Case report

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SEVERE KETOACIDOSIS IN A NEWLY DIAGNOSED PATIENT WITH TYPE 2 DIABETES AND METABOLIC SYNDROME

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Diabetic ketoacidosis (DKA) is well-known complication of type 1 diabetes, however, its presence is increasingly recognized in type 2 diabetes patients, even as initial presentation. Case report Male patient, 54 years old, was hospitalized due to newly diagnosed type 2 diabetes (BG 21,3 mmol/l, HbA1c 10.5%) accompanied with severe diabetic ketoacidosis (pH 7.00, base excess -24,6, serum bicarbonate 6,7 mEg/l). The patient was obese (BMI 35), hypertensive (160/90 mmHg), with extreme dyslipidaemia (TC 25,22 mmol/l, HDL 2,45 mmol/l, TG 31,21 mmol/l). During hospitalization, the patient was diagnosed with acute pancreatitis, cholelithiasis, GERD, and hepatic steatosis. The patient was treated with rehydration, intravenous insulin infusion, antibiotic therapy, proton pump inhibitor, antihypertensive therapy (ACE inhibitor and beta blocker), and dietary restriction. The patient was discharged with NPH insulin once daily, metformin, PPI, ACEi, BB and statin. Six months later BMI was 30,2, FBG 6,2 mmol/l, HbA1c 5.6%, TC 3,91 mmol/l, HDL 1,19 mmol/l, LDL 2.27 mmol/l, TG 0.99 mmol/l, amylase 78, CRP 6,9 mg/l, BP 130/80 mmHG. Seven months later laparoscopic cholecystectomy was done, and nine months later insulin therapy was discontinued. The weight, glycaemic control, lipid status and blood pressure remained stable during follow up of 24 months. The patient continues with metformin, statin, ACEi, and BB. Conclusion In newly diagnosed type 2 diabetes DKA could be from constant hyperglycaemia (glucose toxicity) and the presence of stressors that cause increase lipolysis due to counterregulatory hormones. Majority of patients are able to discontinue insulin after the resolution of DKA.

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Key words: *Type 2 diabetes, diabetic ketoacidosis, metabolic syndrome*

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Introduction

Diabetic ketoacidosis (DKA) is a well known complication of type 1 diabetes mellitus, however, its presence is increasingly recognized in type 2 diabetes patients, even as the initial presentation of type 2 diabetes. DKA is characterized by hyperglycaemia, ketosis and metabolic acidosis (increased anion gap) along with a number of secondary metabolic derangements (1). DKA results from absolute or relative insulin deficiency which is inadequate to prevent ketosis combined with counteregulatory hormone excess (2). Hyperglycaemia results from three processes: increased glyconeogenesis, accelerated glycogenoliysis and impared glucose utilization in peripheral tissues (3). This is magnified by transient insulin resistance due to hormone imbalance itself as well as the elevated free fatty acids (4). The combination of insulin deficiency and increased counterregulatory hormones in DKA leads to release of free fatty acids from adipose tissue (lipolysis) and to unrestrained hepatic fatty acid oxidation in the liver to ketone bodies (5). The most common precipitating factors are infections, inadequate insulin therapy, pancreatitis, myocardial infarction and illicit drug use (6).

The rate of hospitalization due to DKA among adults in USA in 2014 is 7,7 per 1000 persons with diabetes (168,000 discharges) (7). DKA is the most common cause of death in children and adolescents with type 1 diabetes (8). The mortality rate in adults is < 1%, however, a mortality rate >5% is reported in elderly and in patients with concomitant life-threatening diseases (9).

Diagnostic criteria for DKA are shown in Table 1.

Table 1. Diagnostic criteria for DKA (2)

	Mild DKA (plasma glucose > 13,9 mmol/l)	Moderate DKA (plasma glucose > 13,9 mmol/l)	Severe DKA (plasma glucose > 13,9 mmol/l)
Arterial pH	7.25-7.30	7.00 to <7.24	< 7.00
Serum bicarbonate (mEq/l)	15-18	10 to < 15	< 10
Urine ketone	Positive	Positive	Ppositive
Serum ketone	Positive	Positive	Positive
Serum osmolality	Variable	Variable	Variable
Anion gap	> 10	> 12	> 12
Mental status	Alert	Alert/drowsy	Stupor/coma

Treatment of DKA includes replacement of fluids, administration of short-acting insulin IV, replacement of K+, bicarbonate or phosphate supplementation. Frequent assessment of the serum electrolytes (K, Na, Mg, Cl, bicarbonates, phosphates), acid-base status, renal function is necessary, as well as monitoring of blood pressure, pulse, respirations, mental status, fluid intake and output (2).

Case report

In January 2016, male patient, aged 54, was admitted to the Clinic for Endocrinology, Diabetes and Metabolic Diseases of Clinical Center Niš, due to newly diagnosed type 2 diabetes mellitus accompanied with severe diabetic ketoacidosis. The patient complains of symptoms that last for about ten days, including thirst, dry mouth, frequent urination, fatigue, nausea, vomitus, loss of appetite. The patient reported that he was being treated for hypertension for 25 years (ACE inhibitor, beta blocker), also reported that he was overweight for about 15 years. There was a positive family history of diabetes (the mother suffered from type 2 diabetes). The patient is a former smoker (he had smoked 30 years ago) and uses no alcohol.

Physical examination showed signs of dehydration, tachycardia (122/min), hypertension (160/90 mmHg), dyspnea, diffusely painfully sensitive abdomen, obesity (weight 124kg, height 188cm, BMI 35.1).

Laboratory report revealed diabetes mellitus with highly elevated glycaemic parameters (blood glycose 21.3 mmol/l, HbA1c 10.5%) and metabolic acidosis (pH 7,00, serum bicarbonates 6.7 mEq/l, anion gap -24.6). Other clinically significant results included extreme dyslipidaemia (total cholesterol 25.22 mmol/l, HDL cholesterol 2.45 mmol/l, triglycerides 31.21 mmol/l), elevated amylases (459 IU/l), elevated lypases (903 IU/l), elevated inflammation parameters (CRP 106.7 mg/l, WBC 14,0). Electrolytic status was normal.

Additional diagnostic methods have been applied. Esophagogastroduodenoscopy showed esophaphagitis grade B of the distal part of esophagus. Abdominal ultrasound showed hepatic steatosis, cholelythiasis (gallblader calculi up to 13 mm) and increased echogenicity of the pancreatic head.

The patient was treated with rehydration, intravenous insulin infusion, antibiotic therapy, proton pump inhibitor and antihypertensive therapy (ACE inhibitor and beta blocker) and dietary restriction. After the resolution of DKA, NPH insulin was introduced.

Table 2. Regular control six monts later

Parameters	Six months later	Baseline
BMI (kg/m^2)	30.2 (↓)	35.1
FBG (mmol/l)	6.2 (↓)	21.3
HbA1c (%)	5.6 (↓)	10.5
Total cholesterol (mmol/l)	3.91 (↓)	25.22
LDL cholesterol (mmol/l)	2.27	-
HDL cholesterol (mmol/l)	1.19 (↓)	2.45
Triglycerides (mmol/l)	0.99 (↓)	31.21
Amilases (IU/l)	78 (↓)	459
CRP (mg/l)	6.9 (↓)	106.9
BP (mmHg)	130/80 (↓)	160/90

Table 3. Regular controls up to 24 months

Parameters	12 months	18 months	24 months
BMI (kg/m^2)	29.1	28.5	29.5
FBG (mmol/l)	5.5	5.9	5.9
HbA1c (%)	5.2	5.6	5.8
Total cholesterol (mmol/l)	3.56	3.95	3.93
LDL cholesterol (mmol/l)	1.58	1.87	1.89
HDL cholesterol (mmol/l)	1.37	1.32	1.35
Triglycerides (mmol/l)	1.35	1.68	1.52
BP (mmHg)	120/80	130/70	120/70

The patient was discharged 11 days later with significant improvement in glycaemic control and without any subjective symptoms. The patient was discharged with NPH insulin once daily, metformin, PPI (pantoprazole), ACEi (ramipril), BB (bisoprolol) and statin (atorvastatin).

The patient came to regular check-ups and was compliant with dietary requirements and performed the moderate-intensity physical activity. The patient performed regular SMBG (self -monitoring of blood glucose). At control after 6 months a weight loss was obvious, parameters of glycaemic control were much better, hyperlipidaemia and hypertension were satisfactorily controlled, there were no elevated inflammation markers. Relevant parameters are presented in Table 2.

Seven months later laparoscopic cholecystectomy was done, and nine months later insulin therapy was discontinued. The patient continued with metformin, atorvastatin, ACEi and BB. The weight, glycemic control, lipid status, and blood pressure remained stable up to 24 months, as shown in Table 3.

Discussion

Insulin is known to inhibit glyconeogenesis and glycogenolysis and to enhance glucose uptake in peripheral tissues. However, in insulin-resistant states glucose output from the liver is increased (10). In insulin-resistant states the body still remains sensitive to antilypolytic effect of insulin. There are data suggesting that the amount of insulin required to prevent lipolysis is one-tenth of that required for glucose utilization (11). This is the reason why it had been thought that patients with type 2 diabetes did not develop ketoacidosis (type 2 diabetes is a predominantly a disease of increased insulin resistance, so residual beta cell function in these patients could produce enough insulin to prevent ketogenesis but not to satisfy glucose metabolism requirements).

The occurrence of DKA in type 2 diabetes is thought to be due to coexisting stressors, predominantly infections. Other reported causes include myocardial infarction, cerebrovascular accidents, antipsychotic usage, malignancy, poor compliance with medication etc (2, 12). Sometimes no stressors can be found and it can be the initial presentation of type 2 diabetes (13).

The occurrence of DKA in type 1 diabetes is due to the presence of insulinopaenia. A similar mechanism can occur in long-standing type 2 diabetes due to complete loss of beta cell function. However, this is not always the case as same patients present within a few years from diagnosis or at the time of diagnosis, when complete beta cell dysfunction is unlikely (12). The cause could be relative insulin deficiency that comes from constant hyperglycaemia as the result of poor control and the presence of stressors that cause increased lypolysis due to counter regulatory hormones (glucagon, cortisol, growth hormone) (14). Hyperglycaemia itself reduces insulin secretion and glucose removal by down-regulating glycose transporter systems and even reducing insulin gene transcription (mechanisms known as glucose toxicity) (15).

DKA in type 2 diabetes tends to be less severe and potassium level is more likely to be normal (12). Type 2 diabetes patients with DKA tend to have typical insulin resistance features (large body habitus, acantosis nigricans), positive family history, no autoimmune markers, and may require larger insulin doses to correct hyperglycaemia (15). The majority of patients with DKA and newly diagnosed type 2 diabetes are able to discontinue insulin after the acute episode and to continue with oral antidiabetic therapy (up to 66% in some studies) (16). This may be related with beta cell recovery after the resolution of the acute hyperglycemic episode (17). The importance of recognizing DKA as the feature of type 2 diabetes lies in this finding, ensuring that patients are not unnecessarily continued with insulin and providing significant cost, economic and emotional benefit to patients (17).

Some aspects of our case are in accordance with literature data. The patient had features of insulin resistance (obesity, metabolic syndrome, hepatic steatosis). Hyperglycemia was long and uncontrolled (HbA1c 10.5%), most likely leading to further beta cell dysfunction (glucose toxicity). Coexisting stressor was identified (cholecystitis, pancreatitis). After the resolution of DKA, the patient experienced satisfactory glycaemic control with NPH insulin and metformin, being compliant with the dietary regimen and performing regular physical activity. The insulin could be discontinued earlier, but this therapeutic approach was continued probably due to expected surgical intervention. After the surgery insulin was discontinued and the patient remained off insulin for more than a year without any worsening of glycemic control, enabling him to lose some more weight.

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Prikaz bolesnika

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TEŠKA DIJABETIČKA KETOACIDOZA KOD BOLESNIKA SA NOVOOTKRIVENIM DIJABETESOM TIPA 2 I METABOLIČKIM SINDROMOM

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Dijabetička ketoacidoza (DKA) je dobro poznata komplikacija dijabetesa tipa 1, ali njeno postojanje se sve više prepoznaje kod bolesnika sa dijabetesom tipa 2, čak i kao inicijalna prezentacija. Bolesnik muškog pola, star 54 godine, hospitalizovan je zbog novootkrivenog dijabetesa tipa 2 (glikemija 21,3 mmol l, HbA1c 10,5%) praćenog teškom dijabetičkom ketoacidozom (pH 7,00, bazni eksces -24,6, serumski bikarbonat 6,7 mEg/l). Bolesnik je bio gojazan (BMI 35), hipertenzivan (160/90 mmHg), sa ekstremnom dislipidemijom (TC 25,22 mmol/l, HDL 2,45 mmol/l, TG 31,21 mmol/l). Tokom hospitalizacije mu je dijagnostikovan akutni pankreatitis, holelitijaza, GERB i hepatična steatoza. Lečen je rehidratacijom, intravenskom infuzijom insulina, antibiotskom terapijom, inhibitorom protonske pumpe, antihipertenzivnom terapijom (ACE inhibitor i beta blokator), kao i restriktivnom dijetom. Bolesnik je otpušten sa propisanom terapijom: NPH insulin jednom dnevno, metformin, PPI, ACEi, BB i statin. Šest meseci kasnije, BMI je bio 30,2, glikemija našte 6,2 mmol/l, HbA1c 5,6%, TC 3,91 mmol/l, HDL 1,19 mmol/l, LDL 2,27 mmol/l, TG 0,99 mmol/l, amilaza 78, CRP 6,9 mg/l, TA 130/80 mmHg. Sedam meseci kasnije obavljena je laparoskopska holecistektomija, a devet meseci kasnije prekinuta insulinska terapija. Glikoregulacija, telesna težina, krvni pritisak i lipidni status ostali su stabilni tokom praćenja od 24 meseca. Bolesnik nastavlja sa metforminom, atorvastatinom, ACEi i BB. Zaključak je da novodijagnostikovani dijabetes tipa 2 DKA može nastati usled konstantne hiperglikemije (glukotoksičnost) i prisustva stresora koji uzrokuju ubrzanu lipolizu usled povećanja kontraregulatornih hormona. Većina bolesnika mogu da prekinu insulinsku terapiju nakon korekcije DKA.

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Ključne reči: *dijabetes tipa 2, dijabetička ketoacidoza, metabolički sindrom*