Niger J Paed 2015; 42 (2): 154 –157

CASE REPORT

Onyiriuka AN
Iduoriyekemwen NJ
Esin RY

Steroid-induced diabetic ketoacidosis in a 14-year-old boy with steroid-sensitive nephrotic syndrome: Case report and literature review.

DOI:http://dx.doi.org/10.4314/njp.v42i2.17

Accepted: 15th November 2012

Onyiriuka AN (✉)
Iduoriyekemwen NJ, Esin RY
Department of Child Health,
University of Benin Teaching Hospital,
PMB 1111,
Benin City, Nigeria.
E-mail: alpndiony@yahoo.com
didiruka@gmail.com

Abstract: In this report, we described the case of a 14-year-old boy with steroid-sensitive nephrotic syndrome who developed hyperglycaemia and ultimately, diabetic ketoacidosis, following high-dose steroid therapy for a primary renal disease. The nephrotic syndrome was diagnosed based on generalized oedema, massive proteinuria, hypoalbuminaemia and hypercholesterolaemia. Serum creatinine and random blood glucose levels were normal and there was no glycosuria. He was commenced on high dose prednisolone 40 mg 12 hourly and by the 8th day on prednisolone, he achieved remission and was discharged. However, four weeks later, he developed features of diabetic ketoacidosis (DKA) which was confirmed by the presence of hyperglycaemia (random blood glucose19.4 mmol/L), acidosis (serum bicarbonate 10 mmol/L) and ketonuria (2+). The DKA was managed with intravenous fluid (0.9% sodium chloride), continuous insulin infusion and antibiotics. After resolution of the DKA, he was switched to subcutaneous soluble insulin and thereafter, premixed insulin twice daily with a reduction in the dose of prednisolone and was discharged home after 30 days on admission. Blood glucose level has remained within normal range one year after discontinuing insulin and he is still in remission with regard to the nephrotic syndrome at follow up.
Conclusion: The risk of diabetic ketoacidosis should be considered in the course of steroid therapy for nephrotic syndrome. To avoid missing of cases of steroid-induced diabetes mellitus, and ultimately DKA, both fasting and postprandial blood glucose values should be monitored.

Key words: Adolescence, diabetes, ketoacidosis, nephrotic syndrome, steroid therapy.

Introduction

Systemically-administered steroids are effective for treating nephrotic syndrome but they can cause hyperglycaemia. The mechanisms by which steroids cause hyperglycaemia are multifactorial but the predominant one is reduced insulin sensitivity. Other purported mechanisms include increased hepatic gluconeogenesis and impaired peripheral utilization of glucose[1]. The diagnosis of steroid-induced diabetes mellitus (SIDM) is based on the presence of either a fasting blood glucose level of 7.0 mmol/L (126 mg/dl) or greater or a random blood glucose level of 11.1 mmol/L (200 mg/dl) or greater on at least two separate occasions[2].
Although SIDM is an important clinical problem which may warrant hospitalization, it continues to be undervalued in terms of diagnosis, and particularly treatment[3]. Steroid-induced hyperglycaemia and the resultant new-onset diabetes mellitus (NODM) have been variously reported. For instance, in the United Kingdom and the USA (New Jersey Medicaid) the odd ratios for the development of NODM were 1.36 and 2.23 respectively[4,5]. In a prospective study of patients without diabetes but with primary renal disease who were treated with steroid, 42% were found to have 2-hour postprandial blood glucose greater than 200 mg/dl but normal fasting blood glucose values[6]. With regard to the diagnosis of SIDM, some experts have pointed out that if fasting blood glucose values 126 mg/dl (7 mmol/L) or greater are used for its diagnosis , many cases will be missed[7]. However, available reports indicate that occurrence of diabetic ketoacidosis associated with steroid therapy is rare[8,9]. Recent studies indicate that even short-term elevations in blood glucose level may be associated with

renal cell damage, suggesting the need for greater attention to be paid to this clinical entity in patients with a primary renal disease[10].

The purpose of this report is to describe the case of an adolescent boy with steroid-sensitive nephrotic syndrome who developed diabetic ketoacidosis after four weeks of steroid therapy.

Case report

A 14-year-old boy presented in the Nephrology Unit of the Department of Child Health, University of Benin Teaching Hospital complaining of generalized body swelling of 5 weeks duration. Physical examination revealed an adolescent boy with facial puffiness, bilateral pitting pedal/ankle oedema, scrotal oedema , ascites and BMI =17.8 kg/m^2. Blood pressure was 130/80 mmHg. His sexual maturity rating was appropriate for his age. His urea and electrolyte profile was unremarkable. A clinical diagnosis of nephrotic syndrome was made. The laboratory findings confirmed the diagnosis (Table 1). He was commenced on oral prednisolone 60 mg/m^2/day (40 mg 12 hourly). He achieved remission eight days after the commencement of prednisolone and was subsequently discharge home. Four weeks after discharge, he presented in our Children's Emergency Unit with a history of vomiting, poor appetite, generalized body weakness, and restlessness. Further history revealed he has been having polyuria, polydipsia and nocturia for the preceding two weeks. No family history of diabetes mellitus. The patient was not placed on any other medication other than prednisolone and he was not on any herbal remedies. Before commencement of prednisolone, the random blood glucose was normal (5.3 mmol/L) and urine was negative for glucose and ketones and remained normal until he achieved remission on the 8th day of treatment. Physical examination revealed a severely dehydrated, restless, male adolescent in respiratory distress (acidotic breathing). The laboratory findings were hyperglycaemia (blood glucose 19.4 mmol/L), severe acidosis (serum bicarbonate 10 mmol/L), and ketonuria 2+; all consistent with diabetic ketoacidosis (DKA). Steroid-induced diabetic ketoacidosis in an adolescent with steroid-sensitive nephrotic syndrome was therefore considered. Other laboratory findings at presentation with DKA are summarized in table 1.

He was managed with intravenous fluid (0.9% sodium chloride), continuous insulin infusion and intravenous antibiotics. After resolution of the DKA, he was switched to subcutaneous soluble insulin and thereafter, premixed insulin 18 units in the morning and nine units in the evening. He was discharged after 30 days on admission. A clinical review at follow-up visit revealed that he was still in remission with regard to the nephrotic syndrome and his blood glucose values have remained within normal range with no proteinuria or glycosuria. He has been off prednisolone for 18 months now and last urinalysis revealed no proteinuria. His insulin was discontinued and the blood glucose was checked every month for six months initially, and thereafter, every three months. The blood glucose values have remained within normal range for 12 months now.

Table 1: Summary of laboratory findings at point of admission for nephrotic syndrome and diabetic ketoacidosis respectively.

At point of admission for nephrotic syndrome		
Variables	Results	Comments
Proteinuria	Positive (4+)	Massive proteinuria
Haematuria	Negative	In consonance with MCNS
Glycosuria	Negative	No pre-existing diabetes mellitus
24-hour urine protein	3.4g	Massive proteinuria
Serum cholesterol	598 mg/dl	Hypercholesterolaemia
Serum albumin	1.7 g/dl	Hypoalbuminaemia
Spot urinary protein-to-creatinine ratio	21.7[500/23]	Markedly elevated
Serum creatinine	0.6 mg/dl	Normal
At point of admission for diabetic ketoacidosis		
Variables	Results	Comments
Serum sodium	136 mmol/L	Within normal range
Serum potassium	3.9 mmol/L	Within normal range
Serum bicarbonate	5 mmol/L	Severe acidosis
Serum chloride	94 mmol/L	Within normal range
Blood Urea	26 mg/dl	Within normal range
Serum creatinine	1.0 mg/dl	Within normal range
Urinalysis		
pH	6	Acidic
Ketones	Positive 2+	Significant ketonuria
Glucose	Positive 2+	Significant glycosuria
Protein	Trace	Within normal range
Packed cell volume	48%	Within normal range

MCNS= Minimal change nephrotic syndrome

Discussion

In this patient, the clinical diagnosis of nephrotic syndrome as well as diabetic ketoacidosis (DKA) was not difficult. In both conditions, their clinical presentations as well as laboratory findings were consistent with each of the diagnoses. However, some clinical features in this patient need consideration. The patient achieved remission by the eight day on high-dose prednisolone, suggesting a steroid-sensitive nephrotic syndrome (minimal change nephrotic syndrome). This is not surprising as 20 -30% of adolescents with nephrotic syndrome has been reported to have minimal change disease and remission could be achieved within 14 days[11,12]. Absence of glycosuria and the presence of euglycaemia at the time of diagnosis of nephrotic syndrome indicate that the patient did not have diabetic mellitus prior to initiation of steroid therapy. Steroid-induced diabetes mellitus usually resolves after cessation of steroid use, as exemplified in this case. The blood glucose values have remained within normal limits with absence of glycosuria, 12 months after stoppage of insulin therapy. This finding is not surprising as it is consistent with the report of an earlier study[9]. Whether or not the steroid-induced diabetes mellitus experienced by this patient is a marker for the onset of diabetes mellitus in adulthood is not known with certainty. In that regard, we plan to follow him up to full adulthood. Although a high body mass index (BMI) has been reported as a risk factor for steroid-induced diabetes, the BMI of the index patient was within normal limits[6], suggesting that other unidentified risk factors might be involved. Although simultaneous

onset of steroid-sensitive nephrotic syndrome and type 1 diabetes has been reported, it is rare and the estimated frequency is one case in every 3,300,000 inhabitants at risk.[8] In their report, polyuria, polydipsia, hyperglycaemia, ketonuria and glycosuria occurred three weeks after commencement of prednisolone. Two months later, their patient while on insulin relapsed with diabetic ketoacidosis following an upper respiratory tract infection. In contrast, our patient have not relapsed despite stoppage of insulin administration for 12 months, suggesting that the ketoacidosis was steroid-therapy induced as against the simultaneous co-existence of steroid-sensitive nephrotic syndrome and type 1 diabetes.

The results of the fasting and postprandial blood glucose values in our patient need consideration. Eight days after the commencement of prednisolone, urinalysis revealed glycosuria with random blood glucose of 14.2 mmol/L. The fasting blood glucose was 6.5 mmol/L the next morning. This discrepancy between the random and fasting blood glucose values is not surprising as it is consistent with the observation in other studies. For instance, in a prospective study of patients without diabetes but with primary renal disease who were treated with steroid, 42% were found to have 2-hour postprandial blood glucose greater than 11.1 mmol/L (200 mg/dl) but normal fasting blood glucose values[6]. A similar observation was reported by Iwamoto et al[13] among patients with neurological diseases treated with steroid. The clinical implication for the diagnosis of steroid-induced diabetes mellitus is that if fasting blood glucose values of 7.0 mmol/L (126 mg/dl) or greater is used as the only criteria for its diagnosis, many cases will be missed[7]. In patients with primary renal disease on high-dose steroid therapy, both the random and fasting blood glucose values should be monitored to avoid missing the diagnosis of steroid-induced diabetes mellitus. In this regard, in one of the studies in Japan, it was specifically recommended that the monitoring of blood glucose values two hours after lunch should be performed in all patients on high-dose steroid therapy because of the six sampling points, the highest value was obtained two hours after lunch[13]. They further stated that fasting blood glucose values did not contribute to detecting steroid-induced diabetes mellitus.

This patient presented in our Children's Emergency Unit with diabetic ketoacidosis. As reported in other studies, it is uncommon for patients with steroid-induced diabetes mellitus to present with ketoacidosis[9]. For instance, none of the 25 patients on high-dose steroid therapy reported by Iwamoto et al[13] in their study presented with ketoacidosis. The occurrence DKA might be related to steroid-induced insulin resistance, activation of lipolysis in the periphery and ketogenesis.

A review of the literature revealed that controversies still exist mainly with regard to treatment of steroid-induced new-onset diabetes mellitus (SINODM). Insulin administration is the mainstay of therapy of SINODM. In general, two approaches have been suggested with the first, focusing on prandial insulin therapy and the second, on basal insulin therapy. The prandial insulin therapy approach is based on the observation that with once daily dose of steroid, fasting blood glucose are typically normal but rise steadily after breakfast and then lunch, declining towards normal overnight. This rise in glucose level throughout the day is believed to be an evidence of a specific defect in postprandial insulin secretion, which should be amenable to prandial insulin therapy. Concerning the basal insulin therapy approach, Clore et al[2] recommended the use of NPH for patients on prednisolone based on the pharmacokinetics of this steroid. The recommended dose in basal insulin therapy approach is 0.4 U/kg. However, it should be noted that this recommendation is not based on randomized trial, and so, there is no clear cut recommendation on insulin management of SINODM. Therapy should, therefore, be individualized. The index case was managed with the standard protocol for the treatment of diabetic ketoacidosis and then switched to twice daily premixed (short acting plus intermediate acting)insulin after resolution of DKA[14]. The insulin therapy has been discontinued about 12 months ago and blood glucose values have remained with normal limits, representing a further evidence that steroid-induced diabetes mellitus resolves with discontinuation of steroid administration (steroid therapy was discontinued 18 months ago). There is no recurrence of DKA.

Conclusion

In conclusion, in adolescents with steroid-sensitive nephrotic syndrome, the risk of steroid-induced diabetic ketoacidosis should be considered in the course of steroid therapy. Both fasting and postprandial blood glucose values should be monitored to prevent missing of cases of steroid-induced diabetes mellitus and ultimately, DKA.

Conflict of Interest: None
Funding: None

References

1. Rizza RA, Mandarino LJ, Gerich JE. Cortisol-induced insulin resistance in man: impaired suppression of glucose production and stimulation of glucose utilization due to a postreceptor defect of insulin action. *J Clin Endocrinol Metab 1982;54:131-138.*
2. Clore JN, Thurby-Hay L. Glucocorticoid-induced hyperglycaemia. *Endocr Pract 2009;15(5):469-474.*
3. Saigi I, Perez A. Management of glucocorticoid-induced hyperglycaemia. *Rev Clin Esp 2010;210 (8):397-403* [Article in Spanish].
4. Gulliford MC, Charlton J, Latinovic R. Risk of diabetes associated with prescribed glucocorticoids in a large population. *Diabetes Care 2006;29:2728-2729.*

5. Gurwitz JH, Bohn RL, Glynn RJ, Monane M, Mogun H, Avorn J. Glucocorticoids and the risk for initiation of hypoglycemic therapy. *Arch Intern Med 1994;154:97 -101.*
6. Uzu T, Harada T, Sakaguchi M, Kanasaki M, Isshiki K, Araki S, Sugiomoto T, Koya D, Haneda M, Kashiwagi A, Yamamuchi A. Glucocorticoid-induced diabetes mellitus: prevalence and risk factors in primary renal diseases. *Nephron Clin Pract 2007;105 (2):54-57.*
7. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care 1997;20:1183-1197.*
8. Rego Filho EA, Mello SFR, Omuro AM, Loli JOC. Simultaneous onset of steroid-sensitive nephrotic syndrome and type 1 diabetes. *J de Pediatria 2003;79 (6):557-560.*
9. Banac S, Persic M, Cvijovic K. Steroid diabetes in children with Crohn disease. *Acta Med Croatica 2002;56(1):35-38.*
10. Lewko B, Stepinski J. Hyperglycaemia and mechanical stress: targeting the renal podocytes. *J Cell Physiol 2009;221(2):288-295*.
11. Baqi N, Singh A, Balachandra S, Ahmad H, Nicastri A, Kytinski S, Homel P, Tejani A. The paucity of minimal change disease in adolescents with primary nephrotic syndrome. *Pediatr Nephrol 1998;12:105-107.*
12. The primary nephrotic syndrome in children: identification of patients with minimal change nephrotic syndrome from initial response to prednisone – a report of the International Study of Kidney Disease in Children. *J Pediatr 1981:98:561 -564.*
13. Iwamoto T, Kagawa Y, Naito Y, Kuzuhara S, Kojima M. Steroid-induced diabetes mellitus and related risk factor in patients with neurologic diseases. Pharmacotherapy 2004;24:508-514.
14. Wolfsdorf J, Craig M, Daneman D, Dunger D, Edge J, Lee W et al. International Society for Paediatric and Adolescent Diabetes Clinical Practice Consensus Guidelines 2009: Diabetic ketoacidosis. *Pediatr Diabetes 2009;10(Suppl 12):118-133.*