Thirty Years of Personal Experience in Hyperglycemic Crises: Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State

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Context: Diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) cause major morbidity and significant mortality in patients with diabetes mellitus. For more than 30 yr, our group, in a series of prospective, randomized clinical studies, has investigated the pathogenesis and evolving strategies of the treatment of hyperglycemic crises. This paper summarizes the results of these prospective studies on the management and pathophysiology of DKA.

Setting: Our earliest studies evaluated the comparative efficacy of low-dose *vs.* pharmacological amounts of insulin and the use of low-dose therapy by various routes in adults and later in children. Subsequent studies evaluated phosphate and bicarbonate therapy, lipid metabolism, ketosis-prone type 2 patients, and use of rapid-acting insulin analogs as well as leptin status, cardiac risk factors, proinflammatory cytokines, and the mechanism of activation of T lymphocytes in hyperglycemic crises.

Main Outcome: The information garnered from these studies resulted in the creation of the 2001 American Diabetes Association (ADA) technical review on DKA and HHS as well as the ADA Position and Consensus Paper on the therapy for hyperglycemic crises.

Conclusions: Areas of future research include prospective randomized studies to do the following: 1) establish the efficacy of bicarbonate therapy in DKA for a pH less than 6.9; 2) establish the need for a bolus insulin dose in the initial therapy of DKA; 3) determine the pathophysiological mechanisms for the absence of ketosis in HHS; 4) investigate the reasons for elevated proinflammatory cytokines and cardiovascular risk factors; and 5) evaluate the efficacy and cost benefit of using sc regular insulin *vs.* more expensive insulin analogs on the general ward for the treatment of DKA. **(*J Clin Endocrinol Metab* 93: 1541–1552, 2008)**

It has been more than 30 yr since our first publication on the treatment of diabetic ketoacidosis (DKA), entitled "Efficacy of low-dose *vs*. conventional therapy of insulin for treatment of diabetic ketoacidosis" (1). We had based our method of research on the clinical trial design known as a prospective study that compares the effect and value of intervention against a control human subject (2). A prospective, randomized clinical trial is the most definitive tool to evaluate the validity of clinical research and to identify research activities with a potential to improve the quality of health care and control costs through careful comparison of alternative treatment (2). This review describes our journey in the field over the past three decades and summarizes major advances in the pathogenesis and treatment of patients with hyperglycemic crises.

DKA is the most serious hyperglycemic emergency in patients with type 1 and type 2 diabetes mellitus and is associated with significant morbidity and mortality (3). The mortality for DKA before the discovery of insulin was greater than 90%. This was dramatically reduced in subsequent years to less than 50% and was further reduced to less than 20% with the incorporation of

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Abbreviations: ADA, American Diabetes Association; BUN, blood urea nitrogen; CSF, cerebrospinal fluid; DCF, dichlorofluorescein; DKA, diabetic ketoacidosis; GCRC, General Clinical Research Center; HHS, hyperglycemic hyperosmolar state; Iβ_2M, immunoreactive β_2-microglubulin; IRI, immunoreactive insulin; ROS, reactive oxygen species; TBA, thiobarbituric acid.

antibiotics and forced hydration into the therapeutic armamentarium (4). In the 1950s, the mortality of patients with DKA treated with high doses of insulin was reported to be less than 10% (5). In more recent years, the use of standardized written guidelines for therapy has resulted in a mortality rate less than 2%, with higher mortality observed in elderly subjects and in patients with concomitant life threatening illnesses (5, 6).

In the early years of insulin therapy, due to limited supply, small amounts of insulin were used to treat DKA. Although low-dose insulin therapy was found to be effective (7), high-dose insulin therapy became the standard of care (8, 9). Between the 1950s and early 1970s, up to 100 U/h or more were given iv, sc, or im due to perceived insulin resistance. Complicated schemes were devised for the selection of initial and subsequent insulin dosage based on the degree of hyperglycemia, ketonemia, and level of consciousness. These retrospective nonrandomized studies in the 1950s and 1960s were later replaced by prospective randomized studies showing no advantage of high-dose insulin, compared with lower doses (10, 11).

In 1973 Alberti *et al.* (12) reported the results of low-dose im insulin in the management of patients with mild to moderate DKA. They reported that an initial average bolus dose of 16 U followed by 5–10 U of im regular insulin per hour was effective in correcting hyperglycemia and metabolic acidosis (13). This report, however, was taken with some skepticism because it was not a prospective randomized trial. Based on these findings, we initiated a series of prospective randomized clinical studies on the management of DKA. Six major issues needed to be considered and properly addressed before the initiation of these studies:

1. Adequate number of study patients. At our county teaching hospital, the Regional Medical Center, we were able to treat approximately 100 patients with acute hyperglycemic crises per year. This allowed us to have enough power to undertake our first randomized protocol (1).

2. Approval of simple and scientifically valid treatment protocol, by the University of Tennessee Institutional Review Board and the Scientific Advisory Committee of the General Clinical Research Center (GCRC).

3. Establishment of inclusion/exclusion criteria. We were cautious to exclude patients who might have other comorbid conditions that might distract the house staff from focusing on the management of the hyperglycemic state.

4. Administrative support for treatment protocol. It was critical to efficiently transfer eligible DKA patients from the emergency room to the GCRC to complete the protocol with a high degree of accuracy. This was supported by the Chief of Medicine and Physician-in-Chief at the Regional Medical Center, who endorsed the protocol.

5. Dissemination of the protocol to the house staff. The house staff were informed of the approved protocol at various conferences, medicine grand rounds, and in-service training and were given 3×5 in. pocket-size index cards imprinted with the protocol.

6. Simplification of procedures in the GCRC and identification of on-call personnel. To ensure patient safety and increase the confidence level of students and medicine house staff, we established nursing and endocrine service coverage 7 d/wk, 24 h/d in the GCRC under the direction of endocrine staff on call. A critical component to the success of this study was the rapid turnaround of the biochemical profile, which was done in the GCRC, and supported treatment changes on an hour-to-hour basis. This service increased patient safety and resulted in an excellent educational experience.

The results of our first protocol, which took about 2 yr to complete, proved to be gratifying not only to us for providing the scientific community with evidence-based data but also to more than 120 house staff who played a pivotal role in the execution of this program. We therefore acknowledged them as a fourth author in our first publication (1).

DKA Protocols

The major protocols (1976–1986), which are described in Fig. 1 consisted of seven prospective randomized studies in the GCRC (14).

Protocol I: High-Dose *vs.* Low-Dose Insulin in Adult DKA

The first protocol was designed to clarify the controversy surrounding the use of low-dose insulin treatment, addressing the following three questions: 1) Is low-dose im insulin effective in the treatment of DKA; 2) how does low-dose im insulin treatment compare with conventional high-dose therapy; and 3) how do plasma insulin values compare with the two regimens?

From February 1974 until June 1975, 48 patients were admitted to the GCRC, which accounted for approximately 75% of all patients admitted with DKA during that period. Patients were randomized to receive either a high-dose or low-dose insulin regimen. The high-dose regimen was initially based on the blood glucose concentration on admission with a minimum of 10 U insulin iv plus 30 U insulin sc for blood glucose 300–399 mg/dl up to 50 U insulin iv plus 100 U insulin sc for blood glucose $>$ 1000 mg/dl (Fig. 1). This was followed by 50 U of insulin sc per hour. The low-dose regimen of insulin was given according to body weight, *i.e.* 0.22 U/kg of body weight im initially, followed by 5 U/h im. Outcome measurements included duration of treatment for glucose levels to reach 250 mg/dl, pH to reach 7.3, and serum bicarbonate to reach 15 mEq/liter. We observed the following results: 1) admission biochemical profiles in the two groups were not significantly different, validating the randomization process; 2) outcome measurements were not significantly different in the two groups despite the fact that the high-dose group received an average of 263 ± 45 U insulin, compared with 46 ± 5 U for the low-dose group, to achieve a glucose value of 250 mg/dl (Fig. 2) (1); 3) cortisol and glucagon, which were elevated on admission to a similar degree, declined during treatment at the same rate in the two groups; 4) insulin levels were measured in those patients not previously treated with insulin, and it was observed that high-dose therapy produced pharmacological levels (800–1000 μU/ml), whereas low-dose therapy resulted in physiological levels of 60–100 μU/ml (Fig. 3, A and B) (15), and despite these differences, the rate of glucose decline

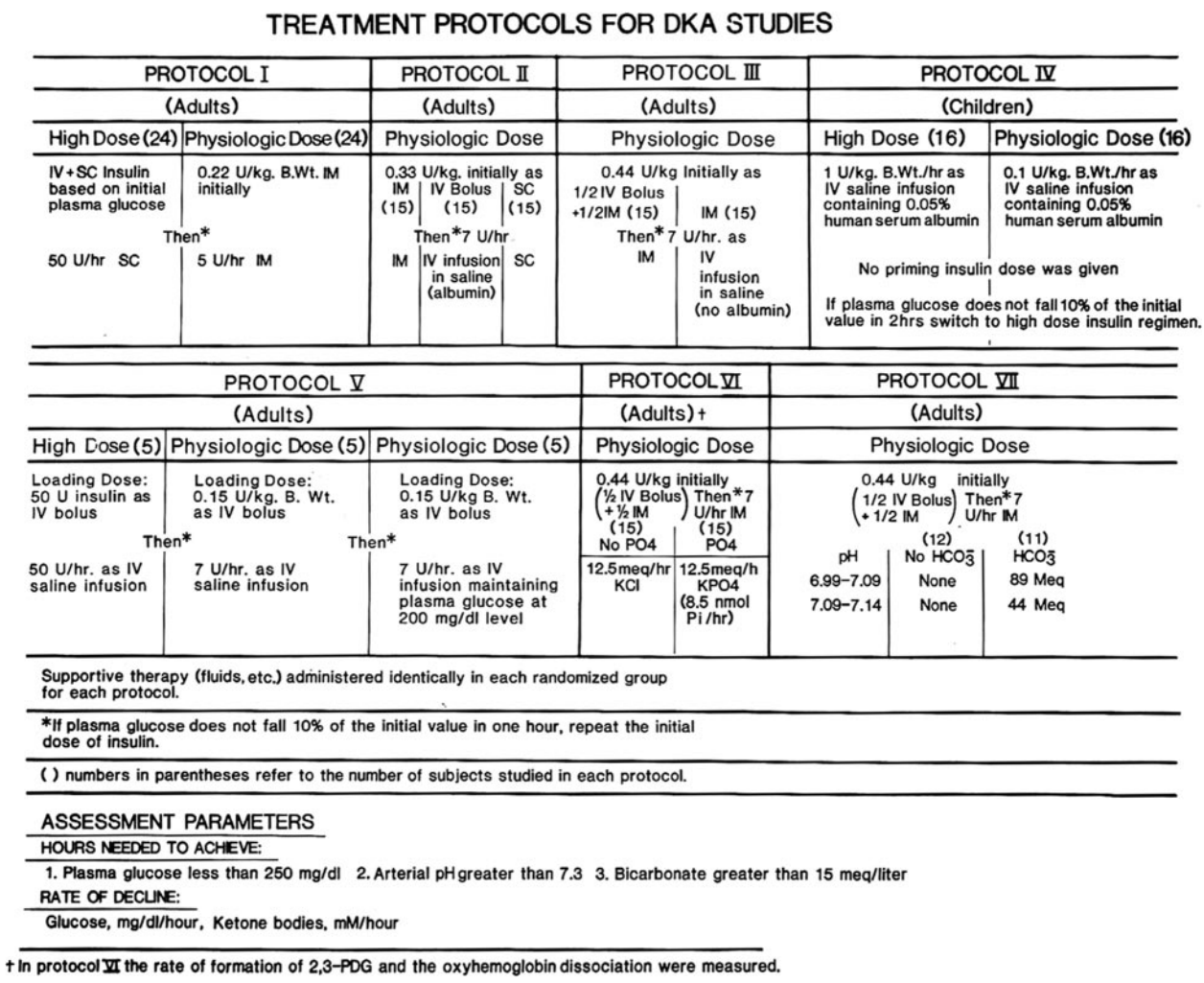

FIG. 1. Treatment protocols for DKA studies (14).

and reduction in ketone bodies was similar in the two groups (Fig. 2); 5) considering the difference in the insulin levels, it was not surprising that the high-dose group had a 25% incidence of hypoglycemia, whereas the low-dose group had none. In addition, seven of 24 in the high-dose group but only one of 24 in the low-dose group developed hypokalemia; and 6) no deaths occurred in either group, even though seven patients in the high-dose and five in the low-dose group were stuporous or comatose on admission. It was of historical interest that during this period of our study, the treatment of patients during resolution of DKA in community hospitals was based on sliding scale insulin using qualitative urine glucose, as blood glucose meters were not widely used. However, later we demonstrated the inaccuracy of urine glucose by dipstick (16), and, therefore, discouraged the further use of sliding scale based on urine glucose testing.

Protocol II: Route of Insulin Administration

In Protocol II the route of insulin administration was studied to determine whether a bolus dose of insulin administered iv would produce the same effect on glucose, ketone bodies, and other metabolic parameters as an identical amount given im or sc. We randomized 45 consecutive patients presenting in DKA. Fifteen subjects in each group received insulin by the iv, im, or sc route, all other aspects of their care remaining the same (17). Regardless of their initial plasma glucose, all patients were given 0.33 U regular insulin per kilogram body weight as an iv, im, or sc bolus. Subsequently 7 U regular insulin per hour were administered by the same route until plasma glucose reached 250 mg/dl. We observed that low-dose insulin was highly effective in treating DKA, but several interesting observations were made: 1) iv insulin resulted in a significant decline in ketone bodies over the first 2 h of treatment, compared with the im or sc groups; 2) the decrement of glucose was significantly more rapid in the iv group over the first 2 h, but the three groups were similar by the eighth hour (Fig. 4); 3) whereas 30–40% of patients in the im and sc groups failed to lower their plasma glucose by at least 10% in the first hour after insulin was begun, 90% of the iv group did so; and 4) plasma insulin concentration in the iv group peaked in the first few minutes to supraphysiologic levels of greater than 3000 μU/ml and then reached a plateau of about 100 μU/ml in 4 h. The im and sc groups experienced a gradual rise over 3–4 h to a peak level of 100 μU/ml (Fig. 3, C–E). All three groups maintained this plateau over 8 h of observation.

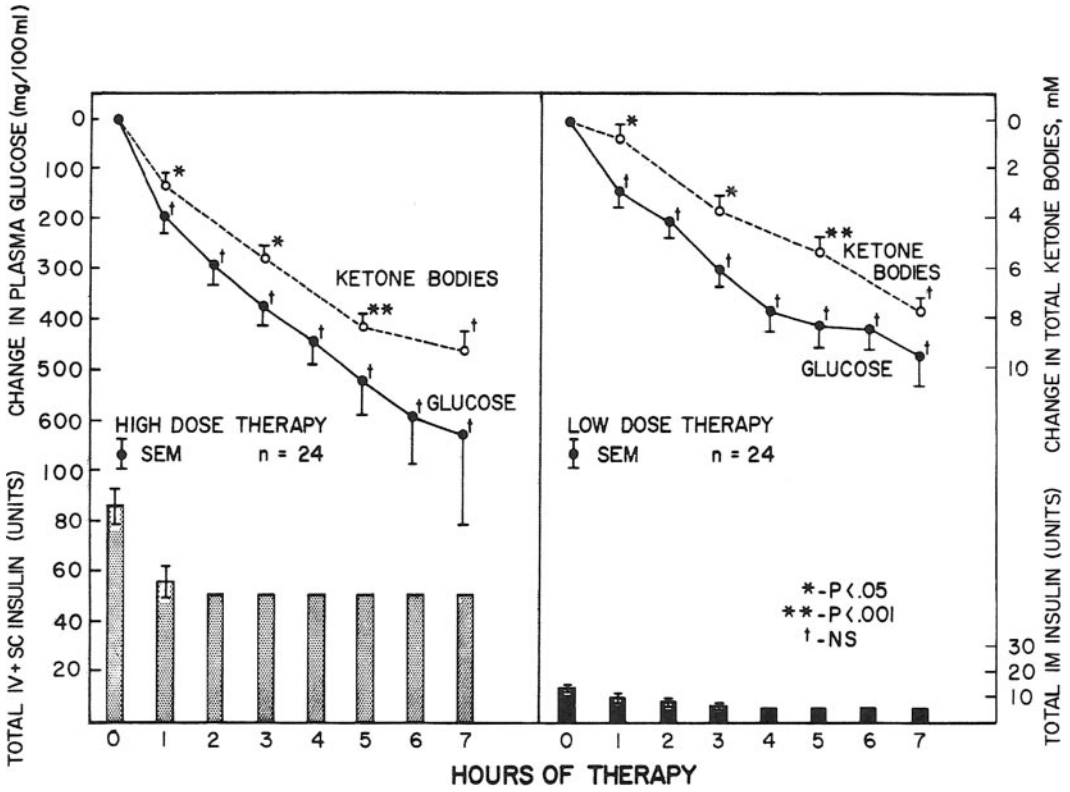

FIG. 2. The efficacy of low-dose *vs.* conventional therapy of insulin for treatment of DKA. Reproduced from Kitabchi *et al.* (1) with permission of the *Annals of Internal Medicine*.

Protocol III: Loading *vs.* No-Loading Insulin

Prompted by these observations, protocol III (18) was designed to answer the following three questions: 1) could the delay in decrement in ketone bodies noted in DKA patients treated with im and sc insulin be prevented by giving an initial loading dose of regular insulin, half iv and half im; 2) how would that approach compare with a group given continuous iv treatment; and 3) is the use of albumin necessary with insulin infusion? In a randomized, prospective study of 30 patients in DKA, 15 patients received a loading dose of 0.44 U/kg body weight of regular insulin, half iv and half im, followed by 7 U/h im, whereas the other 15 patients received a loading dose of 0.44 U/kg im followed by a constant insulin infusion of 7 U/h in albumin-free saline. Recovery parameters were not significantly different in the two groups, indicating that low doses of insulin administered by the priming dose-intermittent im route are as effective as the constant infusion method. It was also shown that the use of iv insulin ameliorated the delay for decremental changes in ketone bodies. This improvement was due to a higher level of plasma insulin when administered iv, compared with the im method (Fig. 3). Furthermore, we demonstrated that it was not necessary to add albumin to the insulin infusate, as we had done in previous protocols.

We then correlated the admission metabolic profiles (Table 1) with the state of consciousness (15). These studies showed that about one third of DKA patients are hyperosmolar and that mental status on admission related to serum osmolality and not to the severity of the acid-base disorder (Fig. 5) (19). Due to the controversy concerning the cause of mental obtundation, we assessed our earlier study of 48 patients with DKA using high- or low-dose insulin (1) in regard to initial biochemical parameters (pH, HCO_3, ketones, glucose, and osmolality) and age in relation to mental status in comatose (n = 13) *vs.* alert patients (n = 35). Generally, comatose patients were older and had higher glucose, blood urea nitrogen (BUN), and osmolality levels but lower levels of bicarbonate, which were significantly different from noncomatose patients. Conversely, plasma pH and ketone bodies were not significantly different between the two groups (Table 2) (20). Furthermore, responses to low-dose therapy were the same in comatose or alert patients, except for hours to reach glucose 250 mg/dl or less.

Protocol IV: High-Dose *vs.* Low-Dose Insulin in Pediatric Patients with DKA

Although our studies and those of others (for review see Ref. 15) provided convincing proof of the efficacy of low-dose insulin protocols in the treatment of DKA in adult subjects, there was insufficient data from randomized prospective investigations to make a similar assertion in children. For that reason we embarked on protocol IV in collaboration with pediatric colleagues (21). In this study we used only the iv route of insulin to avoid possible problems with insulin absorption given im or sc in pediatric patients who might be severely dehydrated, leading to poor tissue perfusion. We

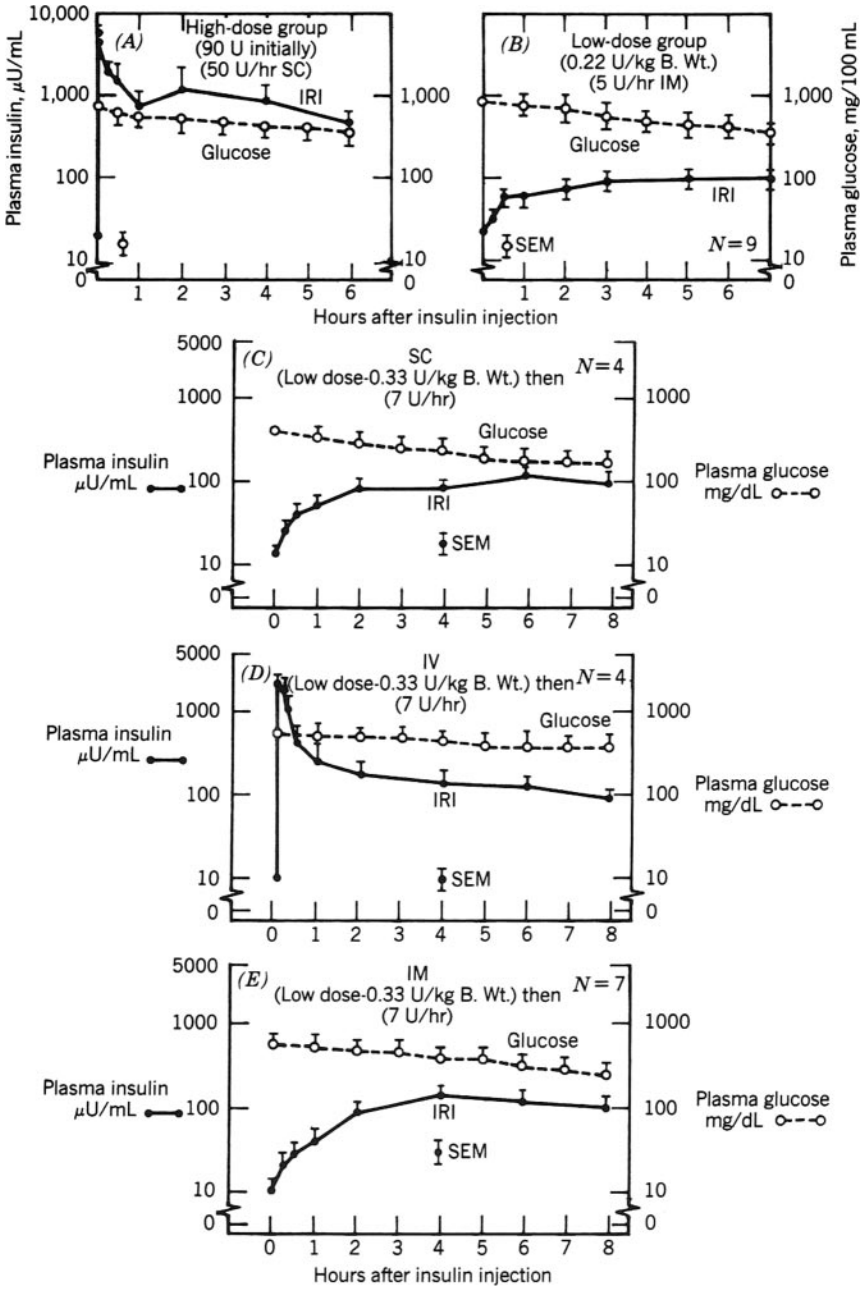

FIG. 3. Comparison of high-insulin dosage (A) with low-insulin dosage group (B) as well as low-dose insulin dosage by the sc (C), iv (D), and im (E) routes in plasma. IRI and its glucose-lowering effect in DKA patients previously untreated with insulin. B. Wt., Body weight. Reproduced, with permission, from Kitabchi *et al.* (15).

compared a low dose (0.1 U/kg·h) *vs.* a high dose (1.0 U/kg·h) of regular insulin in 32 children, 16 in each group. Thanks to randomized assignment, the treatment groups were comparable in all clinical and biochemical aspects on admission. As in adults, low-dose insulin treatment was as effective as high-dose treatment, although glucose reached 250 mg/dl in the high-dose group in 3.4 ± 0.4 h *vs.* 5.4 ± 0.5 h in the low-dose group ($P < 0.01$). Additionally it was noted that: 1) it was not necessary to use a priming dose of insulin when the iv route was used; 2) 12 patients in the high-dose group but only two in the low-dose group developed a blood glucose less than 100 during treatment; and 3) 63% of the high-dose group, compared with only 19% of the low-dose group, had a potassium less than 3.4 mEq/liter. The data indicated that low-dose insulin, despite a slower rate of glucose decline, was as effective as high dose for the treatment of DKA in children. Furthermore, there was less incidence of hypokalemia and a decreased potential for hypoglycemia with the use of more physiological rather than pharmacological amounts of insulin (21).

The efficacy of low-dose insulin regimens was thus established in a strictly controlled environment, but it was not clear whether similar results could be obtained in a community hospital. In a nonrandomized but prospective study, we evaluated the effectiveness of low-dose insulin in a private community university-affiliated hospital under the care of an established diabetologist, with the help of the medical house staff. This study showed that low-dose insulin in DKA is as effective in a private community hospital as in a more academic and controlled environment with no morbidity or mortality (22).

Protocol V: Metabolism of Low-Dose Insulin in DKA

Because there was little known about the renal metabolism of insulin during treatment and after recovery of DKA, we then investigated the urinary clearance of immunoreactive insulin (IRI) during physiological and pharmacological concentrations of IRI (23). Immunoreactive β_2-microglubulin ($I\beta_2M$) was measured simultaneously as a marker of proximal tubular function initially and 2–3 wk later. Ten patients in DKA were randomly assigned to receive either low-dose or high-dose insulin therapy (protocol V). Two to three wk after the correction of hyperglycemia, five patients were restudied. In protocol V we observed the following: 1) an approximately 250-fold increase in urinary and fractional urinary clearance of IRI and a 600-fold increase in $I\beta_2M$ clearance, suggesting that hyperinsulinuria was secondary to a nonspecific defect in tubular luminal uptake of low-molecular weight proteins; 2) because increased IRI clearance was not changed by pharmacologic IRI plasma levels, residual tubular absorptive capacity is not saturable; 3) $I\beta_2M$ but not IRI clearance was significantly improved by the time metabolic control was attained, which suggested a defect tubular transport systems; 4) a therapeutically insignificant fraction of infused insulin was lost in the

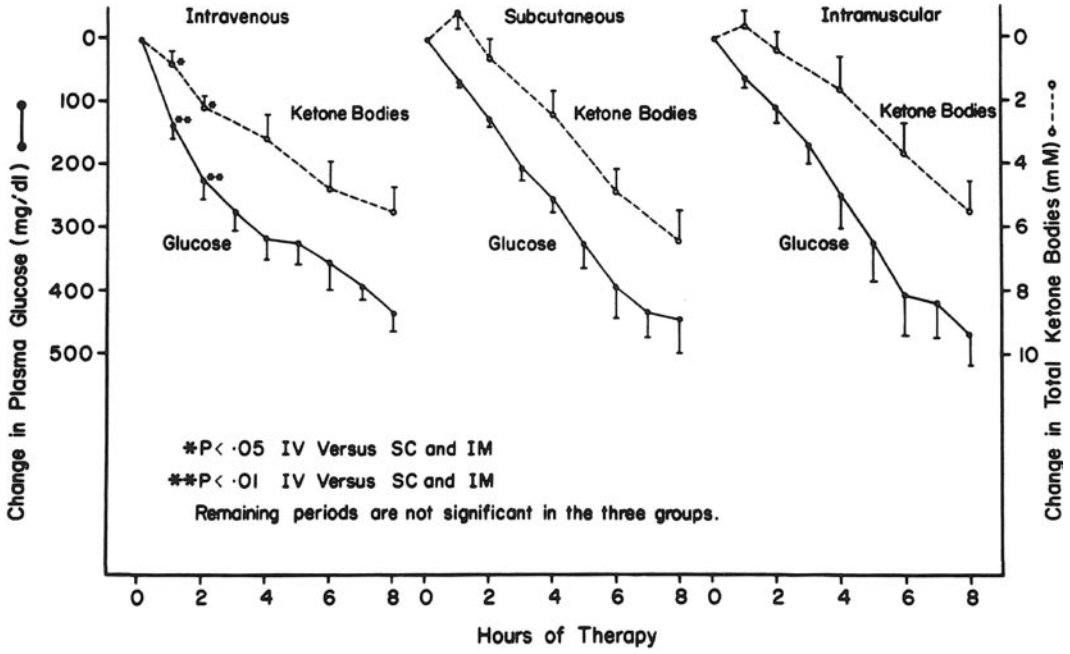

FIG. 4. Comparison of the effects of iv, sc, and im low-dose insulin regimens on changes of plasma glucose and total ketone bodies in patients with DKA. Reprinted from Fisher *et al.* (17), with permission of the *New England Journal of Medicine*.

urine during treatment of DKA; and 5) defective renal tubular luminal uptake (and possibly degradation) of IRI was reversible.

Protocol VI: Use of Phosphate Therapy in DKA

In protocol VI we investigated the long-standing controversy surrounding the use of phosphate therapy in DKA (24). In a prospective, randomized study we evaluated 15 patients with DKA treated with a low-dose insulin protocol who received 12.5 mEq/h of a buffered potassium phosphate salt plus potassium at a rate of 12.5 mEq/h. Another 15 patients were assigned to receive potassium chloride 12.5 mEq/h alone. We found that the phosphate-treated patients had higher levels of 2, 3-diphosphoglyceric acid at the end of 48 h, but the difference was not significant and there was no demonstrable effect on tissue oxygenation or clinical response. Furthermore, phosphate therapy was associated with significantly lower ionized calcium levels. We concluded because of that observation there is reason for caution in the use of phosphate salts in the treatment of DKA, but there are circumstances, as in patients with congestive heart failure,

TABLE 1. Clinical and biochemical profile of DKA patients on admission[a]

	Protocol I[b]		Protocol II (low dose)[c]			Protocol III (low dose)[d]	
	High dose	Low dose	im	sc	iv	iv	im
No. of patients	24	24	15	15	15	15	15
Age (range) (yr)	40.3 (15–70)	38.7 (15–67)	40.7 (19–64)	44.3 (28–75)	37.2 (21–69)	40.6 (20–70)	35.2 (20–68)
Glucose (mg/dl)	697 ± 59	723 ± 61	523 ± 57	579 ± 62	590 ± 58	548 ± 53	584 ± 52
Sodium (mEq/liter)	137.4 ± 1.7	136.5 ± 1.4	134 ± 2	136 ± 2	138 ± 2	132 ± 2	134 ± 1
Potassium (mEq/liter)	5.4 ± 0.2	5.9 ± 0.3	5.5 ± 0.4	5.8 ± 0.3	6.0 ± 0.3	5.7 ± 0.3	5.9 ± 0.3
Bicarbonate (mEq/liter)	8.1 ± 0.7	7.7 ± 0.5	4.3 ± 0.7	5.7 ± 0.8	5.5 ± 0.8	6.6 ± 1.0	6.1 ± 1.0
BUN (mg/dl)	30 ± 5	35 ± 4	33 ± 5	28 ± 4	31 ± 4	22 ± 3	27 ± 5
pH	7.15 ± 0.02	7.13 ± 0.02	7.09 ± 0.02	7.11 ± 0.03	7.10 ± 0.02	7.14 ± 0.05	7.03 ± 0.04
Cortisol (μg/dl)	72 ± 8	78 ± 6	44 ± 7	58 ± 8	68 ± 8	51 ± 8	75 ± 12
Glucgon (pg/ml)	409 ± 53	592 ± 90	588 ± 140	543 ± 167	377 ± 74	649 ± 241	903 ± 263
β-Hydroxybutyrate (mM)	10.3 ± 0.5	11.3 ± 0.6	9.6 ± 0.6	10.0 ± 1.0	10.0 ± 1.0	8.7 ± 1.2	8.8 ± 1.2
Acetoacetate (mM)	3.4 ± 0.3	3.0 ± 0.2	2.9 ± 0.3	3.7 ± 0.4	3.0 ± 0.3	2.8 ± .22	2.6 ± 0.4
Pyruvate (mg/dl)	0.8 ± 0.1	1.0 ± 0.2	0.89 ± 0.2	0.66 ± 0.07	0.74 ± 0.09	0.5 ± 0.1	0.5 ± 0.1
Lactate (mg/dl)	20.6 ± 2.2	25.8 ± 2.4	25.4 ± 5.4	22.2 ± 2.4	20.0 ± 2.5	20.1 ± 4.1	23.7 ± 3.2

Reproduced with permission from Kitabchi *et al.* (15).

[a] Values, when applicable, are mean ± SEM after initial hydration in the emergency room prior to any other therapy.

[b] Kitabchi *et al.* (1).

[c] Fisher *et al.* (17).

[d] Sacks *et al.* (18).

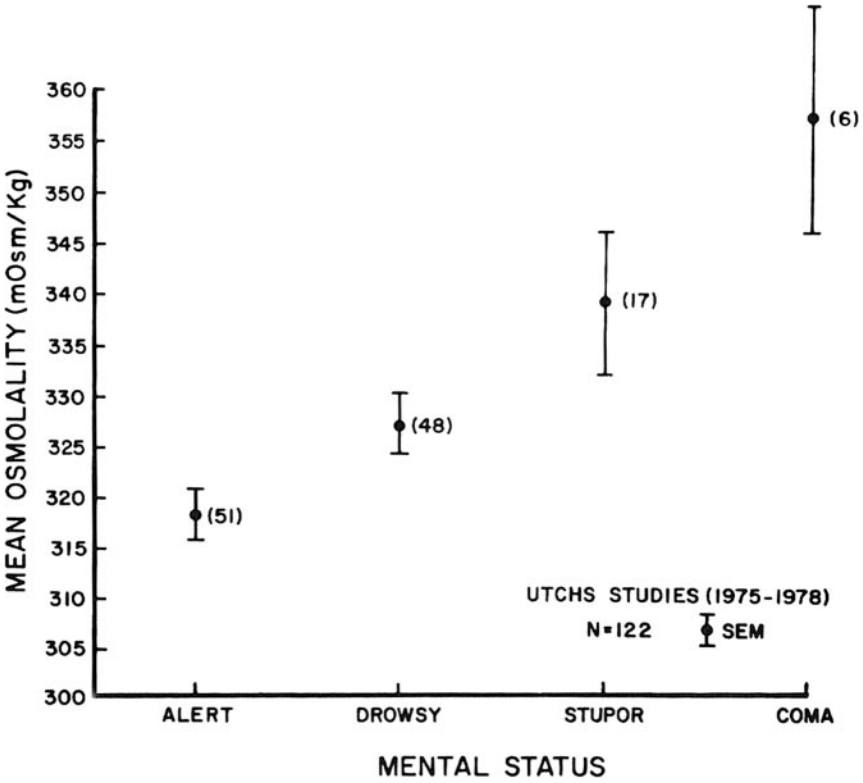

FIG. 5. Calculated serum osmolarity in 122 ketoacidotic patients with relation to mental status at time of admission. Data from Kitabchi *et al.* (1); Fisher *et al.* (17); and Sacks *et al.* (18). Reproduced by permission from Kitabchi and Fisher (19) in *Handbook of Diabetes Mellitus* (Brownlee M, ed.) and Garland ATPM Press. UTCHS, University of Tennessee Center for Health Sciences.

anemia or other conditions associated with hypoxia, when such therapy might be especially indicated.

Protocol VII: Use of Bicarbonate Therapy in DKA

In protocol VII we addressed the impact of bicarbonate treatment in patients with DKA. This issue had been a contentious subject due to the conflicting results from a small number of clinical trials (25). Proponents of bicarbonate therapy point to the potential deleterious effects of acidosis on cardiac hemodynamics. Opponents of bicarbonate therapy have been concerned with possible paradoxical cerebrospinal fluid (CSF) acidosis and a shift in the oxyhemoglobin curve back to the left, resulting in tissue hypoxia. We randomly assigned patients with moderate to severe DKA (pH 6.9–7.14) to either receive bicarbonate or not. Lumbar puncture was performed at baseline, 6–8 h, and 12–24 h during therapy with analysis of the CSF for glucose, bicarbonate, pH, total ketone, and osmolality. There were no significant differences in the rate of glucose or ketone body decline or the rate of increase in pH or bicarbonate between the experimental or control groups. Interestingly, for those patients who had simultaneous measurements of plasma and CSF at baseline, glucose and ketone body levels were significantly lower in the CSF, whereas pH and bicarbonate were significantly higher. We concluded that bicarbonate therapy did not alter recovery outcomes in adults with moderate DKA (pH 6.9–7.14) (26).

Lipid Metabolism in DKA

During the 1970s it was suggested that there was a strong interrelationship among abnormal lipid metabolism, atherosclerosis, and diabetes (27). With the availability of patients in a severe insulin-deficient state such as DKA, we were interested to know whether high triglycerides, cholesterol, and high-density lipoprotein could be reduced by low-dose insulin therapy. The initial values for triglyceride levels after correction for full hydration were 574 ± 188 mg/dl with mean total cholesterol in the normal range (210 ± 5 mg/dl). Our results provided evidence that insulin can actively decrease triglycerides but not cholesterol. However, the lowering of apolipoprotein A-1 by low-dose insulin that occurred may be due to decreased secretion of apolipoprotein A-1 into plasma or increased metabolism (28).

TABLE 2. Admission clinical and biochemical profile and response to therapy of comatose *vs.* noncomatose patients with DKA (from Ref. 20)

	Noncomatose (n = 35)	Comatose (n = 13)	*P* values
Age (yr)	36.1 ± 3.9	50.2 ± 6.8	<0.02
Glucose (mg/dl)	577.5 ± 42.5	988 ± 175.15	<0.01
HCO_3^- (mEq/liter)	8.6 ± 0.72	6.1 ± 0.9	<0.02
pH	7.19 ± 0.25	7.10 ± 0.45	NS
BUN (mg/dl)	24.1 ± 1.2	54.5 ± 5.2	<0.01
Osmolality (mOsmol/kg)	313.6 ± 2.2	365 ± 15.2	<0.01
Ketones (mM)	13.7 ± 0.76	14.3 ± 1.4	NS
Hours to recovery			
Glucose 250 mg/dl or less	5.2 ± 0.6	9.5 ± 2.5	<0.05
HCO_3^- greater than 15 mEq/liter	10.6 ± 1.7	12.9 ± 2.7	NS
pH 7.3 or greater	6.6 ± 1	10.15 ± 2.8	NS
Mentally alert	NA	7.78 ± 4.2	NA

Atypical or Ketosis-Prone Diabetes

More than half of newly diagnosed African-Americans with unprovoked DKA are obese. The majority of such patients display clinical and metabolic features of type 2 diabetes, including a high rate of obesity, a strong family history of diabetes, a measurable pancreatic insulin reserve (29–33), and the ability to discontinue insulin therapy and go through a period of near-normoglycemic remission that may last for a few months to several years (34). This clinical presentation has been reported primarily in Africans and African-Americans but also in other minority ethnic groups (35). This variant of type 2 diabetes has been referred to in the literature as idiopathic type 1 diabetes, atypical diabetes mellitus, type 1.5 diabetes, and more recently as ketosis-prone type 2 diabetes (36, 37). Our studies indicate that at presentation, patients with ketosis-prone type 2 diabetes have markedly decreased pancreatic insulin secretion, which is lower than in obese patients with comparable hyperglycemia but significantly greater reserve than in lean type 1 diabetic patients with DKA (33). Recently it was reported that in subjects with ketosis-prone diabetes, the near-normoglycemic remission is associated with a greater recovery of basal and stimulated insulin secretion and that 10 yr after diabetes onset, 40% of patients with ketosis-prone type 2 diabetes are still noninsulin dependent (35). The underlying mechanisms for β-cell dysfunction in ketosis-prone diabetes are not known; however, preliminary evidence suggests that patients with ketosis-prone type 2 diabetes display a unique propensity to glucose toxicity (38).

Several investigators have consistently reported that subjects with ketosis-prone type 2 diabetes have a nonautoimmune type of diabetes. Studies in different populations indicate that less than 20% of patients have evidence of an associated autoimmune-mediated process. In our studies in African-Americans we found that 17% of obese patients with a history of DKA have one or more positive autoantibodies (islet cell antibody, glutamic acid decarboxylase, insulin autoantibody, and islet cell antibody 512). The prevalence of autoantibodies is similar to that observed in obese subjects with hyperglycemia (16%) but lower than lean DKA patients (66%) (33, 36, 37).

Studies in humans and animal models have shown that muscle and adipocyte tissues exposed to sustained hyperglycemia have reduced insulin binding to its receptor, receptor phosphorylation, and tyrosine kinase activity and phosphorylation of insulin receptor substrate-1. These postreceptor defects result in decreased insulin receptor substrate-1-associated phosphatidylinositol 3-kinase activity and insulin resistance. To investigate the molecular mechanisms underlying hyperglycemia-induced insulin resistance in skeletal muscle on obese patients with ketosis-prone diabetes, we recently performed muscle biopsies 1 d after follow-up and during near-normoglycemic remission at 8 wk of follow-up (39).

We observed that overt hyperglycemia is associated with decreased stimulation of Akt Ser phosphorylation by a physiological concentration of insulin without changes in AktThr phosphorylation. We detected 70% greater Akt expression in muscle of patients in near-normoglycemic remission, largely due to a 94% increase in Akt-2 abundance, compared with the hyperglycemic period. These results indicate that in ketosis-prone diabetes, improvement of metabolic control with insulin therapy is accompanied by increased expression of key elements of the insulin-regulated signaling cascade in skeletal muscle (39).

Leptin Status in DKA and Its Response to Low-Dose Insulin

The availability of a large number of obese and lean DKA patients also provided us the opportunity to evaluate the controversial issues regarding the stimulating effect of insulin on leptin during hyperglycemia (40, 41). We investigated the effect of low-dose insulin therapy in a group of obese and lean DKA patients. These studies demonstrated that baseline values of leptin in DKA were low, but low-dose insulin could significantly stimulate serum leptin levels within 12 h. This effect could be seen as early as 4 h after injection of insulin in obese DKA patients (42). The presence of high levels of epinephrine and cortisol, which have negative and positive effect on leptin secretion, respectively (43, 44), suggested that the role of insulin as an anabolic hormone along with the role of elevated cortisol played important roles in the overall stimulating effect of insulin on leptin (44).

Cardiac Risk Factors and Proinflammatory Cytokines in DKA

Recently the concept of a chronic inflammatory state in diabetes as part of insulin resistance has received considerable attention (45, 46). Having a large group of obese and thin DKA patients and obese nonketotic hyperglycemic subjects in whom no evidence of infection or a history of cardiovascular event was noted, we assessed the status of proinflammatory cytokines (TNFα, ILβ_1, IL-6, IL-8); various cardiovascular risk factors (homocysteine, plasminogen activator inhibitor-1, C-reactive protein, free fatty acids); levels of lipid peroxidation by measuring thiobarbituric acid (TBA)-reacting material; the state of reactive oxygen species (ROS), measured by dichlorofluorescein (DCF); and counterregulatory hormones (cortisol, GH) (47). These studies demonstrated that levels of these parameters were increased by at least 2- to 3-fold over normal levels. Interestingly, however, in DKA patients all these values reached near normal levels (except for homocysteine) with insulin therapy and resolution of glycemic crises within 24 h (see Table 3). We therefore suggested that such a prompt reversal may be due to either an antiinflammatory effect of insulin and/or most likely to nonspecific stress phenomenon brought about by the presence of hyperglycemia and hyperlipidemia (47).

Mechanism of Activation of T Lymphocytes in DKA

To determine whether hyperglycemia or hyperlipidemia could in fact bring about stimulation of cytokines, ROS, and lipid peroxi-

TABLE 3. Proinflammatory cytokines, cardiovascular risk factors, counterregulatory hormones, lipid peroxidation (TBA), and DCF values on admission and resolution of hyperglycemic crises in lean and obese DKA and obese hyperglycemic patients, compared with lean and obese nondiabetic subjects (47)

	Lean DKA		Obese DKA		Obese hyperglycemia		Lean Control	Obese Control
	Adm	Resol	Adm	Resol	Adm	Resol		
TNFα (pg/ml)	22.7 ± 3.6	4.6 ± 0.9[a,b]	28.3 ± 2.8	5.9 ± 0.7[a,b]	24 ± 3.1	5.1 ± 1.3[a,b]	1.7 ± 0.2[a,b]	3.9 ± 0.6[a,b]
IL-1B (pg/ml)	9.8 ± 2.3	1 ± 0.2[a,b]	13.7 ± 2.1	2.4 ± 0.3[a,b]	11 ± 0.8	3.1 ± 0.8[a,b]	1.3 ± 0.2[a,b]	1.9 ± 0.3[a,b]
IL-6 (pg/ml)	14.9 ± 2.6	3.9 ± 1.1[a,b]	12.6 ± 2.1	4.3 ± 0.6[a,b]	10 ± 1.7	3.3 ± 0.7[a,b]	1.8 ± 0.2[a,b]	2.1 ± 0.3[a,b]
IL-8 (pg/ml)	29.3 ± 3.4	10.6 ± 2.3[a,b]	27.4 ± 3.8	12 ± 2.8[a,b]	26 ± 3.4	9.3 ± 2.8[a,b]	4.9 ± 1.4[a,b]	5.5 ± 1.7[a,b]
CRP (mg/liter)	51 ± 3	28 ± 1[a,b]	59 ± 13	34 ± 9[a,b]	28 ± 6	13 ± 3[a,b]	1 ± 0.2[a,b]	2 ± 0.4[a,b]
Homocysteine (μM)	4.7 ± 0.2	3.7 ± 0.2[a,b]	5.9 ± 0.9	5.4 ± 0.7	3.7 ± 0.4	3.1 ± 0.3[a]	1.8 ± 0.1[a,b]	2.2 ± 0.3[a,b]
FFA (mM)	1.6 ± 0.1	0.6 ± 0.1[a,b]	1.4 ± 0.1	0.7 ± 0.1[a,b]	1.2 ± 0.2	0.8 ± 0.1[a,b]	0.5 ± 0.06[a,b]	0.7 ± 0.1[a,b]
DCF (μM)	8.6 ± 0.8	3.7 ± 0.5[a,b]	8.9 ± 1.2	4.1 ± 0.7[a,b]	7.8 ± 0.6	3.8 ± 0.5[a,b]	2.3 ± 0.4[a,b]	3.1 ± 0.6[a,b]
TBA (μM)	3.8 ± 0.7	1.3 ± 0.4[a,b]	4.0 ± 0.6	1.6 ± 0.2[a,b]	3.3 ± 0.5	1.5 ± 0.4[a,b]	0.84 ± 0.1[a,b]	0.9 ± 0.1[a,b]
PAI-1 (ng/ml)	42.1 ± 12.2	4.2 ± 2.1[a,b]	40.4 ± 12.4	13.0 ± 3.4[a,b]	35.4 ± 9.3	7.3 ± 2.4[a,b]	1.4 ± 0.2[a,b]	2.5 ± 0.4[a,b]
GH (ng/ml)	12.3 ± 2.2	3.2 ± 1.0[a,b]	10.0 ± 3.1	4.0 ± 1.2[a,b]	1.6 ± 0.3[a]	0.9 ± 0.2[a,b]	0.8 ± 0.2[a,b]	0.8 ± 0.2[a,b]
Cortisol (μ g/dl)	46.2 ± 2.3	21.7 ± 1.1[a,b]	55.4 ± 5.8	24.6 ± 3.6[a,b]	23 ± 0.9[a]	17.2 ± 1.4[a,b]	14 ± 1.2[a,b]	13 ± 1.1[a,b]

Data are mean ± SE. Resol, resolution; PAI-1, plasminogen activator inhibitor-1; FFA, free fatty acid; CRP, C-reactive protein.

[a] $P < 0.01$ *vs.* lean DKA on admission (Adm).

[b] $P < 0.05$ *vs.* admission value of each group.

dation, we chose human T lymphocytes (T cells) (48) or human aortic endothelial cells (49) and incubated them either in the presence of high glucose or high lipid (50), measuring activation of these cells by assessing lipid peroxidation, ROS, growth factor receptor emergence such as insulin, IL-2 and IGF-I, or elevated proinflammatory cytokines. The results suggested that high concentrations of glucose (15–30 but not 5 mM) and palmitate (but not unsaturated fatty acids) stimulate production of ROS, lipid peroxidation, and cytokine elevation and convert these insulin nonresponsive cells to insulin-responsive cells. We were also able to demonstrate *in vivo* activation of T cells in DKA with production of ROS, lipid peroxidation, and cytokine stimulation (51). Further studies are in progress to assess the mechanism of these phenomena using other models of stress besides hyperglycemia and hyperlipidemia.

Additional Risk Factor for DKA Readmission

We had earlier noted that use of illicit drugs may be a contributing factor in DKA presentation (32). In a recent retrospective study in a large metropolitan university-affiliated hospital, we were able to demonstrate that the use of cocaine was also a significant independent risk factor for recurrent DKA (52).

Rapid-Acting Insulin Analogs in DKA

In June 2000, the first of two rapid-acting analogs of human insulin (lispro or Humalog) became commercially available. We asked whether this new formulation could be used as an alternative route to the use of iv regular insulin in patients with DKA. In a prospective and randomized study, we compared the efficacy and safety of sc insulin lispro every hour with that of a standard low-dose iv infusion protocol of regular insulin in adult patients with DKA (53). Patients treated with sc lispro were treated in the emergency department or regular medicine wards and because of hospital regulations iv-treated patients were managed in the intensive care units. Patients treated with sc lispro received an initial injection of 0.3 U/kg followed by 0.1 U/kg·h until blood glucose was less than 250 mg/dl and then received 0.05–0.1 U/kg·h until resolution of DKA. Patients treated with iv regular insulin received an initial sc bolus of 0.2 U/kg followed by an infusion of 0.1 U/kg·h until blood glucose was less than 250 mg/dl and then 0.05–0.1 U/kg·h until resolution of DKA. The mean duration of treatment until correction of hyerglycemia [blood glucose < 250 mg/dl and resolution of ketoacidosis (pH > 7.30, bicarbonate ≥ 18 mEq/liter) in patients treated with sc lispro (7 ± 1 and 10 ± 1 h, respectively) was not different from patients treated with iv regular insulin (8 ± 1 and 11 ± 1 h, respectively).

Treatment with sc insulin injections on an hourly schedule, however, may be difficult due to the intensity of treatment and shortage of nursing staff on regular wards. To facilitate the management of patients with DKA, we studied whether treatment with sc rapid-acting insulin analogs, given at different time intervals (1 and 2 h), is equally effective as the use of iv regular insulin in patients with DKA. A total of 45 consecutive patients admitted with DKA were randomly assigned to receive sc aspart (Novolog, Novo-Nondisk, Bagsvaerd, Denmark) every hour or every 2 h or iv infusion of regular insulin. Patients treated with aspart sc every hour received an initial injection of 0.3 U/kg followed by 0.1 U/kg·h until blood glucose was less than 250 mg/dl and then received 0.05 U/kg·h until resolution of DKA. Those treated with sc aspart every 2 h received an initial injection of 0.3 U/kg followed by 0.2 U/kg 1 h later and every 2 h until blood glucose was less than 250 mg/dl and then received 0.1 U/kg every 2 h until resolution of DKA. Patients treated with iv regular insulin received an initial bolus of 0.1 U/kg, followed by an infusion of 0.1 U/kg·h until blood glucose was less than 250 mg/dl and then 0.05–0.1 U/kg·h until resolution of DKA. Response to medical therapy was evaluated by assessing the duration of treatment until

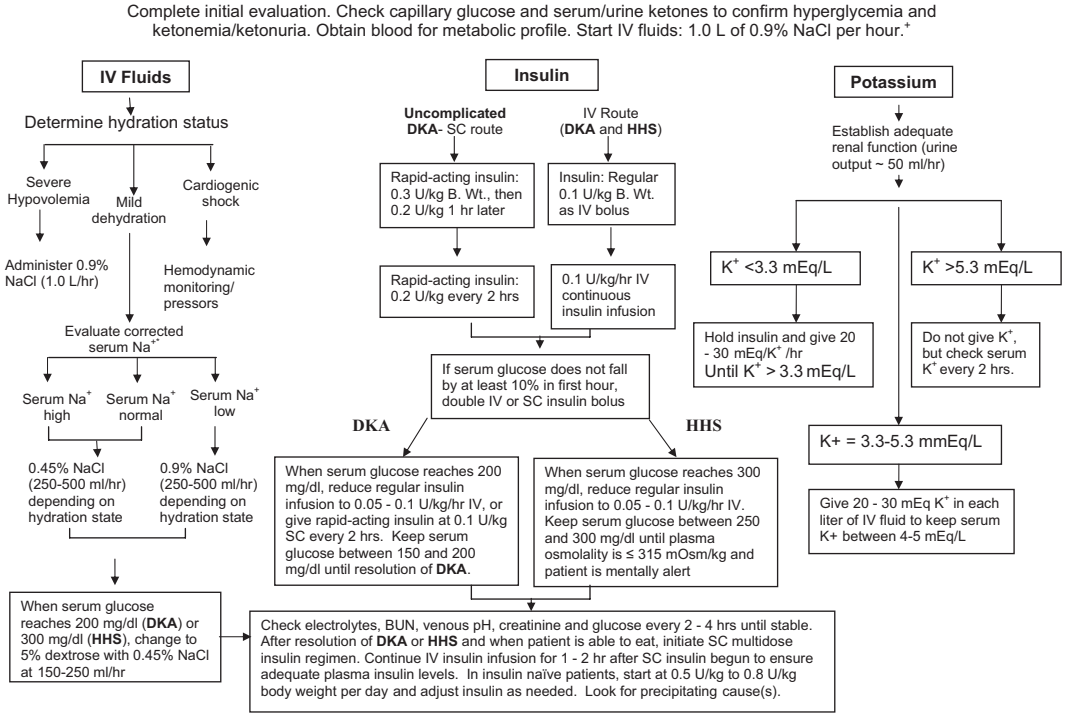

FIG. 6. Protocol for management of adult patients with DKA or HHS (modified from Ref. 58).

resolution of hyperglycemia and ketoacidosis. Similar to our experience with lispro, we observed no mortality, and there were no differences in the length of hospital stay, total amount of insulin administration until resolution of hyperglycemia or ketoacidosis, or the number of hypoglycemic events among treatment groups (54). Table 4 summarizes results of hourly sc injection of lispro *vs.* two hourly sc injection of aspart, compared with continuous infusion of regular insulin given iv, showing no significant difference among the three regimens. However, there was an approximately 30% less cost with the use of fast-acting insulin in the general ward than iv insulin in the intensive care unit. Based on these studies, we concluded that the use of sc rapid-acting insulin analogs every 1 or 2 h represents a safe and effective alternative to the use of iv regular insulin in the management of patients with uncomplicated DKA.

These findings are discussed in the American Diabetes Association (ADA) in-depth technical review on DKA and hyperglycemic hyperosmolar state (HHS), which was completed in 2001 (55), as well as in the ADA position paper on therapy for hyperglycemic crises (56). This document was recently revised in 2006 (57) and updated later (58, 59) (Fig. 6).

Recommendation for Future Clinical Research

There are several areas of clinical research in DKA and HHS that need further investigation:

1. The use of bicarbonate in DKA. Available studies suggest that for pH greater than 7.0 bicarbonate does not provide any advantage. Studies for pH of 6.9–7.0 are limited, and a larger number of subjects is necessary to settle the issue. Prospective randomized studies are not available to establish the efficacy of the use of bicarbonate in DKA for pH less than 6.9. Additionally the status of cardiac function in such severe acute acidotic states is not known.

2. Priming dose of insulin. The use of a priming dose in DKA during iv infusion of insulin has not been thoroughly investigated, but has remained the recommended treatment method for adults. However, in the most recent ADA Consensus Report, the

TABLE 4. Comparative effects of sc fast-acting insulin *vs.* iv regular insulin in DKA

	Aspart sc, 2 h[a]	Lispro sc, 1 h[a]	Regular iv[b]	*P* values
Length of hospital stay (d)	3.9 ± 1.5	4 ± 2	4.5 ± 3.0	NS
Duration of therapy until BG less than 250 mg/dl (h)	6.1 ± 1	7 ± 1	7.1 ± 1	NS
Duration of therapy until resolution of DKA (h)	10.7 ± 0.8	10 ± 1	11 ± 0.7	NS
Amount of insulin until resolution of DKA (U)	94 ± 32	84 ± 32	82 ± 28	NS
Episodes of hypoglycemia	1	1	1	NS
Cost of hospitalization	$10,173 ± 1738	$9816 ± 4981	$17,030 ± 1753	<0.01

Data are means ± SE. Data adapted from elsewhere (53, 54). NS, Not significant; BG, blood glucose.

[a] Treated in general medical wards.

[b] Treated in intensivie care units: insulin dose 0.2–0.3 U/kg sc initially followed 1 h later by 0.1 U/kg·h or 0.2 U/kg/ per 2 h sc.

use of a bolus method has not been recommended for children (60). Therefore, the need for the use of a priming or bolus dose of insulin in adult DKA requires further investigation.

3. The mechanism for lack of ketosis in HHS. Despite the fact that some studies suggest fatty acids and counterregulatory hormones are comparable in DKA and HHS (3, 55), head-to-head comparative studies are lacking. Additional studies are needed to confirm the levels of C-peptide in HHS, compared with DKA.

4. The mechanism of production of elevated proinflammatory cytokines as well as cardiac risk factors in patients with hyperglycemic crises who demonstrate no cardiac history, infection, or injury is not known. Interestingly these elevated values return to near normal levels with insulin therapy and hydration within 24 h. This nonspecific effect of stress requires further investigation.

5. The sc use of regular insulin in DKA. We have demonstrated that the use of fast-acting insulin analogs by the sc route in general wards (in mild or moderate DKA) is as effective as the use of regular insulin by the iv route in the intensive care unit, with cost savings of approximately 30%. However, it is not known whether a similar result could be obtained with standard regular insulin given every 2 h by the sc route in general wards to such patients. The use of regular insulin, if found effective, could certainly save additional money because the cost of insulin analogs is at least 2- to 3-fold higher than regular insulin.

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