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CASE REPORT

Case of subcutaneous insulin resistance syndrome treated with ultra-rapid insulin lispro

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ABSTRACT

Subcutaneous insulin resistance syndrome is a rare condition that causes difficulty in glycemic control due to severe resistance to subcutaneous insulin injections. We herein present a case of a 40-year-old woman with type 2 diabetes mellitus who had been diagnosed with subcutaneous insulin resistance syndrome since the age of 29 years, and had been persistently treated with continuous subcutaneous insulin infusion using a mixture of insulin lispro and heparin. The patient was switched from insulin lispro plus heparin to ultra-rapid insulin lispro; given that it contains treprostinil and citrate, it is expected to have similar effects as heparin, and shows similar glucose-lowering effects and insulin absorption. Our results suggest that treatment with ultra-rapid insulin lispro is effective for subcutaneous insulin resistance syndrome.

INTRODUCTION

Subcutaneous insulin resistance (SIR) syndrome has been characterized as a condition wherein a patient develops severe resistance to subcutaneous insulin injections, but normal sensitivity to intravenous insulin[1]. Reports have shown that treating SIR syndrome with a mixed infusion of insulin lispro and heparin (Lis + Hepa) improves insulin absorption and provides good glycemic control[2,3]. However, attention should be paid to adverse effects, such as bleeding tendencies, due to continuous heparin administration, albeit in smaller doses than usual. We speculated that ultra-rapid insulin lispro (URLi; Lyumjev®; Eli Lilly Japan K.K., Kobe, Japan), which contains treprostinil – a prostacyclin (PGI2) analog – and citrate would provide good insulin absorption from the subcutis due to its similarity to heparin. We herein report our experience with URLi in a patient with SIR syndrome treated with Lis + Hepa.

CASE REPORT

A 40-year-old Japanese woman (92.0 kg; body mass index 36.5; glycated hemoglobin 8.9%) with type 2 diabetes mellitus was admitted to Okayama Medical Center, Okayama, Japan, for treatment modification. She was diagnosed with type 1 diabetes mellitus at the age of 16 years and was thereafter started on insulin injection therapy; however, due to recurrent diabetic ketoacidosis, continuous subcutaneous insulin infusion (CSII) was initiated. Unfortunately, her hyperglycemia persisted even after introducing CSII, which necessitated continuous venous insulin infusion for lowering blood glucose.

The patient was first admitted to our hospital at the age of 29 years due to hyperglycemia and severe insulin resistance (66.0 kg; body mass index 26.2), during which her glycated hemoglobin was 11.5%, despite high doses of insulin (210 U/day of insulin glargine, 50 U of regular insulin before each meal and 270 U/day of regular insulin with CSII; total daily dose [TDD] of 630 U/day). No obvious abnormal eating habits could be identified. Both glutamic acid decarboxylase and insulinoma antigen-2 antibodies were negative, and insulin antibody was 3.4% (reference value <0.4%). The glucagon stimulation test showed a change in C-peptide immunoreactivity (6 min) of 1.1 ng/mL (from 1.5 to 2.6 ng/mL).

Based on the aforementioned results, a diagnosis of type 2 diabetes with severe insulin resistance, and not type 1 diabetes, was established. As such, we subsequently changed the patient's subcutaneous injections to continuous venous insulin infusion of regular insulin and markedly reduced her TDD from 630 to 100–120 U/day; furthermore, she was clinically diagnosed with SIR syndrome. Based on previous reports showing that Lis + Hepa was effective for SIR syndrome, we switched from

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continuous venous insulin infusion to CSII of Lis + Hepa[2,3] (1:1 in volume, with final insulin lispro and heparin concentrations of 50 and 500 U/mL, respectively). Consequently, she was discharged with favorable glycemic control on CSII of Lis + Hepa (TDD 117 U/day).

Despite having continuously received a combination of Lis + Hepa for ~11 years, the patient suffered from suggillation and menorrhagia, which were thought to be caused by continuous heparin administration. As such, the patient requested to be hospitalized for modification of her treatment. On admission, she was treated with CSII of Lis + Hepa with a TDD of 55 U/day. Her laboratory findings and diabetic complication are shown in Table 1. We considered switching from Lis + Hepa to URLi, given that URLi contains treprostinil and citrate, and is more easily absorbed than insulin lispro alone. After fasting overnight, Lis + Hepa 0.2 U/kg or URLi 0.2 U/kg was subcutaneously administered followed by plasma glucose and serum insulin levels' assessment.

Notably, the present results showed that although URLi promoted slightly higher serum insulin levels compared with in Lis + Hepa, both had a comparable glucose-lowering effect (Figure 1). These results showed that switching from Lis + Hepa to URLi would allow the patient to maintain at least similar levels of glycemic control while also maintaining quality of life. She was discharged on CSII of URLi (TDD 43 U/day), and showed marked improvement in glycemic control with thorough diet and exercise at home (Figure 2).

Table 1 | Laboratory findings and diabetic complications on admission

CBC			**Biochemistry**		
WBC	7,000	/μL	TP	7.4	g/dL
RBC	413 × 10^4	/μL	Alb	4.3	g/dL
Hb	11.5	g/dL	AST	29	IU/L
Hct	36.7	%	ALT	20	IU/L
Plt	24.1 × 10^4	/μL	γ-GTP	48	IU/L
Coagulation			BUN	14	mg/dL
APTT	29.4	s	Cre	0.78	mg/dL
PT	9.3	s	PG	400	mg/dL
PT-INR	0.89		HbA1c	8.9	%
Urine			**Diabetic complications**		
Protein	(+)		Peripheral neuropathy	(+)	
Glucose	(4+)		Autonomic neuropathy	(+)	
Ketone	(–)		Retinopathy	(+)	
ACR	607.0	mg/gCre	Nephropathy	Macroalbuminuria	

γ-GTP, γ-glutamyltranspeptidase; ACR, albumin-to-creatinine ratio; Alb, albumin; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CBC, complete blood count; Cre, creatinine; Hb, hemoglobin; HbA1c, glycated hemoglobin; Hct, hematocrit; PG, plasma glucose; Plt, platelet; PT, prothrombin time; PT-INR, international normalized ratio of prothrombin time; RBC, red blood cell; TP, total protein; WBC, white blood cell.

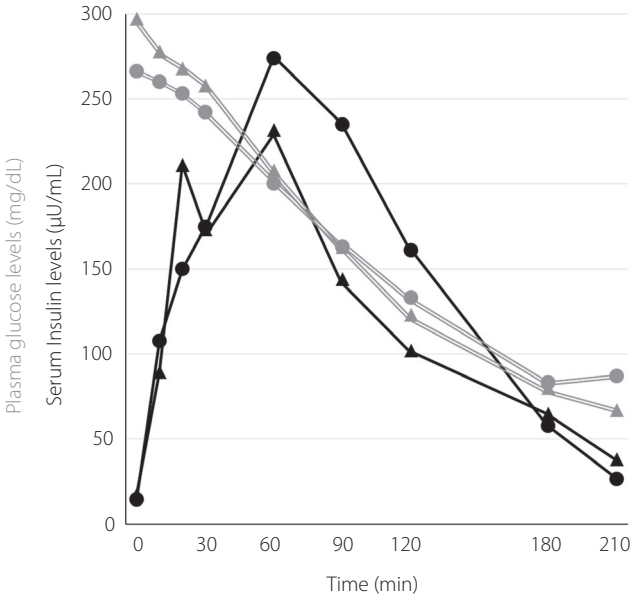

Figure 1 | Comparing the effects of insulin lispro with heparin and ultra-rapid insulin lispro. Insulin lispro with heparin 0.2 U/kg (triangle) and ultra-rapid insulin lispro 0.2 U/kg (circle) were subcutaneously injected. Serum insulin (black solid line) and plasma glucose levels (gray double lines) were measured 3.5 h after each administration.

Following the change in treatment, suggillation and menorrhagia disappeared, although pain during injection was slightly increased.

DISCUSSION

Severe insulin resistance to subcutaneous insulin injection with normal intravenous insulin sensitivity, absence of elevated serum insulin levels after subcutaneous injection and increased insulin degradation in subcutaneous tissues characterizes SIR syndrome[4]. However, confirming insulin degradation enhancement remains challenging, with several cases requiring clinical diagnosis[5]. As previously reported[2,3], treatment with a mixture of Lis + Hepa promoted good glycemic control for patients with SIR syndrome. Although the present case showed reasonably good blood glucose control by Lis + Hepa, she suffered from bleeding tendencies, which impaired her quality of life; therefore, after examining the glucose-lowering effect and absorption rate of URLi, we observed that it was comparable to those of Lis + Hepa and that switching to URLi was feasible.

Two mechanisms have been suggested to explain the effects of Lis + Hepa on SIR syndrome. First, insulin lispro is absorbed into the bloodstream more rapidly than regular insulin[6]. Second, heparin facilitates the diffusion of water-soluble molecules by bearing many negative charges[7], and binds to vascular endothelial growth factors, which induce the permeabilization of the blood vessels[8,9], thereby facilitating the transfer of subcutaneously injected insulin into the bloodstream. URLi is a

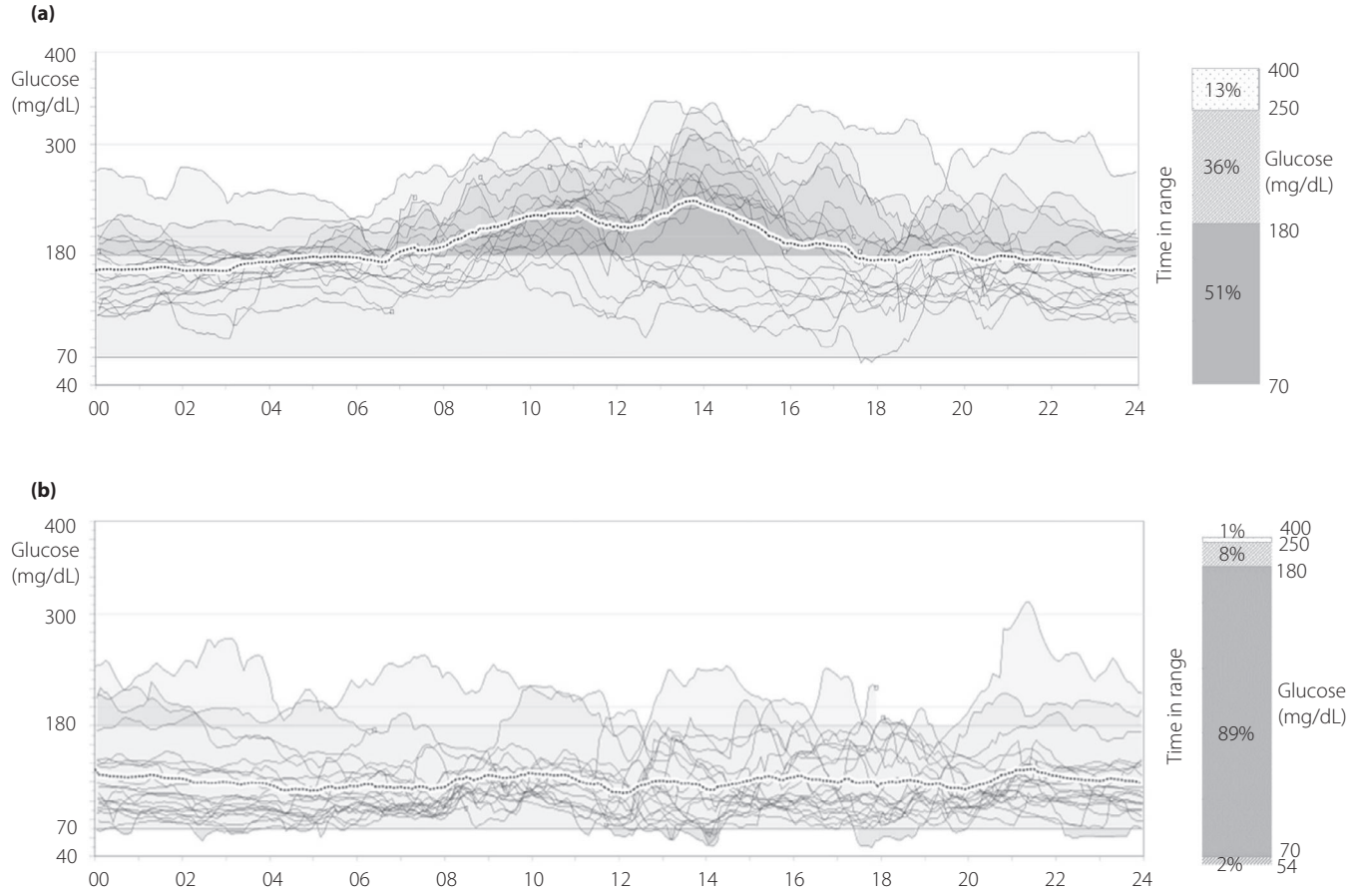

Figure 2 | Continuous glucose monitoring data and time in range (a) 3 weeks before admission and (b) 3 weeks after discharge.

novel insulin formulation that adds two locally acting excipients, treprostinil and citrate, to insulin lispro. Treprostinil is a PGI2 analog that has a direct vasodilator effect and has been used as a therapeutic agent for pulmonary arterial hypertension, and citrate increases local vascular permeability[10]. The addition of these two additives increases local blood flow and accelerates the transportation of injected insulin from the subcutaneous to the bloodstream, which might explain why URLi shows comparable insulin absorption effects as heparin.

In conclusion, we herein report a case of SIR syndrome that achieved good glycemic control with a novel insulin formulation. Although reports have shown that the combination of Lis + Hepa is effective for SIR syndrome, the present report shows that URLi might provide good glycemic control without the use of heparin.

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None.

DISCLOSURE

The authors declare no conflict of interest.

Approval of the research protocol: N/A.
Informed consent: Informed consent was obtained from the patient.
Approval date of registry and registration no. of the study/trial: N/A.
Animal studies: N/A.

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