# Hyperosomolar Coma in Surgical Patients:

## An Iatrogenic Disease of Increasing Incidence

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IN RECENT YEARS reports of hyperosmolar, hyperglycemic, nonketotic diabetic coma (HHNKDC) have proliferated greatly.[1-12] Our experience with ten cases of this syndrome in the past 2 years on the surgical services of the New York University-Bellevue Medical Center is reported. It suggests that the rise of this entity may be due not only to improved detection but also to iatrogenic factors such as the more potent therapeutic modalities of "hyperalimentation" and "hyperdiuresis". The profile of the typical surgical patient now developing HHNKDC is changing in response to improved pre- and postoperative care.

Most of the etiologic factors implicated in the genesis of the HHNKDC state in surgical patients are enumerated in the following categories and also are listed in Table 1.

I. *Susceptible Patient Populations:*

High-risk patients who may develop hyperosmolar coma include all the various categories of diabetes, including the previously undiagnosed or chemical diabetics and the juvenile or maturity-onset types. Patients exhibiting pancreatic insufficiency such as those with acute and chronic pancreatitis and those postpancreatectomy are similarly at high risk. Uremic patients and patients undergoing the hyperglycemic stress of cardiopulmonary bypass are especially susceptible. Particularly disturbing has been the recent genesis of HHNKDC after use of cardiopulmonary bypass in coronary arteriosclerosis in a patient population replete with diabetics due to the increased association of the two diseases. Proposed explanations implicate the hyperglycemic effect of bypass,[8] mediated perhaps by epinephrine release, the destruction of endogenous insulin, induction of a state refractory to exogenous insulin, and the use of dextrose solutions as a pump prime.

II. *Exogenous Glucose Loads:*

In the surgical population HHNKDC usually results from administration of an overwhelming glucose load.[9] As parenteral and enteral alimentation technics have improved so have the complications. The susceptible patient has developed the HHNKDC state after receiving intravenous dextrose solutions of 5 and 50% concentration as well as the newer intravenous "hyperalimentation" solutions, oral "elemental" diets, and tube feedings. Especially dangerous is the simultaneous administration of two or more of these hypertonic media, an ever more common practice as greater therapeutic boldness accompanies increased familiarity and experience in their use.

III. *Hyperglycemic Medications:*

The interaction of several commonly employed medications with hyperglycemic potential in the management of the seriously-ill surgical patient has been a major cause of HHNKDC. Corticosteroids, with well-described gluconeogenic effects,[12] are used before, during, and after operation in often huge doses, as in the management of aspiration pneumonia, a frequent surgical complication. Epinephrine used as a supportive drip or as a bolus has

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TABLE 1. *Etiologic Factors in the Genesis of HHNKDC in Surgical Patients:*

I. Susceptible patient populations:
- A. Previously undiagnosed or chemical diabetics.
- B. Juvenile or maturity-onset diabetics.
- C. Acute and Chronic pancreatitics.
- D. Post-pancreatectomy patients.
- E. Uremic patients.
- F. Patients undergoing cardiopulmonary bypass.
- G. Patients undergoing peritoneal or hemodialysis.

II. Exogenous glucose loads:
- A. Intravenous 5% dextrose solutions.
- B. Intravenous 50% dextrose solutions.
- C. Intravenous "hyperalimentation" solutions.
- D. Oral "elemental" diets.
- E. Tube feeding preparations.

III. Hyperglycemic medications:
- A. Corticosteroids.
- B. Epinephrine.
- C. Glucagon.
- D. Dilantin.
- E. Concentrated dextrose solution used as a cardiotonic.

IV. Dehydrating situations:
- A. Diuresis with furosemide.
- B. Diuresis with ethacrynic acid.
- C. Burn injuries with huge fluid losses.
- D. Starvation and dehydration.

V. Uremia:
- A. Acute and chronic renal failure.
- B. Diabetic nephropathy.
- C. The post-nephrectomy patient.
- D. Renal failure secondary to heart failure.
- E. Massive upper gastrointestinal hemorrhage.
- F. Excessive amounts of dextrose in dialysis solutions.

a pronounced hyperglycemic effect and probably inactivates endogenous insulin. Glucagon has come into increasing use as a cardiotonic agent whose positive inotropic effect is believed to be independent of its hyperglycemic effect. Concentrated dextrose solutions have found a role as cardiotonic agents especially during resuscitative attempts in cardiac arrest. Dilantin has also been reported as a cause of HHNKDC.[3] The simultaneous employment of several of these agents, a not uncommon occurrence, often serves to potentiate the hyperglycemia.

### IV. *Dehydrating Situations:*

The acute and chronic use of the potent diuretics furosemide and ethacrynic acid can easily result in dehydration and hypertonicity.[2] Early survival of seriously burned patients has increased as a result of improved initial resuscitation, but the risk of HHNKDC in this group of patients with huge fluid losses has correspondingly increased.[9] Acute and chronic starvation is a frequent cause of dehydration especially in the geriatric population.[1] Silver nitrate treatment of burn wounds has a pronounced dehydrating effect and has been described as a cause of HHNKDC.

### V. *The Uremic State:*

Improved survival of diabetics has been paralleled by increased numbers of patients with diabetic nephropathy. Decreased renal reserve in these patients and in the large number of surgical patients with acute and chronic renal failure, in the postnephrectomy patient, and in those with renal failure secondary to chronic congestive heart failure, makes them susceptible to hyperglycemia and hypertonicity when challenged with a massive glucose load. Gram negative septicemia with stress ulceration and massive upper gastrointestinal hemorrhage is an increasingly common complication in the care of critically ill surgical patients. The urea overload which results can overwhelm the renal reserve of a surgical patient with even mild renal failure. "Hyperdiuresis" with potent diuretic cocktails in the pre- and intraoperative management of surgical candidates with low creatinine clearances can easily induce a hypertonic state in the immediate postoperative period. Finally, as the technics of peritoneal and hemodialysis find increased application, care must be taken to avoid excessive amounts of dextrose in the dialysis solution.

## Case Reports

### I. *HHNKDC Following Hyperalimentation:*

**Case 1.** A 57-year-old chronic alcoholic man was admitted for treatment of intestinal obstruction and pancreatic insufficiency 1 year following pancreatectomy for chronic pancreatitis. He lapsed into coma and the hyperosmolar, hyperglycemic, non-ketotic state after receiving simultaneous intravenous "hyperalimentation" with 3 liters of Amigen and $D_{50}W$ per day, and oral hyperalimentation with 4 packets of Vivonex "elemental diet" per day, while recovering from exploratory laparotomy and lysis of adhesions. Early detection of the hyperosmolar state with vigorous hydration and immediate cessation of hyperalimentation led to this patient's retrieval and ultimate survival.

**Case 2.** A 55-year-old diabetic man with biopsy-proven esophageal carcinoma was scheduled to receive intravenous hyperalimentation prior to resection of the carcinoma. He accidentally received one liter of intravenous hyperalimentation fluid over a 20-minute period as a result of a nursing error, and immediately lapsed into the HHNKDC state, dying the next morning despite all resuscitative efforts.

**Case 3.** A 45-year-old diabetic man sustained a large area 3rd degree sulfuric acid burn in an industrial accident. He lapsed into the HHNKDC state after a 5-day course of oral hyperalimentation with Vivonex (1–2 packets per day) with simultaneous intravenous infusion of dextrose 5%. Although his HHNKDC cleared with appropriate therapy he ultimately succumbed from his burn injuries.

### II. *HHNKDC Following Cardiopulmonary Bypass:*

**Case 4.** A 59-year-old hypertensive man with maturity-onset diabetes managed for many years with tolbutamide underwent coronary artery bypass surgery for the treatment of angina pectoris and congestive heart failure of 10 years' duration. Cardiopulmonary bypass continued for 7 hours and 13 minutes. Serum

hemoglobin was 252, serum glucose 495, and the serum osmolality 323 immediately postoperatively. Fluid was replaced with dextrose 5%. The patient lapsed into semicoma with a blood glucose of 645 and a $CO_2$ of 15. He recovered after a stormy course.

**Case 5.** A 58-year-old hypertensive man with maturity-onset diabetes had been managed for 5 years with Iletin-NPH and regular insulin. He underwent coronary artery bypass surgery for the treatment of anginal syndrome and congestive heart failure of 2 years' duration. Cardiopulmonary bypass lasted 3 hours and 27 minutes after which the serum hemoglobin was 106. The patient had been receiving furosemide, ethacrynic acid, Mercuhydrin, and Aldactone preoperatively, and had received an oral loading dose of furosemide 320 mg. 4 days prior to operation. Blood glucose was 600 immediately postoperatively and rose to 1,500 with a serum sodium of 160 by the eighth postoperative day when the syndrome of HHNKDC became full-blown. He had been given 40 mg. of furosemide, 50 mg. of ethacrynic acid, and 12.5 Gm. of mannitol intravenously on the seventh postoperative day to maintain urine output. He also had been on a glucagon drip (4 mg./hour) continuously since the first postoperative day to maintain blood pressure. The patient continued to have a serum sodium level of greater than 150 with maintenance of vigorous diuresis. He ultimately died with a sodium level of 187, a glucose of 435 and a BUN of 126 on the 25th postoperative day. His "osmostat" had apparently been irreversibly damaged.

**Case 6.** A 65-year-old man with no personal or family history of diabetes underwent coronary artery bypass for anginal syndrome of 7 years' duration, heart failure of 2 years' duration, and had a history of five myocardial infarctions over the previous 11 years. Cardiopulmonary bypass lasted 5 hours and 31 minutes. For many years he had been maintained on 5 mg. of prednisone daily in the treatment of chronic obstructive pulmonary disease. About one week postoperatively he became confused and lethargic and sustained massive upper gastrointestinal hemorrhage. From the third to the sixth postoperative day he had received 25 mg. of prednisone intravenously at 6-hour intervals as well as doses of Solu-Cortef and Solu-Medrol on the eighth and tenth postoperative days. He was given a dose of 40 mg. furosemide on the second postoperative day, and urine output was never less than 50–100 cc. per hour thereafter. On the eighth postoperative day serum glucose was noted to be 556 and BUN rose to 350 with a serum sodium level of 164. The diagnosis of HHNKDC was made and therapy with insulin and intravenous fructose was instituted. Peritoneal dialysis was begun on the eleventh postoperative day with clearing of a right hemiparesis first noted during the period of dialysis. Serum osmolality was 498 on the tenth postoperative day. In spite of some improvement in the clinical and chemical profiles, the patient sustained a cardiac arrest with hyperkalemia of 7.9 and could not be resuscitated.

III. *HHNKDC After Intravenous Dextrose Infusions:*

**Case 7.** A 45-year-old man had no prior history of diabetes but on admission for pacemaker failure was found to have a blood glucose level of 150. He developed HHNKDC after receiving 50 cc of 50% dextrose in water intravenously along with an infusion of dextrose 5% during resuscitation from cardiac arrest secondary to pacemaker failure. He developed hyperglycemia of 1400 and a peak sodium level of 148. Although he survived the initial episode he succumbed to repeated episodes of ventricular fibrillation 3 weeks after pacemaker replacement.

**Case 8.** A 72-year-old man with no past or family history of diabetes had an admission blood glucose of 200 while receiving an intravenous infusion of 5% dextrose during transfer from another hospital following insertion of a nail and bar for a fractured right hip several days previously. He lapsed into coma with a peak glucose level of 984, peak sodium level of 150, and a peak BUN of 127. He was successfully treated for HHNKDC and survived 3 further months of hospitalization which included gram negative septicemia secondary to urinary tract obstruction, a suprapubic cystotomy, and a suprapubic prostatectomy. Careful attention to his metabolic state prevented subsequent episodes of HHNKDC and he went home in good condition.

**Case 9.** A 40-year-old woman developed HHNKDC on the first postoperative day following suture of a liver laceration and right nephrectomy for a stab wound of the kidney. Admission BUN and serum creatinine levels were normal and never rose above BUN of 29 and a creatinine level of 1.9. Intravenous infusion of dextrose 5% apparently overwhelmed her decreased renal filtration reserve due to a combination of unilateral nephrectomy and diabetic nephropathy in the remaining kidney. She survived after appropriate therapy.

IV. *HHNKDC Following Total Pancreatectomy:*

**Case 10.** A 40-year-old man with no past or family history of diabetes developed HHNKDC in the immediate postoperative period after undergoing total pancreatectomy for liposarcoma of the head and body of the pancreas. He remained in coma and died despite vigorous resuscitiative therapy.

## Discussion

The classic profile of the surgical patient developing HHNKDC in previous reviews[4,6,9] has been male, elderly, with a mean age of 70, and the etiologic factor has simply been to infuse 5% dextrose intravenously in the postoperative period. Approximately two-thirds of previously reported patients had known diabetes diagnosed prior to the onset of HHNKDC. Our patients however are younger, with a mean age of 53, and only one-third had diabetes diagnosed prior to the onset of HHNKDC. The etiologic factors were much more diverse.

The risk of precipitating the HHNKDC Syndrome is compounded when the two popular methods of "hyperalimentation," intravenous and oral, are employed simultaneously. A spate of iatrogenic deaths is to be expected if surgeons seeking to render aggressive care administer simultaneous intravenous hyperalimentation and oral elemental diets in a sincere attempt to "build up" the severely malnourished surgical patient. Even the simultaneous employment of intravenous dextrose 5% and oral elemental diet is probably dangerous.

Increasing numbers of diabetic patients will be undergoing the hyperglycemic stress of cardiopulmonary bypass for coronary artery surgery due to the association of diabetes and early coronary arteriosclerosis. The cases of HHNKDC observed in our initial series demand that extreme caution be exercised in the use of 5% dextrose as a pump priming solution. The combination of diabetes, acute and chronic diuresis, glucagon, epinephrine, and intravenous dextrose can lead to the lethal complex of HHNKDC and cerebrovascular thrombosis. The three

coronary artery patients we reported were either overtly diabetic or on chronic corticosteroid therapy prior to operation. They shared a common history of severe congestive heart failure requiring potent diuretic therapy preoperatively. All had prolonged cardiopulmonary bypass with elevated serum glucose and hemoglobin levels. All received potent diuretic therapy in the postoperative period and the major replacement fluid was 5% dextrose solution. All were maintained on epinephrine drips for varying periods and in one case a glucagon drip was continued for several days. None of our coronary artery patients had prior history of renal disease, however, all had mildly elevated BUN (mean of 27) and Creatinine (mean of 1.5) preoperatively. All developed renal failure postoperatively with a mean BUN of 206 and mean creatinine level of 5.2. Attention must be paid to the hyperosmolar effect of the overvigorous use of the "hyperdiuretics" furosemide and ethacrynic acid. The employment of the hyperglycemic agents glucagon, epinephrine, and 50% glucose used as cardiotonics poses an added threat to the diabetic patient with congestive heart failure and low cardiac output. Serum osmolality and glucose levels should be monitored freuently during "hyperalimentation" and following cardiopulmonary bypass of diabetic patients.

What is usually considered a normal glucose load may be sufficient to precipitate HHNKDC in patients with extensive burns, postpancreatectomy pancreatic insufficiency, uremia, and postnephrectomy renal insufficiency.

The syndrome of HHNKDC is best prevented because treatment leaves much to be desired, with the mortality of treated patients running greater than 50%. The damage to the hypothalamic "osmostat" is often irreversible. Our surviving patients all shared early detection and vigorous and often heroic treatment of the hyperosmolar state. As more diabetic patients undergo coronary artery bypass surgery, as the incidence of chemical and overt diabetes rises in our population due to gene penetrance, as surgeons become more aggressive in the employment of the newer therapeutic modalities of "hyperalimentation" and "hyperdiuresis" with inevitable overlap, the incidence of iatrogenic hyperosmolar, hyperglycemic, non-ketotic, diabetic coma will inevitably increase. Awareness of the ease of genesis of the syndrome, scrupulous monitoring of the metabolic status of the surgical patient and some restraint in the simultaneous use of some of the more potent weapons in our therapeutic arsenal, will go a long way in stemming this potential tide of iatrogenic catastrophes.

## Conclusions

1) HHNKDC is an iatrogenic disease of increasing incidence in the surgical patient population, and it is preventable in many cases.

2) Resuscitative treatment of HHNKDC is successful in less than 50% of cases.

3) The age group of surgical patients developing HHNKDC is a much younger one than that described in the medical literature. and the mean age continues to decrease.

## Summary

Experience with 10 recent cases of hyperosmolar hyperglycemic nonketotic diabetic coma in surgical patients is presented with the aim of alerting the surgical profession to the risk of iatrogenic genesis of this usually lethal syndrome. The etiologic factors are presented and the interaction of various precipitating elements is discussed in the context of the case presentations and a changing profile of the typical surgical patient developing the hyperosmolar syndrome.

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