrine, norepinephrine, and parathyroid hormone (PTH) in ketoacidotic diabetic patients [pH 7.03 ± 0.05 (SEM); n = 8] and in patients (n = 2) with nonketotic hyperglycemia (BG, 29.8 mmol/L and 46.8 mmol/L). The cumulative net fluid balance after rehydration was 4364 ± 690 ml. Basal insulin was inappropriately low, and IRCP was below the normal range (1.5 ± 0.5 ng/ml). Serum osmolality fell during hypoosmolal rehydration (n = 9) from 335 ± 11 to 315 ± 9 mosmol/kg. Rehydration with hypoosmolal fluid with bicarbonate added at a pH of less than 7.2 induced a fall in BG ranging from 6.1 mmol/L to 22.6 mmol/L, or of 16.7% to 79.8% of the initial BG level, as well as a decrease in plasma lactate and urinary glucose. These effects were paralleled by a decrease in IRG, cortisol, epinephrine, norepinephrine, aldosterone, and PRC. No fall in BG was seen in one patient whose dehydrated state was maintained by infusion of isotonic saline. Low dose insulin treatment was initiated in all patients immediately when no further fall in blood glucose levels was achieved.

We conclude that rehydration improves the metabolic situation in severe diabetic hyperglycemia and ketoacidosis by reducing (a) the availability of counterregulatory hormones and (b) peripheral insulin resistance on a cellular level. Thus, proper rehydration will support the beneficial action of simultaneous low dose insulin treatment in patients with severe hyperglycemia. DIABETES *28*:577–584, June 1979.

The development of diabetic ketoacidosis is generally attributed to absolute and irreversible insulin deficiency,[1] since serum levels of insulin were found to be unmeasurable or inappropriately low in relation to hyperglycemia.[2–5] However, reevaluation of this suggestion showed that both ketoacidotic[6,7] and hyperosmolal[8] diabetic patients retain some capacity for the release of C-peptide (CP). Furthermore, it has been demonstrated that diabetic ketoacidosis is accompanied by a transient insulin resistance that is possibly due to multiple factors such as lowered pH[9] and increased release of counterregulatory hormones.[10] The observations in a ketoacidotic state include elevated levels of glucagon,[11,12] catecholamines,[13] cortisol,[14,15] and, in part, growth hormone (GH).[16,17] Gerich and co-workers[18] demonstrated that suppression by somatostatin of both glucagon and GH release significantly delayed the development of a ketoacidosis after withdrawal of insulin treatment in diabetic subjects.

In addition, hyperglycemia and ketoacidosis are associated with osmotic diuresis and a considerable loss in body fluid, which amounts to up to 100 ml water per kilogram of body weight. These fluid losses have been estimated both as fluid deficit during insulin withdrawal[19,20] and as water retention after treatment of diabetic ketoacidosis.[21]

The treatment of choice of diabetic ketoacidosis has been until recently rapid replacement of insulin deficiency by large doses of insulin ranging from 50 to 400 U for the first hour of therapy,[22] administered either subcutaneously or intravenously or by insulin infusion.[23] This concept of high dose insulin replacement with insulin doses of up to 177,500 U[24] has been challenged by the successful use of low dose insulin infusion for the correction of severe diabetic hyper-

This study was presented in part at the Second World Congress on Intensive Care, Paris, September 19–23, 1977.

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Accepted for publication 2 February 1979.

glycemia.[25–28] In addition to insulin administration, adequate fluid and electrolyte replacement has been recommended to facilitate recovery of the patient's own homeostatic defenses.[22] The contributions of water and electrolyte replacement toward normalization of blood glucose levels are, however, unknown.

This study was initiated by the observation of a fall in blood glucose in a severely hyperglycemic diabetic patient during plain rehydration when erroneously the insulin infusion had not been started. Similar observations have been described in 12 out of 18 patients within 3 h when saline was given alone.[29] Our investigation was undertaken consecutively to test the hypothesis as to whether or not rehydration per se improves, in severely hyperglycemic diabetic patients, blood glucose levels and reverses deterioration of hormone release including both that of counterregulatory (glucagon, cortisol, norepinephrine, epinephrine, GH), and of other hormones (human pancreatic polypeptide [hPP], parathyroid hormone [PTH], prolactin [PRL], plasma renin concentration [PRC], and aldosterone). Low dose insulin infusion was started immediately when no further fall in blood glucose (BG) was achieved.

PATIENTS AND METHODS

Patients. Ten severely hyperglycemic diabetic patients (Table 1), aged 16–69 yr, were included in the study. Three of them were female, seven were male; none were infected. Ideal body weight was ±10% within the normal range in four, below normal in two, and greater than normal in four patients (Tables, Metropolitan Life Insurance, 1959). Eight diabetic patients had ketoacidosis (defined as arterial pH less than 7.25, urinary ketones greater than 2+ at a 1:2 dilution, and BG greater than 20 mmol/L); nine had elevated lactate levels. Nine patients were in a hyperosmolal state, and two were hyperglycemic (BG, 29.8 mmol/L and 46.8 mmol/L), with a pH of 7.47 and 7.5, respectively. Three of the severely hyperglycemic subjects (nos. 1,4,8) were not previously known to be diabetic. Four of the patients (nos. 2,3,9,10) had been on insulin treatment before admission to the hospital, and three (nos. 5,6,7) were on oral antidiabetic medication. Data on the duration of diabetes, blood pressure (BP), pulse rate, temperature (°C), and treatment required *after* recovery are also included in Table 1.

Protocol. All patients were studied in an intensive care unit with hourly controls of BG, and vital functions and central venous pressure (CVP) being monitored continuously. The period of plain fluid replacement lasted as long as a fall in BG was observed. Rehydration was achieved by hypoosmolal fluid containing one-half normal saline (77 mmol/L) and glucose-1-phosphate (10 mmol/L) with added sodium chloride, and/or potassium chloride, and/or bicarbonate to obtain an osmolality of 220 mosmol/kg water. In addition, calcium (2.25 mmol/6 h; calcium gluconicum) was administered intravenously as a bolus. The infusion rate was tightly controlled by monitoring CVP. The infused fluid volumes were 1,000 ml/h (CVP < 0 cm water), 500 ml/h (CVP, 0–+3 cm water), 250 ml/h (CVP, +3–+6 cm water), 100 ml/h (CVP > +6 cm water), and 0 ml/h (CVP > +15 cm water). Fluid replacement was strictly parenteral. The patients were not allowed to eat or drink during the rehydration period. Bicarbonate was given at a pH of less than 7.2. Low dose insulin infusion (2–6 U/h) was started immediately when BG ceased to fall. The study was approved by the Research Committee of the hospital, and the patients themselves or a member of the immediate family was informed of the nature and purpose of the study before giving consent to participate.

Methods. Concentrations of BG (mmol/L; normal, 3.9–5.5 mmol/L) and of urinary glucose were determined enzymatically (Boehringer Mannheim), as were plasma lactate levels (mmol/L; normal, 0.5–1.5 mmol/L). Sodium, potassium, pH, and serum osmolality (measured by freezing point depression) were determined in the routine biochemical laboratory. Methods and standards used for the estimation of immunoreactive glucagon (IRG, pg/ml), insulin (IRI, μU/ml), GH (ng/ml), and cortisol (μg/dl) have been described previously.[30–33] Antibodies for the radioimmunoassay of cortisol were obtained from Dr. Vecsei (Heidelberg) and used at a final concentration of 1:100,000. Kits for the estimation of serum immunoreactive C-peptide (IRCP, ng/ml) and PRL (ng/ml) were purchased from Serono. hPP was estimated radioimmunologically by a double antibody technique using reagents [rabbit anti-hPP (Lot 615–1054B–248–19; final dilution 1:1,000,000), hPP standard (Lot 615–1054B–200–4), and bovine pancreatic polypeptide (bPP; Lot 615–D63–295)] kindly provided by Dr. R. E. Chance (Lilly Research Laboratories, Indianapolis, In-

TABLE 1
Clinical data of the patients admitted with severe hyperglycemia

Patient no.	Age (yr)	Sex	Percent ideal body weight	Duration of diabetes (yr, months)	BG (mmol/L)	pH	Lactate (mmol/L)	Osmolality (mosmol/kg)	Urinary ketones	BP (mm Hg)	Pulse rate	Temperature (°C)	Treatment after recovery (insulin U/day)
1	57	F	116	3 months	29.8	7.5	2.2	293	±	140/80	90	36.4	24
2*	28	M	106	21 yr	34.1	6.94	5.7	348	>++	120/90	115	36.3	52
3*	27	M	115	6 yr	41.6	7.01	5.9	345	>++	150/80	140	37.2	60
4	16	M	71	1 month	28.3	7.16	4.6	327	++	90/60	100	36.1	52
5	36	M	138	1 yr	48.3	7.22	4.4	409	++	140/90	110	36.4	Buformin
6	69	F	135	5 months	46.8	7.47	6.0	328	±	170/100	140	36.1	Glibenclamide
7	36	M	89	3 yr	28.9	6.97	2.7	320	>++	170/90	125	36.4	40
8	16	F	92	5 months	24.9	7.13	1.1	320	>++	150/80	120	36.6	32
9*	18	M	90	3 yr	37.4	7.04	3.9	351	>++	120/70	120	37.0	60
10*	36	M	108	5 yr	22.8	6.8	1.8	321	>++	190/115	100	36.4	36

* Patients on insulin treatment before admission. n = 10. BG, blood glucose; BP, blood pressure.

TABLE 2
Hormone concentrations in healthy controls

	x ± SEM	n		x̄ ± SEM	n
IRG (pg/ml)	99 ± 19	8	PRC (GU × 10^{-4}/ml)	0.3 ± 0.1*	12
IRCP (ng/ml)	2.35 ± 0.07	20		1.7 ± 0.3†	12
IRI (μU/ml)	15 ± 2	20	Aldosterone (ng/100 ml)	7.8 ± 2.3*	12
hPP (pg/ml)	93 ± 11	20		28.2 ± 8.4†	12
GH (ng/ml)	0.7 ± 0.1	8	Cortisol (μg/100 ml)	10.5 ± 2.0	15
PRL (ng/ml)	11 ± 3.7	15	Epinephrine (ng/ml)	0.05 ± 0.03	22
PTH (ng/ml)	0.46 ± 0.05	22	Norepinephrine (ng/ml)	0.2 ± 0.08	22

* During sodium repletion (120 mmol Na^+/day) and recumbency.
† During sodium depletion (10 mmol Na^+/day) and upright position. IRG, immunoreactive glucagon; IRCP, immunoreactive C-peptide; IRI, immunoreactive insulin; hPP, human pancreatic polypeptide; GH, growth hormone; PRL, prolactin; PTH, parathyroid hormone; PRC, plasma renin concentration.

diana). Borate buffer containing 0.1 g bovine serum albumin/dl (BBSA: 8.25 g boric acid, 2.7 g NaOH, 7.44 g Na_2EDTA, 0.1 g merthiolate were dissolved in distilled water and adjusted to 1 L; pH 8.0 was adjusted with HCl) was used for all dilutions. A disequilibrium method was applied. Incubation time was 2 days each for first, second, and third incubation at 4°C. Bovine PP was labeled by a modification of the chloramine-T method[34] using 5 μg bPP, 0.8 μg chloramine-T, and 0.2 μg $Na_2S_2O_5$. The amount of labeled bPP added per tube was 15 pg. Parathyroid hormone (PTH, ng/ml) was estimated by a modification of the radioimmunoassay method of Arnaud et al.[35] using antibody AS 211/41 (Wellcome Laboratories, Beckenham, England) and human PTH (h–PTH, MRC 75/549) as a standard. Epinephrine (ng/ml) and norepinephrine (ng/ml) were determined by a double isotope derivative radioenzymatic analysis.[36] Values of hormone concentrations in healthy controls are given in Table 2. The interassay coefficient of variation for radioimmunoassay data ranged from 5.6 to 9.2%. Data in the text, tables, and figures are presented as mean ± SEM (n). For statistical analyses, the Student's *t* test for paired and unpaired groups was employed as applicable.

RESULTS

Metabolic and endocrine variables were followed closely during rehydration of the severely hyperglycemic patients. Figure 1 shows the effect of hypoosmolal fluid replacement and positive fluid balance (4364 ± 690 ml) on the group mean of plasma osmolality, BG, and the plasma concentrations of IRCP and IRI. It is apparent that hypoosmolal fluid-electrolyte replacement induced a consistent fall in plasma osmolality that was accompanied by a decrease in BG of 1.1 ± 0.1 mmol/L^{-1}/h^{-1}. BG plateaued at the end of the rehydration period. Plasma IRCP and IRI remained unchanged throughout the observation period. IRCP levels were below normal basal values ($P < 0.05$). Hypoosmolal rehydration lasted from 4 to 20 h (10.9 ± 1.6 h; x̄ ± SEM), with cumulative fluid balance amounting to 2450–8520 ml (4364 ± 690 ml). Hypoosmolal fluid replacement induced a fall in serum osmolality of 4–46 mosmol/kg (19.7 ± 5.3 mosmol/kg; $P < 0.005$) corresponding to 1.2–14% of the serum osmolality found at admission. The parallel fall in BG ranged from 6.1 mmol/L to 22.6 mmol/L (11.7 ± 2.1 mmol/L), or from 16.9 to 79.8% (36.2 ± 6.5%) (Table 3).

The response of slow hypotonic rehydration on variables involved in electrolyte balance is depicted in Figure 2. It is demonstrated that fluid replacement was accompanied by a rise in serum sodium from 131 ± 1.1 mmol/L to 139 mmol/L, whereas serum potassium fell only to a small extent. This effect was accompanied by a positive net cumulative balance of sodium and potassium (Figure 2B).

The fall in BG on hypoosmolal rehydration was paralleled (Table 4) by a decrease of elevated levels of PRC, aldosterone, and cortisol. Basal plasma concentrations of norepinephrine and epinephrine were elevated 10-fold and 20-fold, respectively, when compared with those in normals. A significant fall in plasma epinephrine and norepinephrine was also observed during rehydration in parallel with that of BG. The decrease in plasma IRG was consistent in each patient but showed a wide variability of individual values.

FIGURE 1. Cumulative fluid balance and the effects of hypoosmolal rehydration on blood glucose (BG), serum osmolality, and the plasma levels of immunoreactive C-peptide (IRCP) and insulin (IRI) in severely hyperglycemic diabetic patients (x̄ ± SEM; n).

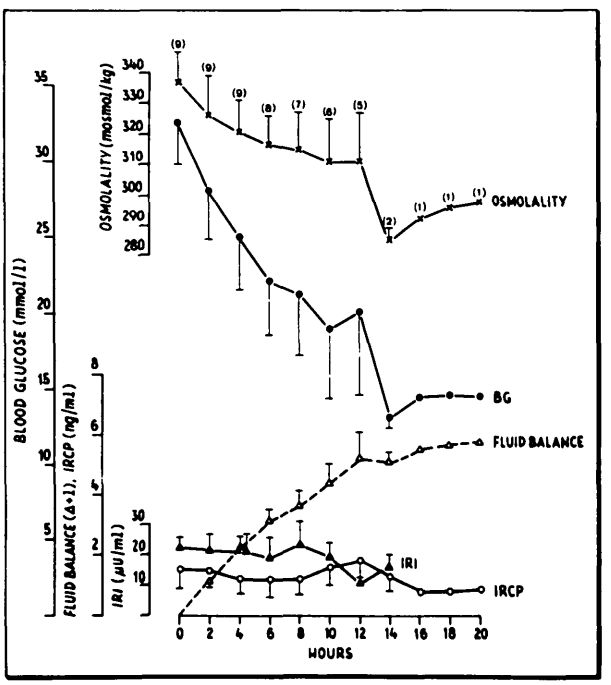


TABLE 3
Duration of rehydration, cumulative fluid balance, change in serum osmolality, and in BG vs. basal in the patients at the end of hypoosmolal fluid replacement and before the start of low dose insulin treatment

Patient no.	Duration of rehydration (h)	Cumulative fluid balance (ml)	Serum osmolality		BG		
			(mosmol/kg)	(%)	(mmol/L)	(%)	(mmol/L/h)
1	12	+4800	−5	−1.7	−12.3	−44.6	−1.02
2	8	+2880	−23	−6.6	−8.8	−25.8	−1.1
3*	6	+3390	+23	+6.6	+1.0	+2.4	+0.16
4	20	+6080	−30	−9.1	−22.6	−79.8	−1.1
5	12	+8520	−41	−10.0	−8.2	−16.9	−0.7
6	14	+5690	−46	−14.0	−22.4	−47.8	−1.6
7	6	+2810	−10	−3.1	−7.5	−25.9	−1.25
8	10	+2670	−9	−2.8	−9.6	−38.5	−0.96
9	4	+2450	−9	−2.5	−7.4	−19.7	−1.8
10	12	+3380	−4	−1.2	−6.1	−26.7	−0.5
x̄ ± SEM†	10.8 ± 1.6	4364 ± 690	19.7 ± 5.3	−5.6 ± 1.5	−11.7 ± 2.1	−36.2 ± 6.5	1.1 ± 0.1

* Fluid replacement by isotonic saline.
† Excluding patient no. 3, who received isotonic saline only. BG, blood glucose.

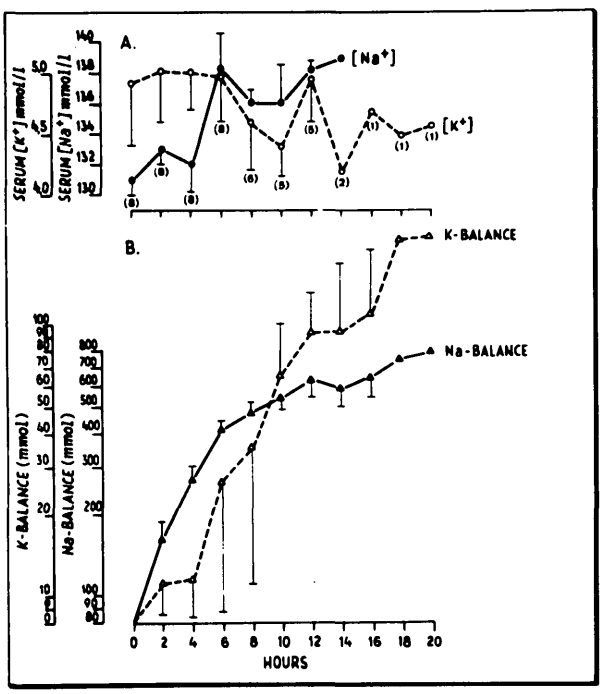
Basal plasma GH concentrations were above normal ($P < 0.01$) and did not change during rehydration. Plasma levels of hPP were elevated vs. normal ($P < 0.0005$), but decreased in only five out of seven patients after hypoosmolal fluid replacement, whereas levels of PRL and PTH were in the normal range and showed no significant tendency to fall.

A comparison of the absolute values of metabolic variables obtained before and after hypoosmolal rehydration is presented in Table 5. Data describing the state of the patients after rehydration were grouped independently from the individual duration of fluid replacement with plateauing of blood glucose as the determining factor. Fluid replacement with hyoosmolal fluid containing bicarbonate induced a significant rise in blood pH and serum sodium concentration, whereas osmolality ($P < 0.005$), BG ($P < 0.0005$), and lactate ($P < 0.005$) fell. No change was observed in serum potassium. Urinary glucose excretion (g/2 h) was also reduced in the course of hypoosmolal fluid replacement ($P < 0.05$).

One diabetic individual (patient no. 6) with a hyperosmolal hyperglycemic state whose BG and lactate levels fell during rehydration almost to the normal range was put on oral glibenclamide 16 h after initiation of hypoosmolal fluid replacement (Figure 3).

Rather than a decrease, a small rise in BG (Figure 4A) was observed in a hyperglycemic patient (no. 3) with a ketoacidosis as long as he received fluid replacement by isotonic saline. In this individual (Figure 4B), plasma sodium rose within 6 h from 130 mmol/L to 144 mmol/L, as did serum osmolality (345 mosmol/kg water to 368 mosmol/kg water), PRL, and pH (7.01 to 7.17), whereas IRG, GH, aldosterone, cortisol, norepinephrine, and epinephrine fell. No change was observed in this diabetic patient in regard to PTH, IRI, IRCP, and PRC. Unsuccessful rehydration by isotonic saline was followed immediately by a bolus of intravenous insulin (8 U) and an insulin infusion (5 U/h). This measure (Figure 4A) caused a prompt fall in BG and in plasma lactate. Clinically, all patients were doing well during and after the period of hypoosmolal rehydration.

FIGURE 2. Effect of hypoosmolal rehydration on the serum concentrations and the net cumulative balance of sodium and potassium in severely hyperglycemic diabetic patients (x̄ ± SEM; n).



DISCUSSION

Ketoacidotic and nonketoacidotic severe hyperglycemia is associated usually with dehydration and metabolic derangements.[19,37,38] The observed fluid loss in diabetic ketoacidosis amounts to up to 7–15% of body weight[37] and is paralleled by the loss of ions such as sodium, potassium, chloride, calcium, magnesium, and phosphate. Furthermore, it is accompanied by an elevation in the plasma concentrations of IRG,[11,12] catecholamines,[13] cortisol,[14,15] and GH.[16,39] Severe volume depletion in diabetic ketoacidosis is also a state of secondary aldosteronism with marked elevations of plasma renin activity and of aldosterone.[40,41] These indices together with some other endocrine variables

TABLE 4
Effect of hypoosmolal rehydration on plasma concentrations of endocrine variables

	Time (h)												
	0	2	4	6	8	10	12	14	16	18	20	End of rehydration	P
IRG (9) (pg/ml)	741 ± 247	496 ± 140	407 ± 106	356 ± 89	274 ± 57	236 ± 53	254 ± 58	285 ± 75	250	270	320	245 ± 32	NS
GH (9) (ng/ml)	4.6 ± 1.6	4.5 ± 1.9	5.2 ± 2.0	4.3 ± 1.3	3.2 ± 1.3	4.2 ± 2.3	2.7 ± 1.2	3.0 ± 2.5	4.4	4.0	2.1	4.5 ± 1.6	NS
PRL (8) (ng/ml)	19.4 ± 7.0	16.6 ± 6.0	16.5 ± 7.0	19.0 ± 8.0	17.0 ± 9.0	20.0 ± 11.0	16.0 ± 7.0	7.7 ± 3.8	3.8	6.6	5.2	13.3 ± 5.0	NS
PTH (5) (ng/ml)	0.47 ± 0.05	0.31 ± 0.06	0.28 ± 0.06	0.31 ± 0.06	—	—	—	—	—	—	—	0.36 ± 0.05	NS
hPP (7) (pg/ml)	691 ± 200	358 ± 146	438 ± 101	490 ± 165	685 ± 356	457 ± 110	437 ± 101	—	—	—	—	581 ± 246	NS
PRC (7) (GU × 10^{-4}/ml)	13.2 ± 4.6	9.1 ± 3.0	6.4 ± 2.6	4.9 ± 1.9	3.9 ± 1.7	3.1 ± 1.8	3.3 ± 2.3	1.3 ± 0.5	1.5	1.3	1.5	3.8 ± 1.4	<0.05
Aldosterone (8) (ng/100 ml)	83 ± 25	46 ± 12	38 ± 9	36 ± 9	36 ± 13	40 ± 14	35 ± 14	15 ± 4	15	12	11	28.9 ± 9.1	<0.05
Cortisol (9) (μg/100 ml)	50.4 ± 4.9	41.6 ± 6.0	35.0 ± 5.0	33.0 ± 6.0	29.3 ± 8.0	24.6 ± 8.0	32.6 ± 8.0	21.9 ± 7.0	15.0	10.5	10.2	29.3 ± 6.2	<0.0025
Epinephrine (6) (ng/ml)	2.6 ± 1.5	2.5 ± 1.9	0.3 ± 0.1	0.2 ± 0.03	0.2 ± 0.07	0.2 ± 0.05	0.1 ± 0.04	0.14 (1)	0.12	0.16	0.22	0.14 ± 0.03	<0.05
Norepinephrine (6) (ng/ml)	3.8 ± 1.1	3.2 ± 1.0	1.9 ± 0.5	1.2 ± 0.4	1.4 ± 0.4	0.9 ± 0.6	1.0 ± 0.4	0.14 (1)	0.10	0.12	0.24	1.10 ± 0.3	<0.05

Data on the respective plasma hormone concentrations at the end of hypoosmolal rehydration were grouped independently from the individual duration of fluid replacement with plateauing of blood glucose as the determining factor. $\bar{x}$ ± SEM (n). P vs. basal values.

IRG, glucagon; GH, growth hormone; PRL, prolactin; PTH, parathyroid hormone; hPP, human pancreatic polypeptide; PRC, plasma renin concentration.

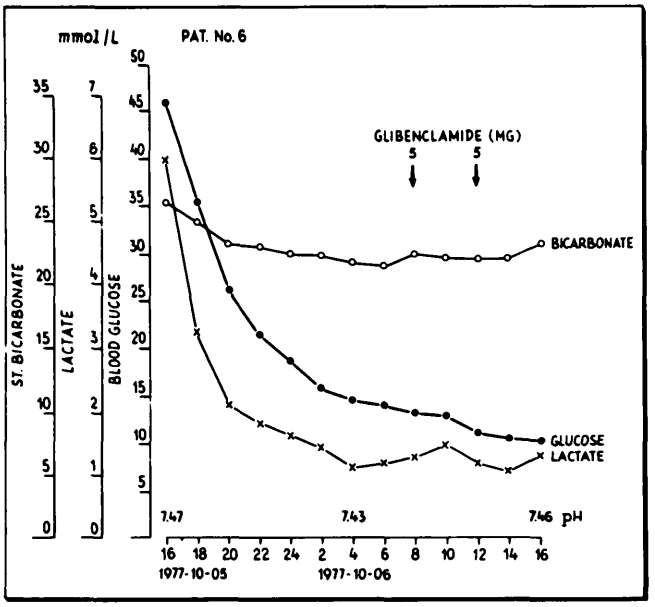
TABLE 5
Values of metabolic variables before and after hypoosmolal rehydration

	Rehydration		
	Before	After	P
Na^+ (mmol/L)	131 ± 1.1 (9)	137 ± 1.1 (9)	<0.0025
K^+ (mmol/L)	4.7 ± 0.5 (9)	4.9 ± 0.3 (9)	NS
pH*	7.04 ± 0.05 (7)	7.21 ± 0.04 (7)	<0.005
Osmolality (mosmol/kg)	335 ± 11 (9)	315 ± 9 (9)	<0.005
Glucose (mmol/L)	32.4 ± 2.7 (9)	22.1 ± 3.1 (9)	<0.0005
Lactate (mmol/L)	3.6 ± 0.6 (9)	1.6 ± 0.2 (9)	<0.005
Urinary glucose (g/2 h)	21.7 ± 3.7 (9)†	11.9 ± 3.2 (9)‡	<0.05

* Ketoacidotic patients only.
† First 2 h of hypoosmolal rehydration.
‡ Last 2 h of hypoosmolal rehydration.
$\bar{x}$ ± SEM; n (number) is in parentheses.

such as prolactin, PTH, and hPP were used in this study to assess the efficacy of fluid replacement in ketoacidotic and nonketoacidotic hyperglycemia. The hormones were measured because they are known to act as counterregulatory hormones[10,42–44] to interfere with water and electrolyte metabolism,[40,41] or to be elevated in juvenile-onset type diabetes.[45] Thus it has been described by others[46] that withdrawal of insulin in otherwise well-controlled diabetic patients caused a rise in plasma glucagon that was linked significantly to an increase in plasma ketone bodies. A supporting role of glucagon for the development of ketoacidosis was also suggested by the finding that administration of somatostatin delays the development of hyperketonemia after withdrawal of insulin replacement in insulin-dependent diabetic patients.[18] Similarly, a ketogenic action has been described for the administration of steroids,[42] catecholamines,[43] and GH.[44] There is, however, no convincing evidence that any one of these hormones acts as a prime mover for the development of diabetic ketoacidosis, although all of them may well aggravate ketoacidosis in the presence of relative or absolute insulin deficiency.

FIGURE 3. Effect of rehydration on blood glucose (BG) and the plasma levels of lactate and standard bicarbonate in a severely hyperglycemic (BG, 46.8 mmol/L), nonketotic diabetic patient (no. 6). Note that both BG and plasma lactate fell and treatment with glibenclamide was initiated when BG levels reached 14 mmol/L.



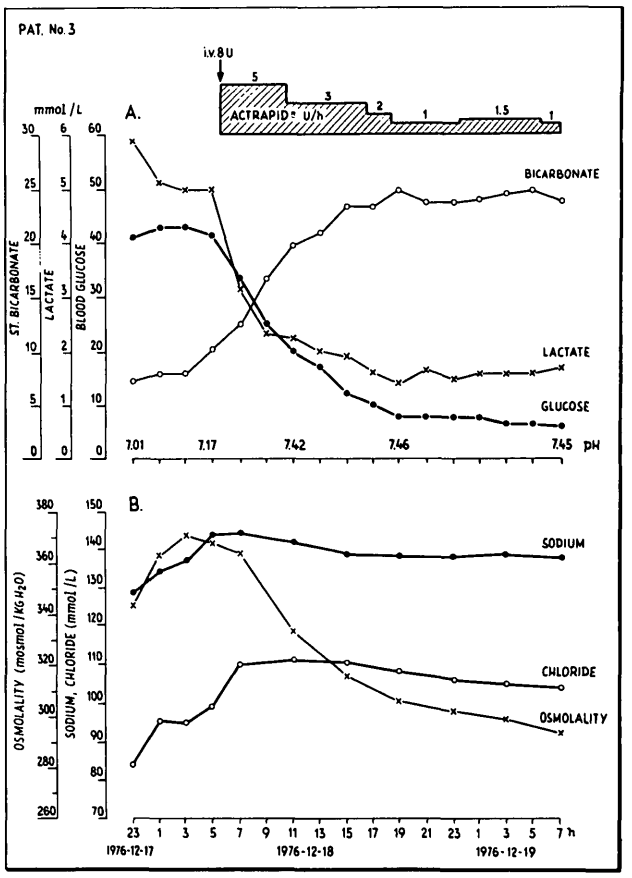


FIGURE 4. Failure of fluid replacement by isotonic saline to lower blood glucose in a severely hyperglycemic (BG, 41.6 mmol/L), ketoacidotic diabetic patient (no. 3). A prompt fall of BG and plasma lactate with parallel normalization of standard bicarbonate and pH occurred only on insulin administration.

In this context, it has to be emphasized that the data obtained by our study demonstrate that fluid replacement by a slightly hypoosmolal solution per se is effective in severely hyperglycemic diabetic patients, both in lowering BG, to some extent ranging from 0.5 to 1.8 mmol/L/h, plasma lactate levels, and urinary glucose excretion. The maximal decrement in BG was 22.6 mmol/L. A fall in plasma glucose concentration of 450 mg/dl within 2 h, i.e., 12.5 mmol/L/h, on infusion of saline alone has also been described.[29] The observed rise in blood pH has to be explained by bicarbonate administration and does not necessarily reflect improvement of ketogenesis. Plasma concentrations of counterregulatory hormones, PRC, and aldosterone fell, as shown previously by others during insulin treatment of diabetic ketoacidosis.[15,39,41,46] Plasma IRG fell consistently in all patients after fluid replacement. Due to the wide variability of individual values, the mean of IRG concentrations after fluid replacement was not significantly different from that calculated for base-line conditions. The

insulin levels in the upper range of normal were inappropriately low for the observed BG levels. Plasma concentrations of hPP in the patients were both above those of normal controls and of juvenile-onset diabetic patients,[45] but did not fall consistently during infusion of hypotonic fluid.

According to the above findings, it appears feasible that intravascular volume depletion *and* cellular dehydration provide the adequate stimuli for the release of multiple hormones as an emergency reaction, as was shown for urinary 17 OH-corticoids,[47] and that fluid replacement can stop counterregulatory hormone release. In addition, glucose utilization was improved by cellular rehydration. The latter finding was supported both by fall in lactate levels and in urinary glucose excretion. These observations suggest that the inappropriately low plasma concentrations of insulin observed in diabetic coma regain their biologic activity after fluid is replaced and act by lowering blood glucose levels to some extent. This effect could be explained by an improved insulin sensitivity of rehydrated cells as compared with the dehydrated state, or, in other words, by a decrease in peripheral insulin resistance on rehydration. Initial fluid replacement before insulin treatment also avoids the rise in GH that is encountered in diabetic ketoacidosis 1 h after initiation of insulin administration.[17]

Furthermore, it has to be kept in mind that hyperosmolal dehydration per se is well known by pediatricians to induce severe hyperglycemia in nondiabetic infants of up to 780 mg/dl.[48,49] This secondary hyperglycemia may occur with and without ketosis.[49] In these cases, a rise in plasma GH and glucagon levels has been described.[50] Glucose intolerance and intermediate to severe hyperglycemia has also been observed after burns both in children and in adults.[47,51] Similarily, elevated BG levels ranging from 120 to 685 mg/dl have been seen in 22 of 25 children being dehydrated by diarrhea and vomiting.[52] In patients with hypernatriemic dehydration, hyperosmolal hyperglycemia normalized on correction of fluid losses and the use of insulin has been discouraged in these children, even when concomitant hyperglycemia was severe. It has been emphasized that if this hyperglycemia is mistaken for diabetes mellitus and insulin is given, the rapid fall of BG could lead to cerebral overhydration with drowsiness, coma, and death.[53]

The impact of both dehydration and elevated serum osmolality on blood glucose concentration is demonstrated by the failure to induce a fall in BG in patient no. 3 before low dose insulin treatment. In this patient, dehydration was maintained in contrast with all other patients by infusion of isotonic saline, and serum osmolality even rose, as did BG (Figure 4). Since fluid replacement by isotonic saline induced a fall in BG in only 12 out of 18 severely hyperglycemic patients[29] as compared with 9 out of 9 rehydrated in this study by hypoosmolal fluid, the latter seems to be superior for restoring insulin sensitivity of dehydrated target tissues.

Thus it appears that marked hyperglycemia, which is initiated by absolute or relative deficiency or by other causes, induces via osmotic diuresis and its attendant loss of fluid and electrolytes cellular dehydration and possibly insulin resistance. This effect would impair glucose utilization even further, induce additional fluid loss, and initiate a vicious cycle leading eventually to severe insulin resistance and hyperosmolal coma.

We conclude from our findings that rehydration of a hyperosmolal, severely hyperglycemic diabetic patient reduces insulin resistance and facilitates the biologic response of the previously dehydrated cell toward insulin. Treatment of such a hyperosmolal state demands strictly controlled fluid replacement and by this means restoration of insulin sensitivity. The use of proper rehydration during the last decade might explain the fall in the reported insulin requirement for the treatment of diabetic therapy.[25–30,54] For practical treatment of severe hyperglycemia, we feel that proper hypoosmolal rehydration has to be initiated in parallel with low dose insulin treatment (2–6 U/h), thereby improving response of the respective target tissues for insulin action and ameliorating glucose utilization.

ACKNOWLEDGMENTS

This study was supported in part by grants M2–2777 and 3875 of the Fonds zur Förderung der Wissenschaftlichen Forschung Österreichs.

Grateful thanks go to Ms. Astrid Hofer and Ms. Erika Nowotny for skilled technical assistance and to Ms. Christa Strasser for secretarial help.

REFERENCES

[1] Cryer, P. E.: Diagnostic Endocrinology. New York, Oxford University Press, 1976, p. 180.

[2] Chiumello, G., DelGuerico, J., and Bidone, G.: Effects of glucagon and tolbutamide on plasma insulin levels in children with ketoacidosis. Diabetes *17*:133–35, 1968.

[3] Baker, L., Kaye, F., and Root, A. W.: The early partial remission of juvenile diabetes mellitus. The roles of insulin and growth hormone. J. Pediatr. *71*:825–31, 1967.

[4] Illig, R., and Prader, A.: Remission of juvenile diabetes. Lancet *2*: 1190, 1968 (Letter).

[5] Parker, M. L., Pildes, R. S., Chao, K. L., Cornblath, M., and Kipnis, D. M.: Juvenile diabetes mellitus, a deficiency in insulin. Diabetes *17*:27–32, 1968.

[6] Block, M. B., Mako, M. E., Steiner, D. F., and Rubenstein, A. H.: Diabetic ketoacidosis: evidence for C-peptide and proinsulin secretion following recovery. J. Clin. Endocrinol. Metab. *35*:402–06, 1972.

[7] Heding, L. G.: Radioimmunological determination of human C-peptide in serum. Diabetologia *11*:541–48, 1975.

[8] Genuth, S. M.: Clinical remission in diabetes mellitus. Studies of insulin secretion. Diabetes *19*:116–21, 1970.

[9] Walker, B. G., Phear, D. N., Martin, F. I. R., and Baird, C. W.: Inhibition of insulin by acidosis. Lancet *2*:964–65, 1963.

[10] Ginsberg, H. N.: Investigation of insulin resistance during diabetic ketoacidosis: Role of counterregulatory substances and effect of insulin therapy. Metabolism *26*:1135–46, 1977.

[11] Assan, R., Hautecouverture, G., Guillemant, S., Dauchy, F., Protin, P., and Derot, M.: Evolution de paramètres hormonaux (glucagon, cortisol, hormone somatotrope) et énergétiques (glucose-acides gras-glycerollibre) dans 10 acidocétoses graves traiteés. Pathol. Biol. *17*:1095–1105, 1969.

[12] Müller, W. A., Faloona, G. F., and Unger, R. H.: Hyperglucagonemia in diabetic ketoacidosis. Am. J. Med. *54*:52–57, 1973.

[13] Christensen, N. J.: Plasma norepinephrine and epinephrine in untreated diabetics during fasting and after insulin administration. Diabetes *23*:1–8, 1974.

[14] Jahnke, K., and Buro, F.: Das Coma diabeticum. Verh. Deutsch. Ges. Inn. Med. *76*:359–70, 1970.

[15] Gerich, J. E., Martin, M. M., and Recant, L.: Clinical and metabolic characteristics of hyperosmolar nonketotic coma. Diabetes *20*:228–38, 1971.

[16] Unger, R.: High growth hormone levels in diabetic ketoacidosis: a possible cause of insulin resistance. J.A.M.A. *191*:149–51, 1965.

[17] Alberti, K. G., and Hockaday, T. D.: Diabetic coma: serum growth hormone before and during treatment. Diabetologia *9*:13–19, 1973.

[18] Gerich, J., Lorenzi, M., Bier, D., Schneider, V., Tsalikian, E., Karam, J., and Forsham, P.: Prevention of human diabetic ketoacidosis by somatostatin: evidence for an essential role of glucagon. N. Engl. J. Med. *292*: 985–89, 1975.

[19] Atchley, D. W., Loeb, R. F., Richards, D. W., Jr., Benedict, E. M., and Driscoll, M. E.: On diabetic acidosis. A detailed study of electrolyte balances following the withdrawal and reestablishment of insulin therapy. J. Clin. Invest. *12*:297–326, 1933.

[20] Butler, A. M., Talbot, N. B., Burnett, C. H., Stanbury, J. B., and McLachlan, E. A.: Metabolic studies in diabetic coma. Trans. Assoc. Am. Phys. *60*:102, 1947.

[21] Martin, H. E., Smith, K., and Wilson, M. L.: The fluid and electrolyte therapy of severe diabetic acidosis and ketosis: a study of twenty nine episodes (twenty-six patients). Am. J. Med. *24*:376–89, 1958.

[22] Bradley, R. F.: Diabetic ketoacidosis and coma. *In* Joslin's Diabetes Mellitus, A. Marble, P. White, R. F. Bradley and L. P. Krall, Eds. Philadelphia, Lea & Febiger, 1971, pp. 361–416.

[23] Froesch, E. R., Bühlmann, A., and Rossier, P. H.: Das Coma diabeticum in heutiger Sicht. Verh. Deutsch. Ges. Inn. Med. *72*:199–220, 1966.

[24] Tucker, W. R., Klink, D., Goetz, F., Zalme, E., and Knowles, H. C., Jr.: Insulin resistance and acanthosis nigricans. Diabetes *13*:395–99, 1964.

[25] Faber, K., and Holst, J. E.: Die Behandlung des Coma diabeticum ohne Zufuhr von Kohlehydraten. Acta Med. Scand. *65*:461–73, 1927.

[26] Kraegen, E. W., Smythe, G. A., and Lazarus, L.: Plasma glucose response to physiological increments of serum insulin in man. Proc. Endocrinol. Soc. Aust. *14*:27–31, 1971.

[27] Alberti, K. G. M., Hockaday, T. D. R., and Turner, R. C.: Small doses of intramuscular insulin in the treatment of diabetic "coma." Lancet *2*:515–22, 1973.

[28] Heber, D., Moltich, M. E., and Sperling, M. A.: Low dose continuous insulin therapy for diabetic ketoacidosis. Arch. Intern. Med. *137*:1377–80, 1977.

[29] Page, M. McB., Alberti, K. G. M. M., Greenwood, R., Gumaa, K. A., Hockaday, T. D. R., Lowy, C., Nabarro, J. D. N., Pyke, D. A., Sönksen, P. H., Watkins, P. J., and West, T. E. T.: Treatment of diabetic coma with continuous low dose infusion of insulin. Br. Med. J. *2*:687–90, 1974.

[30] Waldhäusl, W., Bratusch-Marrain, P., Dudczak, R., and Deutsch, E.: The diabetogenic action of somatostatin in healthy subjects and in maturity onset diabetics. J. Clin. Endocrinol. Metab. *44*:876–83, 1977.

[31] Waldhäusl, W., and Lewandowsky, J. A.: Measurement of plasma renin concentration (PRC) by use of exogenous substrate and radioimmunoassay. Eur. J. Clin. Invest. *3*:1–9, 1973.

[32] Herkner, K., Nowotny, P., and Waldhäusl, W.: Die Bestimmung von Aldosteron in Harn and Plasma. J. Chromat. *146*:273–81, 1978.

[33] Waldhäusl, W., Herkner, K., Nowotny, P., and Bratusch-Marrain, P.: Combined 17α- and 18-Hydroxylase deficiency associated with complete male pseudohermaphroditism and hypoaldosteronism. J. Clin. Endocrinol. Metab. *46*:236–46, 1978.

[34] Greenwood, F. C., Hunter, W. M., and Glover, J. S.: The preparation of 131-I-labelled human growth hormone of high specific activity. Biochem. J. *89*:114–23, 1963.

[35] Arnaud, C. D., Tsao, H. S., Littledike, T., Laakso, K., and Bischoff, J.: Radioimmunoassay of human parathyroid hormone in serum. J. Clin. Invest. *50*:21–34, 1971.

[36] Engelman, K., and Portnoy, B.: A sensitive double isotope derivative assay for norepinephrine and epinephrine. Circ. Res. *26*:53–57, 1970.

[37] Jahnke, K.: Coma diabeticum: *In* Handb. d. Inneren Medizin, Vol. 7, 2B. K. Oberdisse, Ed. Berlin, Heidelberg, New York, Springer-Verlag, 1977, pp. 605–708.

[38] Waldhäusl, W., and Pall, H.: Diabetisches Koma. Intensivmedizin *11*:305–16, 1974.

[39] Cryer, P. E., and Daughaday, W. H.: Diabetic ketoacidosis: Serial plasma growth hormone concentrations during therapy. Diabetes *19*:519–23, 1970.

[40] Christlieb, A. R., Assal, J. P., Katsilambros, N., Williams, G. H., Kozak, G. P., and Suzuki, T.: Plasma renin activity and blood volume in uncontrolled diabetes. Diabetes *24*:190–93, 1975.

[41] Christlieb, A. R.: Renin-angiotensin-aldosterone system in diabetes mellitus. Diabetes *25* (Suppl. 2):820–25, 1976.

[42] Schade, D. S., and Eaton, R. P.: Induction of ketoacidosis by steroids in diabetic man. Diabetes *25* (Suppl. 1):330, 1976 (Abstract 39).

[43] Schade, D. S., and Eaton, R. P.: The regulation of plasma ketone body concentration by counterregulatory hormones in man. I. Effects of norepinephrine in diabetic man. Diabetes *26*:989–96, 1977.

[44] Alberti, K. G. M. M., Barnes, A. J., Bloom, S. R., Holloway, P. A. H., Johnston, D. G., and Ørskov, H.: The role of hormones in the pathogenesis of severe diabetic ketoacidosis: implications for treatment. *In* Diabetes. J. S. Bajaj, Ed. Amsterdam-Oxford, Excerpta Medica, International Congress Series *413*, 1977, pp. 367–73.

[45] Floyd, J. C., Jr., Fajans, S. S., Pek, S., and Chance, R. E.: A newly recognized pancreatic polypeptide; plasma levels in health and disease. Rec. Prog. Horm. Res. *33*:519–70, 1977.

[46] Alberti, K. G. M., Christensen, N. J., Iversen, J., and Ørskov, H.: Role of glucagon and other hormones in development of diabetic ketoacidosis. Lancet *1*:1307–11, 1975.

[47] Rosenberg, S. A., Brief, D. K., Kinney, J. M., Herrera, M. G., Wilso, R. E., and Moore, F. D.: The syndrome of dehydration, coma and severe hyperglycaemia without ketosis in patients convalescing from burns. N. Engl. J. Med. *272*:931–38, 1965.

[48] Perkins, K. C.: Hyperglycemia without ketosis or hypernatremia. Am. J. Dis. Child. *128*:885, 1974.

[49] Stevenson, R. E., and Bowyer, F. P.: Hyperglycemia with hyperosmolal dehydration in non-diabetic infants. Pediatrics *77*:818–23, 1970.

[50] White, A., Handler, P., and Smith, E. L.: Principles of Biochemistry, 5th edit. New York, McGraw-Hill, 1973, pp. 412–513; 1072–1104.

[51] Bailey, B. N.: Hyperglycemia in burns. Br. Med. J. *2*:1783–85, 1960.

[52] Mandell, F., and Fellers, F. X.: Hyperglycemia in hypernatremic dehydration. Clin. Paediatr. *13*:367–69, 1974.

[53] Finberg, L.: Hypernatremic (hypertonic) dehydration in infants. N. Engl. J. Med. *289*:196–98, 1973.

[54] Campbell, L. V., Lazarus, L., Casey, J. H., and Kraegen, E. W.: Routine use of low dose intravenous insulin infusion in severe hyperglycaemia. Med. J. Aust. *2*:519–22, 1976.