Cross-Reactivity of Insulin Immunoassays Important for Insulin Analogue Detection in Factitious Hypoglycaemia

Sir,

Read with interest the article by Deep Dutta *et al*.[1] where they described the efficacy of lispro insulin in diabetes. With the increasing use of insulin analogues, a new dimension has been added to the diagnosis of factitious hypoglycaemia. We recently managed a case of factitious hypoglycaemia due to intake of lispro insulin, which was missed by routine insulin assay and was detected by insulin assay with cross-reactivity with lispro.

A man known to have type 2 diabetes, on treatment with insulin and antidiabetic drugs, presented with a history of 3–4 episodes of hypoglycaemia over the preceding 1 month. All antidiabetic drugs and insulin were withheld; however, symptoms of hypoglycaemia persisted. He was admitted for evaluation.

Renal and liver functions were normal. He underwent a supervised fast for inducing hypoglycaemia. Twelve hours after the last calorie intake, the patient had diaphoresis, sweating and tremors. Plasma glucose was 33 mg/dl, with ketones < 0.3 mmol/L, serum insulin 9.12 µU/ml and C-peptide 1.2 ng/ml, suggesting an endogenous hyperinsulinism. Urine sulfonylurea screen was negative. Considering endogenous hyperinsulinism we proceeded with localisation studies, contrast-enhanced computed tomography (CECT) abdomen revealed doubtful 2.2*1.9 cm lesion in the tail of the pancreas, which corroborated with endoscopic ultrasound and contrast-enhanced magnetic resonance imaging (CE-MRI). Gallium DOTANOC did not show any somatostatin receptor (SSTR)-expressing lesion. Exendin scan revealed uptake in the pancreatic tail. Considering these findings, he underwent distal pancreatectomy. In the immediate postoperative period, the patient had hyperglycaemia and required insulin for glycaemic control. He was discharged on insulin and antidiabetic drugs. Surprisingly, the histopathology examination of the surgical specimen revealed a normal pancreas without any evidence of insulinoma.

Two months post-surgery, he presented with a recurrence of hypoglycaemia, which persisted even after all drugs and insulin were stopped. He was readmitted for evaluation. The critical sample during hypoglycaemia revealed plasma glucose of 30 mg/dl, with insulin 0.4 µU/ml, C-peptide 0.35 ng/ml and serum ketones 0.2 mmol/l, growth hormone of 23.5 ng/ml and cortisol of 25.6 µg/dl. Insulin levels were measured using the Roche Elecsys assay. Repeat analysis of the critical sample by Abbott analyser revealed serum insulin of 32.4 µU/ml and C-peptide of 0.4 ng/ml, suggestive of exogenous insulin intake. Further questioning revealed the current intake of lispro insulin.

In retrospect, the urine sulphonyl urea screen report was rechecked. It was negative for glimepiride, glipizide, glyburide, nateglinide, repaglinide, acetohexamide, chlorpropamide and tolazamide. There was no mention of gliclazide. On reviewing literature, we found that cross-reactivity of drugs with radioimmunoassay for sulphonylureas varies from 100% to nil. So, small quantities of sulphonylureas with low cross-reactivity with assay can be missed.[2,3]

Psychiatry consultation was arranged. He was started on cognitive behavioural therapy and escitalopram. His hypoglycaemia resolved.

The patient's hypoglycaemic profile was different in both instances. The first instance, where both insulin and C-peptide were elevated, can probably be due to sulphonylurea intake which was missed in the urine sulphonylurea screen.[3] Factitious hypoglycaemia due to exogenous insulin is suggested by increased insulin and suppressed C-peptide during hypoglycaemia.

The inclusion of certain moieties at specified locations distinguishes insulin analogues from human insulin. This makes it challenging to identify these alterations in the assays due to their low cross-reactivity with insulin immunoassays.[4] Roche Elecsys assay does not exhibit any cross-reactivity with any insulin analogues, but they are picked up with Abbott analyser. Understanding the differences in cross-reactivities between different analysers and insulin analogues is crucial when interpreting insulin assays and evaluating hypoglycaemia.[4]

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Conflicts of interest

There are no conflicts of interest.

Sachin K. Raj, Setu Gupta, Alpesh Goyal, Viveka P. Jyotsna

Department of Endocrinology and Metabolism, AIIMS, New Delhi, India

Address for correspondence: Dr. Viveka P. Jyotsna, Department of Endocrinology and Metabolism, AIIMS, New Delhi, India.
E-mail: vivekapjyotsna@gmail.com

References

1. Dutta D, Nagendra L, Bhattacharya S, Sharma M. Efficacy and safety of ultra-rapid lispro insulin in managing type-1 and type-2 diabetes: A systematic review and meta-analysis. Indian J Endocrinol Metab 2023;27:467-75.
2. Giurgea I, Ulinski T, Touati G, Sempoux C, Mochel F, Brunelle F, *et al*. Factitious hyperinsulinism leading to pancreatectomy: Severe forms of Munchausen syndrome by proxy. Pediatrics 2005;116:145-8.

3. Kwong PYP, Teale JD. Screening for sulphonylureas in the investigation of hypoglycaemia. J R Soc Med 2002;95:381-5.
4. Lotierzo M, Galvez T, Conquet G, Verani Q, Aguilhon C, Rangeard I, *et al*. Accurate selection of insulin immunoassay to discern factitious hypoglycemia: A case report. Acta Diabetol 2023;60:315-7.

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