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Case Report

Abnormal Urinary C-Peptide Levels in a Patient with Type 2 Diabetes and Heart Failure Treated with GLP-1 Receptor Agonists and an ARNI

Kentaro Takahashi, Satoshi Yoshino, Sho Sekiguchi, Mio Okada, Kenya Okada, Mai Sue-Nagumo, Masashi Yoshikawa, Masaya Uehara, Hiroki Ito, Shunichi Matsumoto, Kazuhiko Horiguchi, Shuichi Okada, and Eijiro Yamada*

Department of Medicine and Molecular Science, Gunma University Graduate School of Medicine, 3-39-15 Showa-machi, Maebashi, Gunma, Japan 371-8511.

***Corresponding author:** Eijiro Yamada, Department of Medicine and Molecular Science, Gunma University Graduate School of Medicine, 3-39-15 Showa-machi, Maebashi, Gunma, Japan 371-8511.

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Abstract

This study presents a case involving a patient diagnosed with Type 2 Diabetes (T2D) and heart failure, focusing on the atypical elevation of Urine C-Peptide (UCPR) levels. The patient, an 85-year-old male, received treatment for minimal-change nephrotic syndrome with Prednisolone (PSL) alongside multiple diabetes medications including GLP-1 receptor agonists, specifically Liraglutide (LIRA) initially and later Dulaglutide (DURA) and Semaglutide (SEMA). Despite adjustments in medication and discontinuation of sacubitril/valsartan, an Angiotensin Receptor-Neprilysin Inhibitor (ARNI), UCPR levels remained significantly elevated, indicating unusual insulin secretion.The study highlights the potential influence of ARNI on UCPR levels and insulin secretion, despite various GLP-1 receptor agonists administered. Glucagon stimulation tests indicated sufficient basal insulin secretion but limited additional secretion, contradicting the notably high UCPR values. The persistent elevation in UCPR, even after discontinuing ARNI, implies an impact on renal C-peptide clearance. These findings underscore the complexity of assessing insulin secretion in patients with T2D and heart failure, suggesting a potential link between ARNI use, GLP-1 receptor agonists, and altered UCPR levels. Further investigations into the mechanisms underlying ARNI's effect on UCPR and insulin secretion are warranted to better understand and manage such cases.

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Keywords: Type 2 Diabetes (T2D); Heart Failure; Urine C-Peptide (UCPR); GLP-1 Receptor Agonists; Angiotensin Receptor-Neprilysin Inhibitors (ARNI)

Introduction

Deficient insulin function including insulin resistance and decreased insulin production is a characteristic of Type 2 Diabetes (T2D) [1]. Evaluating C-Peptide (CPR) levels in relation to blood glucose is essential, and urine CPR (UCPR) levels reflect insulin secretion both during fasting and postprandial periods [2].

As the global population ages, comorbid T2D and heart failure are becoming notable concerns, leading to the use of Angiotensin Receptor-Neprilysin Inhibitors (ARNI). ARNIs inhibit both the nEPRILYSIN (NEP) and Renin-Angiotensin-Aldosterone (RAS) systems [3]. These medications influence sodium natriuretic peptide levels and affect compounds such as Glucagon-Like Peptide-1 (GLP-1), which is secreted in response to a meal [4].

We present a case with T2D and heart failure with an atypically elevated UCPR that was treated with GLP-1 receptor agonists and an ARNI.

Case Presentation

Prednisolone (PSL) was used to treat minimal-change nephrotic syndrome in an 85-year-old male with T2D. Due to elevated blood glucose levels, we initiated treatment with GLP-1 receptor agonists. Liraglutide (LIRA; 0.3 mg) was initially prescribed. The dose was later increased to 0.9 mg. This drug was administered along with Metformin (Met), Pioglitazone (Pio), and Mitiglinide (Mit). His blood glucose control improved with gradual reduction in PSL, and Pio and Mit were subsequently discontinued (Figure 1). The patient attempted to switch from LIRA to SGLT2 inhibitors; however, this switch resulted in an increase in blood glucose levels, prompting a return to LIRA (Figure 1). Six months later, after his HbA1c levels improved, the patient attempted to replace LIRA with repaglinide. However, his HbA1c level increased to 9.0%, resulting in hospital admission. He was treated with 0.3 mg LIRA along with initiation of insulin glargine (Figure 1).

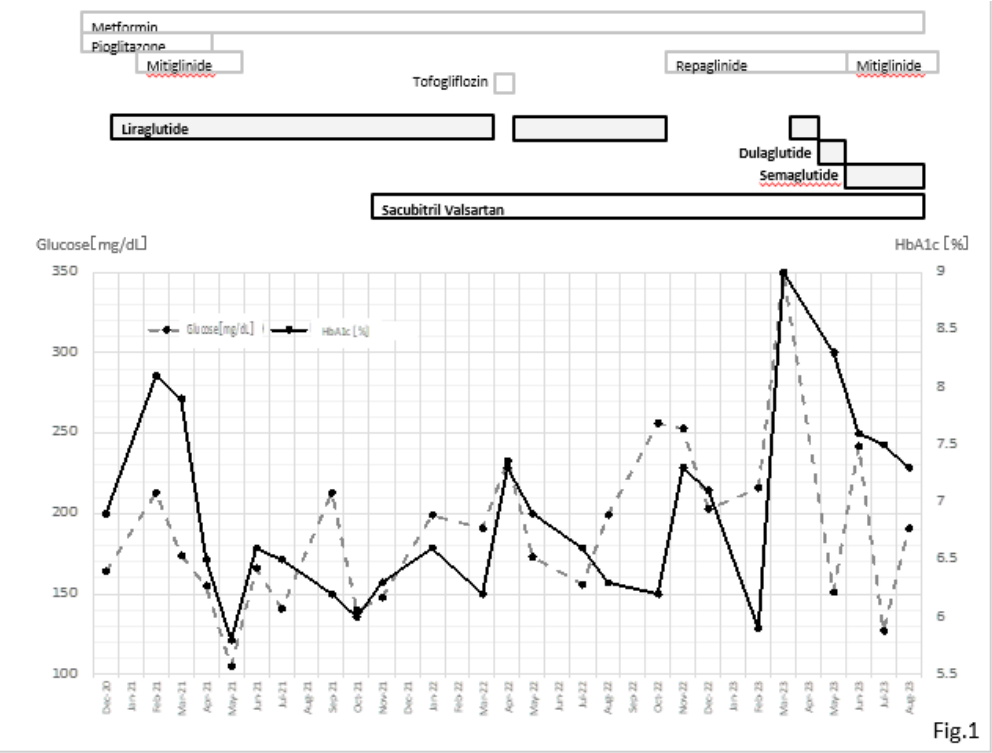

Figure 1: Upper panel; drug administration history. Lower panel; sequential changes in plasma glucose (PG, gray, dotted line) and HbA1c (black, solid line) levels under ad libitum conditions.

His height and weight were 163 cm and 63 kg, respectively. The patient had a history of myocardial infarction and had previously undergone a coronary artery bypass graft surgery. His medications included sacubitril/valsartan (an ARNI), carvedilol, ivabradine, nicorandil, sotalol, aspirin/lansoprazole combination tablets, and rosuvastatin. His laboratory test results, including hormone levels, were normal (Figure 2A, 2B, 2C).

A

	Clinical values (normal range)
WBC (/μL)	8400 (3300-8600)
Hb (g/dL)	13.0 (13.7-16.8)
Platelets x10^4 (/ μL)	20.9 (15.8-34.8)
Total protein (g/dL)	6.4 (6.3-7.9)
Albumin (g/dL)	3.9 (3.9-5.0)
Total bilirubin (mg/dL)	0.7 (0.3-1.2)
AST (U/L)	18 (13-33)
ALT (U/L)	16 (8-42)
LDH (U/L)	191 (124-222)
ALP (U/L)	46 (38-113)
γGTP (U/L)	16 (10-47)
CK (U/L)	74 (62-287)
AMY (U/L)	57 (49-136)
Blood urea nitrogen (mg/dL)	15 (8-20)
Creatinine (mg/dL)	0.79 (0.65-1.07)
Na (mEq/L)	137 (137-145)
K (mEq/L)	3.9 (3.5-4.8)
Cl (mEq/L)	102 (100-107)
T-Cho (mg/dL)	113 (128-219)
HDL-C(mg/dL)	40(38-63)
LDL-C(mg/dL)	55(59-139)
TG (mg/dL)	93 (30-149)

	Clinical values (normal range)
Blood glucose (mg/dL)	203 (80-110)
HbA1c (%)	9.0 (4.6-6.2)
Insulin antibody concentration(U/L)	<125(<125)
Insulin antibody combination rate(%)	<0.4(<0.4)
Anti-GAD antibody(U/mL)	<5.0(<5.0)
Free T3 (pg/mL)	2.6 (2.1-3.1)
Free T4 (ng/dL)	1.09 (0.75-1.42)
Human growth hormone (ng/mL)	0.13 (<2.10)
CEA(ng/mL)	2.4(0-5.0)
CA19-9(U/mL)	<2(0-37)

B

	0 min (normal range)	6min
Blood glucose (mg/dL)	111 (80-110)	124
Serum C-peptide (ng/mL)	6.0 (0.74-3.18)	7.1
Immunoreactive insulin (U/L)	8.7 (2.1-19.0)	23.2

C

	Term 1	Term 2	Term 3	condition 1	condition 1	condition 2
Urine C-peptide	769 μg/day	903 μg/day	1006 μ g/day	894 μg/gCr	1240 μg/gCr	507 μg/gCr
Measurement method	CLEIA	CLEIA	CLEIA	ECLIA	CELIA	CLEIA
Inspection agency	in-hospital	in-hospital	Tosoh Bioscience	BML	LSI	in-hospital
GLP-1 analogues	Liraglutide	Dulaglutide	Dulaglutide	Semaglutide	Semaglutide	Semaglutide
Sacubitril Valsartan	use	use	none (2 days)	use	use	none (2 weeks)

Fig.2

Figure 2: (A) Laboratory findings. (B) Results of glucagon stimulation test. (C) Urinary C-peptide test results (conducted six times). Term 1–3 represents the results of the urine collection test during hospitalization, while condition 1–2 represents the results of spot urine tests conducted during outpatient visits. The table includes information on the testing method, testing company, type of GLP-1 receptor agonists used, and whether there was discontinuation of sacubitril/valsartan.

While the patient was on LIRA, the glucagon stimulation and UCPR tests indicated sufficient basal insulin secretion but limited additional secretion with notable UCPR levels of 769 μg/day (Figure 2B, Figure 2C, Term 1). His UCPR was re-evaluated 3–4 days after switching from LIRA (0.3 mg) to dulaglutide (DURA; 0.75 mg/week). However, the UCPR remained notably elevated at 903 μg/day (Figure 2C, Term 2). We hypothesized that sacubitril/valsartan might have influenced the abnormally elevated UCPR levels. However, even after discontinuing sacubitril/valsartan for 2 days and utilizing a different testing facility, his UCPR remained abnormally high (Figure 2C, Term 3). Finally, insulin was discontinued, and the patient was discharged with the following medications: dulaglutide (DULA; 0.75 mg per week), Met (250 mg twice daily), and miglitol (10 mg three times daily). After discharge, we modified the testing methodology from Chemiluminescent Enzyme Immunoassay (CLEIA) to Electrochemiluminescence Immunoassay (ECLIA) to account for variations in the testing methodology; however, the outcomes stayed the same (Figure 2C, condition 1). Ultimately, after sacubitril/valsartan was discontinued for 2 weeks, similar tests were conducted, and a decreasing trend in his UCPR was observed; however, the values remained high when he was taking 0.25 mg Semaglutide (SEMA) (Figure 2C, condition 2).

Discussion

Recent evidence suggests that NEP plays a substantial role in glucose metabolism [5]. Although circulating neprilysin levels are linked to body mass index and metabolic syndromes, the glucose-lowering effects of ARNIs, which inhibit both NEP and RAS, are not fully understood [5]. For instance, sacubitril, an NEP inhibitor, inhibits GLP-1 degradation and modulates adrenomedullin and angiotensin 2 levels, subsequently affecting insulin secretion and resistance [5,6]. NEP degrades GLP-1 and liraglutide at multiple sites [5,7]. Therefore, assessing the effects of NEP inhibition in patients receiving GLP-1 receptor agonists is crucial. In this case, LIRA and once-weekly formulations (such as DURA and SEMA) were used. In each instance, an improvement in blood glucose levels accompanied by elevated UCPR was observed, suggesting that the degradation of these GLP-1 receptor agonist's analogs by NEP was inhibited by sacubitril. Notably, these effects persisted after the ARNI was discontinued while SEMA was administered.

The findings in this case suggest that NEP inhibition may result in increased GLP-1-mediated insulin secretion. Our case also highlights the discrepancy between serum CPR and UCPR. Glucagon stimulation tests indicated that basal insulin secretion was maintained; however, additional secretion was reduced, contradicting the high urinary C-peptide values (Figure 2B). Studies of Japanese subjects have suggested a correlation between serum CPR (SCPR) and UCPR which can be expressed as UCPR = (SCPR – 2.3)/0.02 [8]. Moreover, a correlation between changes in C-Peptide Post-Glucagon Stimulation (ΔCPR) and UCPR has been described, which can be expressed as UCPR = (ΔCPR – 0.15)/0.01 [9]. In this case, the estimated UCPR was approximately 90–180, indicating a notable discrepancy which suggests that NEP inhibition led to altered urinary clearance of CPR. In this context, the kidney serves as the primary site of CPR degradation. However, the specific mechanisms remain unclear. Peptide degradation is conducted by NEP, which is highly expressed at the brush border of the renal proximal tubule cells [10].

One limitation of this study is the assay method used to measure CPR levels. However, we employed two testing methods (CLEIA and ECLIA) and obtained consistent results from four different testing companies. Further, the study did not assess changes in GLP-1 concentrations before and after ARNI administration.

In conclusion, although a few cases of elevated UCPR due to ARNI use have been reported [11], this is the first case of a patient with increased UCPR levels after being administered three different GLP-1 formulations. Marked increases in the UCPR were observed with LIRA, DURA, and SEMA, irrespective of the formulation. These effects persisted even after the ARNI was discontinued for two weeks during SEMA use, suggesting that ARNIs may affect renal CPR clearance. Through intracellular G-protein signaling, CPR binds to cell membranes and performs a range of physiological functions, including diabetic neuropathy, nephropathy, and anti-inflammation [12]. The potential influence of ARNI in elevating UCPR and complicating insulin secretion assessments requires further investigation.

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Compliance with Ethical Standards

Disclosure of potential conflicts of interest: None of the authors have any potential conflicts of interest associated with this report.

Human rights statement and informed consent: No human studies involved. Informed consent statement: Informed written consent was obtained from the patient for publication of this report and any accompanying images.

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