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CASE REPORT

Case of type 2 diabetes mellitus with edema resulting in subcutaneous insulin resistance syndrome

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ABSTRACT

Subcutaneous insulin resistance syndrome caused by obesity, induration at the injection site, skin temperature and other factors is common clinically, whereas resistance events caused by edema are relatively rare. This article introduced a case of a woman with type 2 diabetes mellitus with heart failure edema. Her blood glucose control was significantly associated with the level of edema. Excluding other factors, it can be concluded that edema might lead to subcutaneous insulin resistance syndrome, even if the edema at the injection site is not obvious.

INTRODUCTION

Subcutaneous injection of insulin is a conventional treatment for diabetes. Intravenous insulin and hypodermic insulin normally have similar effects[1]. It is rarely reported that a patient with hypodermic injection of insulin has no response, but intravenous injection has a good response, which is called subcutaneous insulin resistance (SIR) syndrome[2].

CASE REPORT

A 77-year-old woman with diabetes was treated with 7-U insulin injections t.i.d., and acarbose 50 mg t.i.d. + sitagliptin 100 mg q.d. orally. Her self-monitoring of blood glucose was poor, random blood glucose was 30 mmol/L and glycated hemoglobin was 10.1% at admission.

After admission, she was given continuous subcutaneous injection of insulin pump. The daily insulin amount was 36 U (recombinant human insulin lispro) on day 1, including 18 U basal insulin and 6-6-6 U large dose for three meals. Her blood glucose fluctuated between 16.3 and 25.8 mmol/L throughout the day, and a total of 26 U insulin was added divided into multiple injections at different times to control glycemic spikes. The insulin amount was 62 U for 24 h.

Considering the patient's poor glycemic control, the insulin dosage was adjusted to 54.9 U on day 2. The blood glucose fluctuated between 15.1 and 23.3 mmol/L throughout the day, so 43 U insulin was added. Metformin was added to increase insulin sensitivity. The total insulin amount was 98 U for 24 h, which was far beyond the total amount required by a normal human body (her weight was 62 kg). The replacement of injection equipment, pipelines and injection sites failed to significantly improve the control effect during the day. The patient's insulin antibody test was negative.

On day 3, the patient was switched to an intravenous insulin pump (biosynthetic human insulin) continuous injection. The total amount of insulin was 45 U for 24 h, and her blood glucose fluctuated between 6 and 15 mmol/L throughout the day.

The patient's blood glucose level suggested that insulin was still effective, so it was considered that the patient might not be insensitive to insulin lispro. On day 4, the intravenous insulin pump continuous injection was replaced by subcutaneous insulin pump injection with biosynthetic human insulin for continuous injection. The dosage of insulin was 63.4 U and another 28 U insulin was added. Sitagliptin was combined to control

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blood glucose. The blood glucose fluctuated between 19.9 and 24.9 mmol/L throughout the day. The amount of insulin was 91.4 U for 24 h. This showed that the blood glucose control after subcutaneous injection was still not ideal after the change of insulin varieties.

Other factors affecting the subcutaneous absorption of insulin were considered. The patient had a history of cardiac insufficiency. On admission, there was obvious pitting edema in both lower limbs, but no obvious swelling in other parts, pro-B-type natriuretic peptide (proBNP) was 880 pg/mL. On day 3, her proBNP was 1,070 pg/mL, which showed that heart failure was aggravating, but no obvious edema at the site of insulin injection (the abdomen) was observed. Considering that the patient's hypodermic insulin malabsorption might be related to the edema, the diuretic dosage was doubled to reduce the edema (torasemide 10 mg i.v. q.d.). At the same time, the patient was switched to insulin intravenous pump for maintenance again from day 5.

Over the following 3 days, the patient's total insulin was approximately 50 U for 24 h, and her blood glucose was controlled within 4.8–11.2 mmol/L. On day 8, the patient's edema reduced significantly in both lower limbs. Subcutaneous injection of insulin was used again. The daily dose of insulin was 50 U. The fluctuation of blood glucose was 7.9–12.9 mmol/L. On day 10, the patient's edema disappeared. We wanted to add sodium–glucose cotransporter 2 inhibitor, because it could reduce edema at the same time as lowering glucose, which was suitable for the patient's condition. However, we finally decided not to do so, because the patient urinated frequently at night (usually 2–7 times during 1 night), and sodium–glucose cotransporter 2 inhibitor might aggravate the patient's nocturia symptoms. The patient was discharged from hospital, and the treatment regimen was maintained after discharge.

One month later, the patient's outpatient follow up showed recurrence of edema in both lower limbs, and proBNP of 2,440 pg/mL. Fasting and postprandial blood glucose were 11.7 mmol/L and 16.1 mmol/L, respectively, and the patient was treated with insulin plus metformin and sitagliptin, because metformin improves insulin sensitivity and does not increase the risk of heart failure. The total amount of insulin was 46 U. The doctor prescribed a diuretic to relieve the edema and increased the total amount of insulin to 64 U. The patient's edema had completely disappeared 3 months later. Her daily dose of insulin is 56 U, and her blood glucose is well within the target.

The protocol for the research project has been approved, and this study was approved by the Medical Ethics Committee of Zhejiang Provincial People's Hospital. The approval number is 2021QT206 and the approval time is 2021.5.31.

DISCUSSION

Subcutaneous injection is the most common administration route for insulin, and the subcutaneous absorption directly affects patients' blood glucose control. There are many factors affecting insulin absorption, including obesity, skin temperature, injection site and so on[3]. However, the failure of subcutaneous insulin injection caused by heart failure is rarely reported. The present patient was a rare case of type 2 diabetes mellitus with SIR syndrome due to heart failure.

There was a clear correlation between glycemic control in this patient and the insulin administration route. Unfortunately, we did not detect changes in the plasma-free insulin level after subcutaneous injection, which is a limitation of this report. Paulsen *et al.*[4] advised that clinical symptoms of SIR syndrome should be accompanied by no increase in the plasma-free insulin level and increased insulin degradation activity in subcutaneous tissues after subcutaneous injection. However, most reported cases of SIR syndrome were clinically diagnosed, and plasma-free insulin levels after administering a subcutaneous insulin injection[5] and insulin degradation at the tissue levels could not be determined in the cases[2]. Therefore, the diagnosis of SIR syndrome might not necessarily require changes in plasma-free insulin levels.

Factors influencing the subcutaneous absorption of insulin can be divided into three categories: (i) insulin preparation (physical and chemical factors); (ii) injection site/patient (physiological/endogenous factors); (iii) and injection technology (exogenous factors)[6]. First, in terms of physical and chemical factors, factors such as the type of insulin and excipient were considered. As the present patient chose quick-acting/short-acting insulin, this kind of insulin was more easily absorbed by subcutaneous tissue after modification than human insulin. In addition, the patient had changed the insulin variety during hospitalization, which did not show any effect. Second, the insulin pump was firmly connected to the patient's body through the infusion catheter, and exogenous factors can be excluded because there were no influencing factors, such as incorrect needle removal timing and needle reuse. Finally, the physiological/endogenous factors, including parts of the body, skin temperature, fat thickness, smoking, exercise and complications related to diabetes, were considered. During hospitalization, the patient's body temperature was stable; she had no bad habits, such as tobacco smoking and alcohol consumption; the patient's body mass index was in the normal range; and no obvious obesity was observed. After the switch to subcutaneous injection, glycemic control was not improved.

A major cause of SIR syndrome is subcutaneous blood flow at the injection site[7]. When heart failure occurs, the quantity of blood released from heart is reduced, and venous backflow is blocked. It brings about a rise in capillary fluid static pressure and lymphatic backflow is blocked, which further leads to sodium/water subcutaneous retention, called edema[8]. Enlargement of connective tissue cells, muscle fibers and glandular epithelial cells caused by edema will squeeze the capillaries to a certain extent, which further leads to slow blood flow velocity. Meanwhile, the accumulation of a large amount of fluid will affect the diffusion of insulin, which leads to the occurrence of

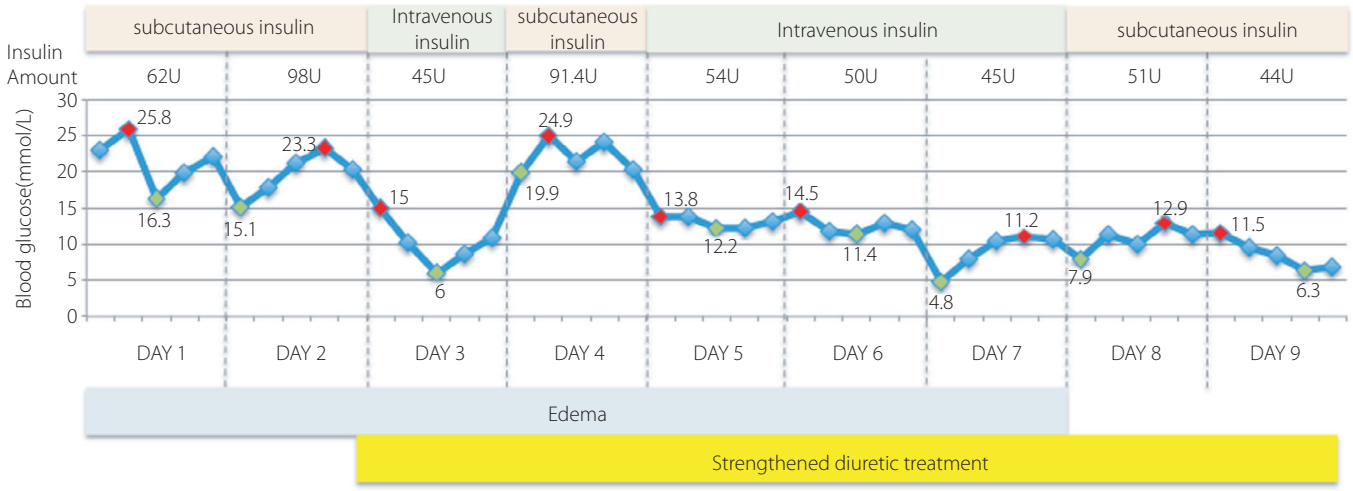

Figure 1 | The edema and blood glucose curve of the patient after admission. The vertical axis is the blood glucose (mmol/L), the horizontal axis is the duration of hospital stays from admission. The injection method of insulin used every day is in the first line. The insulin amount for 24 h used every day is in the second line. The duration of edema (grey line) and intensive diuretic treatment (yellow line) are in the last two lines. When edema was severe, the blood glucose was not well controlled using subcutaneous insulin, and the effect became better after intensive diuretic treatment.

SIR. Ariza-Andraka *et al.*[9] found that the rate of insulin absorption was delayed by edema. The effect was even more pronounced in people with type 2 diabetes mellitus.

The present patient had type 2 diabetes mellitus. In the first 3 days, the edema of her lower limbs was severe, and her proBNP level also confirmed the severity of heart failure. As she was an older woman, her abdominal tissue was relatively loose. The edema of her abdomen was not as obvious as that of the lower limbs, which could be easily noticed, but it could still be present. During this period, she did not respond well to subcutaneous insulin therapy. After the edema almost completely subsided on day 8, her response to subcutaneous insulin therapy improved significantly. Figure 1 shows the patient's edema and blood glucose curve after admission. There was a clear correlation between edema progression and the effect of subcutaneous insulin therapy. The outpatient follow up of the patient further confirmed the correlation. In conclusion, the patient's SIR syndrome might have been induced by edema.

Edema as a result of chronic complications, such as nephropathy and cardiopathy, often occurs in long-standing diabetes patients. Recent clinical trials showed that there is a common pathophysiology between diabetes and heart failure. Type 2 diabetes mellitus is one of the risk factors for the occurrence of heart failure, and an increasing number of patients with both diabetes and heart failure have been diagnosed clinically[10]. The present case suggests that in the clinical treatment of diabetes patients with heart failure, we should also be vigilant about the influence of edema on the efficacy of subcutaneous injection of insulin, and actively eliminate the inducement of edema to achieve the purpose of lowering blood glucose.

DISCLOSURE

The authors declare no conflict of interest.

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