



Was It a Case of “Flatbush Diabetes” with Severe Hypertriglyceridemia?

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Abstract

We present a case of a morbidly obese 27 years male patient who was admitted with sudden onset abdominal pain and crashed into diabetic ketoacidosis as new-onset diabetes and discuss the possible etiology of this combined picture of acute pancreatitis and severe hypertriglyceridemia. Flatbush diabetes was, meanwhile, thought of due to his morbid obesity that in turn raised our suspicion of acute insulin-requiring type 2 diabetes mellitus versus T1 diabetes mellitus. Ketosis-prone diabetes or Flatbush diabetes is a syndrome in which diabetes commences with ketoacidosis in patients who are glutamic acid decarboxylase and antiislet cell antibody negative and have no known precipitating causes. They are usually middle-aged, overweight, or mildly obese, and in many reports, they are likely to be male with a family history of type 2 diabetes mellitus; they present with new-onset severe hyperglycemia and ketosis or frank diabetic ketoacidosis. After intensive initial insulin therapy, many patients become insulin-independent and can be well controlled on diet plus oral medications or, more rarely, diet alone.

Keywords

- ▶ Flatbush
- ▶ hypertriglyceridemia
- ▶ ketoacidosis (DKA)
- ▶ insulin

Introduction

Patients presenting with diabetic ketoacidosis (DKA) may have a clinical course similar to those with type 2 diabetes mellitus (T2DM) to that of type 1 diabetes mellitus (T1DM). It was described by Winter et al in a study of atypical maturity-onset diabetes of youth where they initially thought to have T1DM since several presented with ketosis.¹ All patients were glutamic acid decarboxylase (GAD), and anti islet cell antibody negative with an increase in frequencies of human leukocyte antigen (HLA) DR3 and DR4 was found. All patients required initial insulin therapy, yet after months of treatment, they were no longer dependent on insulin, and they were treated with diet alone or diet plus oral agents. A small percentage may continue to require insulin therapy. Never-

theless, recurrent ketoacidosis is unusual, and the clinical course is like a patient with T2DM.²

Case Report

History

A 27-year-old Arab male was previously healthy and presented with sudden onset abdominal pain 3 hours before hospital arrival. He started to have diffuse severe abdominal pain 3 hours after his dinner. The pain was progressive and radiating to his back and upper chest, and he could not sit due to the severity of his pain (pain score >10). It was associated with nausea, vomiting, sweating, and shortness of breath. He had four episodes of vomiting that is food content, non-projectile, nonbilious, and nonbloody in nature. The week

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before he had these symptoms, he noticed increasing tiredness, although his working nature did not change. Otherwise, no polyuria, polydipsia, or weight loss was noted. He also gave a history of gaining more than 35 kg in the previous 3 years.

There was nothing relevant in the past medical and surgical history, and he was not on any regular medication. He accepted that he is a big eater with erratic eating patterns due to the shifting nature of his job. There was a positive family history of T2DM.

Social history: Single agricultural engineer, nonsmoker, and nonalcoholic.

Physical Examination

His body weight was 148 kg and height 173 cm, with a body mass index of 49.45 kg/m². Vital signs were as follows: temperature (tympanic) was 37.3°C, heart rate was 119 bpm, respiratory rate was 25br/min, systolic blood pressure was 129 mm Hg, and diastolic blood pressure was 51 mm Hg, and oxygen saturation on air was 98.0%.

He was initially alert and oriented to time, person, and place. The tachycardia and tachypnea and moderate distress were noted. He had a rounded face as part of his morbid obesity. However, there were no stigmata of chronic hypertriglyceridemia or cushingoid features. His abdomen was diffusely tender. No organomegaly. The rest of the examination was unremarkable.

Laboratory Investigations

Random blood glucose was 16.2 mmol/L (4.4–6.4 mmol/L). Venous blood glucose on arrival showed pH: 7.29, Bicarb of 11 mmol/l, Gluc: 15 mmol//L, anion gap of 21, and serum K 4.3 mmol/L. His urinalysis demonstrated +3 ketonuria and +2 glycosuria. Serum amylase was 188 units/L (28–100 units/L) and serum lipase was 687 IU/L (13–60 IU/L). Lipid panel revealed a total serum cholesterol of 10.45 mmol/L (3.9–5.2 mmol/L), high-density lipoprotein cholesterol of 0.36 mmol/L (1.10–1.60 mmol/L), low-density lipoprotein cholesterol of 0.30 mmol/L (< 2.59 mmol/L), and serum triglyceride of 21.34 mmol/L (0.5–1.70 mmol/L). He had normal liver function tests and kidney function tests. Autoantibodies were negative (anti-islet antigen 2 antibodies were less than 8 IU/mL, anti-GAD antibodies less than 5 IU/mL, and antiinsulin antibodies: negative).

Imaging

An abdominal computed tomography scan revealed a picture of acute pancreatitis manifested by the presence of swollen pancreas with peripancreatic fluid and fat stranding. No evidence of loculated collection or pneumoperitoneum.

Final Diagnosis

Acute pancreatitis secondary to familial hypertriglyceridemia
Ketoacidosis-prone diabetes (KPD).

Management and Outcome

Upon admission, the patient was treated for DKA by the local hospital protocol. He was started with intravenous (IV) fluids

followed by IV insulin, fluid resuscitation, and KCl replacement. He was out of DKA and his pancreatic enzymes remarkably improved. Nevertheless, he was continued on IV insulin for severe hypertriglyceridemia for longer time to address his severe hypertriglyceridemia and the trend. Once triglyceride reached 5 mmol/L level, he was switched over to a basal-bolus subcutaneous insulin regimen and started on a combination of fenofibrate and atorvastatin. Subcutaneous heparin was instituted as well. In time he perked up and closed the anion gap.

Following diagnosis, the main aim of treatment was to optimize his blood glucose levels and manage symptoms. Lifestyle modification and other parameters were put into consideration as well. He was followed up with endocrinology, dietician, and bariatric surgery clinics for consults since patients with Flatbush diabetes, which we suspect this patient has, usually need insulin for a brief period. Their diabetes can be controlled either on diet alone or diet plus oral medications. The plan for our patient is to have counseling for a genetic study about the severe hyperlipidemia profile he presented with. Moreover, at the time of examination, his diabetes had shown reduced dependence on therapy, which we noted even before leaving the hospital.

Discussion

The term “Flatbush diabetes” has been in use since the 1980s, which was typified in some patients presenting with DKA who have a clinical course not dissimilar to that of patients with (T2DM) compared with patients with T1DM. Winter et al described a form of atypical maturity-onset diabetes of youth in 12 of 129 young black Americans.³ These patients were initially thought to have T1DM since several patients presented with ketosis and required initial insulin therapy. After weeks to months, they were no longer dependent on insulin. This atypical diabetes occurred in 9 of 12 families in two generations and was not associated with islet-cell autoantibodies. The recognition that adult black Americans with T2DM could initially present with DKA with no known precipitating cause (19 of 21 patients) was described by Banerji et al³ under the rubric “Flatbush diabetes.” This syndrome was characterized by the acute onset of severe hyperglycemia with ketoacidosis requiring hospital admission and treatment with insulin and fluid and electrolyte replacement. After several weeks to months, 12 of 21 patients no longer required insulin and could be treated with diet alone.

A small percentage may continue to require insulin therapy. Recurrent ketoacidosis is unusual, and the clinical course is like a patient with T2DM.

There are two fundamental questions in assessing the mechanisms responsible for KPD. The first is, are there a unique set of circumstances that lead to acute disruption of metabolic regulation leading to severe hyperglycemia and ketoacidosis that resolve by restoring euglycemia? The second is, do patients who develop KPD have unique abnormalities of β -cell function and/or insulin resistance that are part of their metabolic regulatory systems. Acute studies can

address the first question at or shortly after the presentation of KPD. The second question is addressed by evaluating the metabolic state of ketosis-prone diabetic patients after the acute event has resolved and during long-term near-normoglycemic follow-up.

Alpha and β -cell functions were evaluated in 15 sub-Saharan Africans with KPD who were insulin-free and normoglycemic and 15 matched normal control patients by Choukem et al in Paris.⁴ Fasting plasma glucose and insulin levels were high. However, fasting plasma glucagon was not significantly different between the patients with KPD and the control patients. In response to an oral glucose challenge, early insulin secretion was markedly decreased, 2-hour plasma insulin was increased, and 2-hour plasma glucagon was the same between KPD patients and normal controls. An arginine stimulation test showed that KPD patients had markedly diminished insulin and C-peptide secretion, but similar glucagon responses compared with the control population. During a euglycemic insulin clamp, there was no difference in baseline glucagon levels and no difference in glucagon suppression during the clamp between KPD patients and the normal controls. The studies did show that glucagon suppression relative to hyperglycemia was impaired, as is characteristic of T2DM, but that basal and stimulated levels were similar to normal controls.

Umpierrez et al assessed the possibility that patients with KPD might have an increased sensitivity to lipotoxicity.⁵ After patients had achieved near-normoglycemic control off insulin (~12 weeks), 48-hour IV infusions of 20% intralipid on β -cell function (plasma insulin and C-peptide levels) throughout the infusions were measured. There was no difference in the β -cell response in patients with KPD compared with obese patients who presented with severe hyperglycemia or nondiabetic obese controls. The insulin secretory responses to arginine infusions were likewise unaffected by the IV intralipid in all three cohorts.⁵

The reasons for the development of severe hyperglycemia are either overweight or obese patients with KPD or the obese nonketosis-prone patient with T2DM remain unknown. Diabetes is newly diagnosed in these patients at their admission to the hospital for insulin treatment. The inability of glucose to stimulate insulin secretion appears to be the central abnormality leading to severe hyperglycemia with or without ketoacidosis and persists for several days to weeks despite normalization of the plasma glucose. The ability of nonglycemic pharmacologic agents (glucagon and arginine) to stimulate insulin secretion during the acute phase indicates that even during the acute hyperglycemia, there is a small store of insulin within the β -cell that is not physiologically available but can be used to differentiate these patients from patients with classical T1DM.

Hypertriglyceridemia has become the third most typical cause of acute pancreatitis after gall stone-related pancreatitis and alcohol-induced pancreatitis.⁶ The risk of hypertriglyceridemia-induced acute pancreatitis usually occurs in patients with serum triglyceride levels ≥ 1000 mg/dL (≥ 11.3 mmol/L), but the risk of acute pancreatitis increases when

serum triglyceride levels remain consistently above 500 mg/dL (5.65 mmol/L).⁷

The pathogenic mechanism of hypertriglyceridemia-induced acute pancreatitis is not fully understood, but it has been shown that the hydrolysis of triglycerides by pancreatic lipase leads to the accumulation of substantial amounts of free fatty acids in the pancreas.⁸ Free fatty acids play a significant role in increasing the levels of interleukin 1 and tumor necrosis factor-alpha that works as the initiators of the inflammatory cascade leading to the activation of other inflammatory cytokines, which propagates the inflammatory processes in acute pancreatitis.⁹

Acute pancreatitis can cause significant morbidity and mortality, with almost 50% of mortality occurring within the first 14 days of presentation. Initial management of hypertriglyceridemia-induced pancreatitis is similar to treating acute pancreatitis caused by other etiologies. It includes IV fluids hydration, correction of electrolyte disorders, bowel rest, and analgesics.

Heparin and insulin infusion are the primary therapies used in the acute phase to reduce triglyceride levels. Heparin stimulates the release of lipoprotein lipase (LPL), which attaches to endothelial cells and decreases serum triglyceride levels. However, long-term infusion of heparin can lead to depletion of LPL, resulting in rebound elevation of serum triglyceride levels.¹⁰ Insulin is highly effective in stimulating the stimulating LPL activity and increasing the degradation of chylomicron, and it leads to a significant reduction in serum triglyceride levels both in people with and without diabetes mellitus.^{11,12}

Patients with severe acute pancreatitis induced by severe hypertriglyceridemia may occasionally require plasmapheresis to induce an acute reduction in serum triglyceride and chylomicron levels. Dehal and Adashek reported improvement in morbidity and mortality of patients with hypertriglyceridemia-induced pancreatitis treated with plasmapheresis.^{10,13}

Conclusions

The recognition and understanding of KPD are of considerable importance to clinicians. It is now recognized that many patients presenting with DKA, mainly if they are non-Caucasians, may have an atypical form of T2DM and not T1DM. These patients require hospitalization with insulin and fluid and electrolyte replacement. A significant percentage of these patients become insulin-independent after several weeks to several months of insulin treatment, and their glycemia can be managed with ordinary diet alone (remission) or diet plus oral agents for many years. Sulfonylurea therapy has been shown to prolong remissions in patients with ketosis-prone and acute severe hyperglycemia presentations.^{14,15} There are some differences in the syndrome depending on the racial or ethnic background of the population.

Consent for Publication

The authors confirm that the patient provided an informed consent for publishing on anonymous basis.

Authors' Contributions

All authors participated in the clinical care of the patients, conceptualization, data collection, drafting, and finalization of the manuscript.

Compliance with Ethical Principles

There is no need for prior ethical approval in our institution for single case report.

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None.

Conflict of interest

None declared.

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