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Case Report

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Correction of Over-Dosed Insulin in a Type-2- Diabetic Led to a Better Control of Glycemia and Arterial Hypertension: A Case Report

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Abstract

Introduction: An association between hypoglycemia and arterial hypertension has been proposed. Here, we report a case of an elderly type-2 diabetic presenting with hypertensive crisis, which improved after insulin-dose reduction.

Case Presentation: A 73-year-old, male type-2 diabetic of Caucasian ethnicity was hospitalized for hypertensive crisis and weakness attributed to a diabetic polyneuropathy. Prior to hospitalization, a fixed-dose insulin therapy (160 units per day) and a triple antihypertensive therapy (urapidil, valsartan, bisoprolol) were prescribed. Symptomatic hypoglycemic episodes were not reported. On admission, hyperglycemia from 15-19 mmol/L was present, hemoglobin A1c was 11.2%. On the third day in hospital, the fixed-dose insulin therapy was switched to an intensive insulin therapy with a cumulative daily dose of 46 units. Metformin, empagliflozin, and dulaglutide were added. Despite insulin-dose reduction, intermittent blood-glucose tests showed a considerable decrease of preprandial blood-glucose values to 11-15 mmol/L, antihypertensive medication was reduced by discharge. 22 months later, the diabetes therapy consisted of metformin, liraglutide, and insulin glargine (26 units per day). Antihypertensive medication was further reduced, and hemoglobin A1c was 6.6%. As a likely explanation, undocumented, asymptomatic hypoglycemic events were the cause for post-hypoglycemic, hormonal stimulation determining hyperglycemia and hypertensive crisis at admission. The insulin reduction to a quarter of the initial daily cumulative insulin dose performed at the 3rd day after admission translated into a better glycemic and blood-pressure control.

Conclusions: Here, insulin reduction likely corrected an initial insulin overdose leading to counterregulations facilitating hypertension.

Keywords: case report, insulin, Type-2 Diabetes, Hypoglycemia, Hypertension

Introduction

Hypoglycemia represents a hazard of insulin therapy, especially in cardiovascular high-risk patients [1,2]. Hypoglycemia unawareness associates with increased glucose concentrations in the brain most likely due to an up-regulation of insulin-independent glucose-transport mechanisms to the brain [3]. In addition, recurrent hypoglycemic episodes are associated with dementia [4]. An autonomic neuropathy or polyneuropathy does not associate with hypoglycemia unawareness [5]. In geriatric diabetes patients on insulin therapy, glycated hemoglobin A1c (HbA1c) does not correlate with

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less hypoglycemic episodes suggesting that a higher HbA1c goal does not suffice to reduce the risk for hypoglycemia in this cohort [6]. In patients experiencing hypoglycemic episodes, the post-hypoglycemia-induced catecholamine release and/or activated sympathetic nervous system may contribute to the development of arterial hypertension [7]. In a cohort study of hospitalized insulin-treated diabetics presenting with hypertensive crisis or with hypoglycemia, the hypoglycemic burden was similar [8]. Here, we present a type-2 diabetic with an elevated HbA1c, despite an ongoing high-dose insulin therapy, who had a hypertensive crisis prior to hospitalization. Although hypoglycemic episodes were not proven, a rapid reduction of insulin dose led to a sustained improvement of glycemic control and allowed for reduction of antihypertensive medication.

Case Presentation

A 73-year-old male diabetic of Caucasian ethnicity was admitted to a Neurology Department of tertiary-referral hospital with progressive weakness and vertigo occurring for one week prior to admission.. He had a background history of diabetic polyneuropathy, and clinical examination showed decreased muscle reflexes and hypopallesthesia. The patient depended on a wheelchair for 4 years before hospitalization. However, he still managed to walk distances of up to 10 m using a walking aid. Electrophysiological investigation showed a sensorimotor axonal and demyelinating peripheral neuropathy. As concomitant diseases, substituted hypothyroidism and metabolic syndrome with obesity (weight: 105 kg, height: 184 cm, body-mass index: 31.0 kg/m²), dyslipidemia, arterial hypertension and type-2 diabetes for more than 20 years were known. Four years before hospitalization, a unilateral knee and hip-replacement surgeries were performed. Shortly prior to hospitalization, urapidil (60 mg thrice a day) was added to his known antihypertensive medications with valsartan (160 mg BID) and bisoprolol (5mg BID) for an uncontrolled arterial hypertension. Diabetes therapy consisted of fixed-dose prandial human insulin (Actrapid®, 40 units thrice a day) and basal insulin analog (insulin glargine, 40 units QD) with a cumulative insulin dose of 160 units per day. This regimen was verified by the spouse and the treating family physician. Lipohypertrophies at insulin injection sites were not present. On admission, arterial hypertension still was uncontrolled. HbA1c was elevated (11.2%), kidney function was not impaired. Asymptomatic hypoglycemic episodes were not captured by preprandial blood-glucose test results, symptomatic ones were not reported.

The patient was admitted to an Intermediate-Care Unit for hypertensive crisis. Hyperglycemic episodes of up to 18.9 mmol/L were captured in intermittent blood- glucose tests (Table 1). From day 3 on, the insulin therapy was switched to an intensive insulin therapy with a cumulative insulin dose of 46 units per day. A continuous glucose monitoring was not performed. As for oral antidiabetics, metformin (500 mg QD), empagliflozin (10 mg QD), and dulaglutide (1.5 mg per week) were added. Antihypertensive medication was reduced from 3 to 2 drug classes during index hospitalization. Routine laboratory results at admission were unrevealing (Table 2). As Table 3 shows, insulin dose further decreased in follow-up visits during the ensuing 22 months accompanied by a decrease of glycated hemoglobin A1c to 6.6% and by less antihypertensive medications prescribed. Three months after discharge, a 24-hour blood-pressure monitoring showed a normal blood pressure with a mean day-time systolic blood pressure of 131mmHg, a mean day-time diastolic blood pressure of 88mmHg.

The decrease of antihypertensive therapy, the decrease of antihypertensive medications lagged behind the decrease of insulin dose. Ultimately, the corresponding daily defined dose (DDD) of antihypertensive medications changed from a DDD of 7 at hospital admission to a DDD of 2 at the last

Table 1: Intermittent blood-glucose results derived from capillary blood during index hospitalization (in mmol/L, for conversion to mg/dL multiply the results by 18.02).

Time	2 – 3 h	7 – 8 h	11 h	16 - 17 h	18 – 19 h	20 - 21 h	22 - 23 h	23 – 0 h
Day 1						8.9		
Day 2			15.7	11.5			6.5	
Day 3		11.8	18.9	10.8		11.8		7.5
Day 4		11.3	19.9	11.7	9.5	12.3		
Day 5		16.4	16.7	16.3		15.1	15.9	
Day 6			17		9.8	12.3		
Day 7		14.9	13.7	8.3		10.4		
Day 8		12.1	11.4	11		11.9		
Day 9		12.7	11.3	10.5		11.8		
Day 10		11.4	13.2	10		11		
Day 11		8.9	10.7					

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Abobarin-Adeagbo A, et al., J Pharm Pharmacol Res 2023
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Table 2: Laboratory test results from hospital admission and from follow-up 22 months after discharge.

Laboratory parameter	unit	Reference range	Day of admission	22-months follow-up visit
Sodium	mmol/l	136-145	137	140
Potassium	mmol/l	3.4-4.5	4.2	4.7
Calcium	mmol/l	2.20-2.55	2.2	2.31
Glucose	mmol/l	4.11-6.05	12.03	9.79
HbA1c	%	NA	11.2	6.6
eGFR	ml/min/1.73m²	> 60.00	63.27	73.7
Creatinine	µmol/l	62-106	101	88
Urea	mmol/l	2.76-8.07	7.5	6
ASAT	µkat/l	202.3-416.5	0.53	0.43
ALAT	µkat/l	2.0-21.0	0.6	0.45
GGTP	µkat/l	< 5.0	0.67	0.48
Troponin T	ng/l	0.17-0.85	34	19.5
NT-pro BNP	ng/l	< 125	174	NA
C-reactive protein	mg/l	< 1.00	1.3	0.4
Hemoglobin	mmol/l	8.4-11.1	8.8	8.9
Leukocyte count	Gpt/l	3.70-9.90	7.6	7.9
Platelet count	Gpt/l	140-360	96	113
International normalized ratio				
		0.85-1.15	1.11	1.05

Table 3: Body weight (Wt), Hemoglobin A1c (HbA1c), systolic and diastolic blood pressure, classes, daily defined dose (DDD), and prescription information of antihypertensive medications (Rx) and diabetes therapies from hospital admission until 22 months after discharge. If there was more than one result per visit, the mean was given.

Months after hospital admission (n)	Weight (kg)	Hb A1c (%)	Blood pressure (mmHg)	Anti-hyperten-sive drug classes (n)	Defined Daily Dose of anti-hyperten-sive Rx (n)	Daily cumulative dose of antihypertensive medication (mg)	Daily cumulative dose of non-insulin diabetes medication (mg)	Insulin units per day (n)
0	105	11.2	161/105	3	3+2+2	Urapidil (180), Valsartan (320), Bisoprolol -10	NA	160
0.3	NA	NA	151/81	3	2+2	Valsartan (320), Bisoprolol (10)	Metformin (500), Empagliflozin (10), Dulaglutide (1.5/7)	46
3	NA	6.9	153/88	3	1+2+2	Moxonidine (0.6), Valsartan (320), Bisoprolol (10)	Metformin (1000), Dulaglutide (1.5/7)	46
5	NA	NA	126/76	3	1+2+2	Amlodipine (5), Valsartan (320), Bisoprolol (10)	Metformin (2000), Dulaglutide (1.5/7)	42
8	96.6	4.9	106/68	3	1+2+2	Amlodipine (5), Valsartan (320), Metoprolol (96.5)	Metformin (2000), Liraglutide (0.6)	30

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Abobarin-Adeagbo A, et al., J Pharm Pharmacol Res 2023
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9	NA	NA	135/81	3	1+2+2	Amlodipine (5), Valsartan (320). Metoprolol (96.5)	Metformin (2000), Liraglutide (1.2)	30
12	95	6.2	150/88	3	1+2+2	Amlodipine (5), Valsartan (320), Metoprolol (96.5)	Metformin (2000), Liraglutid (1.2)	28
15	97.3	6.4	150/87	3	0.5+1+0.5	Amlodipine (2.5), Valsartan (160), Bisoprolol (2.5)	Metformin (2000), Liraglutide (1.2)	24
16	NA	NA	149/97	3	0.5+1+1	Amlodipine (2.5), Valsartan (160), Bisoprolol (5)	Metformin (2000), Liraglutide (1.2)	24
21	NA	6.4	168/94	2	1+1	Valsartan (160), Bisoprolol (5)	Metformin (2000), Liraglutide (1.2)	26
22	94.7	6.6	136/96	2	1+1	Valsartan (160), Bisoprolol (5)	Metformin (2000), Liraglutide (1.8)	26

follow-up visit, 22 months after discharge. Diabetes therapy ultimately consisted of metformin (2 g BID), liraglutide (1.8 mg QD), and insulin glargine (26 units QD). The SGLT-2 inhibitor was discontinued shortly after discharge due to side effects. During 22 months of follow-up, body weight moderately decreased to 94.7 kg (body-mass index: 28.0 kg/m²). The patient's mobility improved one year after discharge. For the first time in 6 years, the patient was able to leave his flat alone using a walking aid. 22 months after index hospitalization, the patient was re-hospitalized for minor stroke with a fully reversible facial paresis on the right and dysphasia. Additional exams suggested a cerebral ischemic event in the cerebral media artery, proved bilateral carotid sclerosis without need for intervention. An echocardiography exam revealed a normal systolic left-ventricular function, moderate left-ventricular hypertrophy and a moderate mitral stenosis. Holter electrocardiogram showed sinus rhythm and a reduced heart rate variability (standard deviation of normal beats: 64 ms). The stroke prevention was changed from aspirin to clopidogrel. Otherwise, the diabetic and antihypertensive medication remained unchanged.

Discussion

Here, for the first time, we present an association between considerable insulin-dose reduction and improved blood pressure control in an elderly patient suffering from uncontrolled arterial hypertension. The initial reduction to a quarter of the initial daily cumulative insulin dose translated into a better glycemic and blood-pressure control. Undocumented, asymptomatic hypoglycemic events with reactive hyperglycemia within the framework of the Somogyi effect are the presumed cause for poor glycemic control during the first days of index hospitalization. At index hospitalization, the reduction of exogenous insulin to a quarter of the initial daily cumulative dose translated into better glycemic control during the final days in hospital, i.e. no hyperglycemic episodes were documented during hospitalization. Therefore, an initial overdose of insulin is likely. The preprandial hyperglycemic episodes ranging between 15 – 19 mmol/ shortly after admission may be explained by preceding hypoglycemic episodes due to overdosed insulin in terms of reactive hyperglycemia. As a limitation, a continuous glucose monitoring was not performed in this patient. Especially in elderly patients, hypoglycemia unawareness is more prevalent than in a middle-aged patient cohort [9].

Hypothetically, the improved control of arterial hypertension and the improved physical activity were due to less hormonal counterregulations to asymptomatic hypoglycemic episodes from day 3 in hospital on, once insulin dosage was reduced substantially. Although hypoglycemic episodes were not captured in this patient, the presence of asymptomatic hypoglycemic episodes cannot be ruled out either. Specifically, preprandial blood-glucose tests do not rule out hypoglycemic episodes between two tests, and hypoglycemia-related symptoms may be lacking. In the context of hypoglycemia, an uncontrolled arterial hypertension was shown to be present in a prospective observational study [8]. The present case confirms this study result [8] associating uncontrolled arterial hypertension with hypoglycemia in an insulin-treated diabetic: on admission, arterial hypertension was treated with the highest number of antihypertensive medications, yet still was uncontrolled, while the cumulative insulin dose was highest. During the index hospitalization, the antihypertensive medication was reduced from 3 to 2 drug classes when insulin therapy was reduced from 160 units per day to 46 units per day. From the

Abobarin-Adeagbo A, et al., J Pharm Pharmacol Res 2023
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literature [10,11] both metformin added to insulin (HbA1c decrease by 0.6%) and dulaglutide added to insulin (HbA1c decrease by 1.0 to 1.9%) do not explain the absolute reduction by 4.6% in the present case by the 22 months follow-up, while cumulative insulin dose was reduced from 160 to 26 units per day. As for the improved blood-pressure control, the weight loss over time does not explain the reduction of antihypertensive medications during index hospitalization, as more than two thirds of insulin-dose reduction and more than half of antihypertensive-medication reduction occurred within the first month after admission. Over the long run, weight loss associated with a better insulin sensitivity, thus enabling a further insulin-dose reduction.

Conclusions

Especially in elderly type-2 diabetes patients, the introduction of insulin should be conducted cautiously. Alternatives such as incretin mimetics should be considered, if oral antidiabetics are contraindicated or insufficient. Continuous glucose monitoring is recommended in patients on high-dose insulin to identify possible post-hypoglycemic hyperglycemia.

List of abbreviations

ALAT	Alanine aminotransferase
ASAT	Aspartate transaminase
BID	twice daily
DDD	Defined daily dose
eGFR	estimated glomerular filtration rate
GGT	gamma glutmyltransferase
HbA1c	glycated hemoglobin A1c
kg	kilogram
L	litre
m	metre
mmHg	millimeters of mercury
NA	Not applicable
NT-pro BNP	N-terminal-pro B-type natriuretic peptide
QD	once daily
SGLT-2i	sodium-glucose transporter-2 inhibitor

Declarations

Ethics approval and consent to participate

Not applicable

Consent for Publication

A signed, informed consent for publication of this case report was obtained from the patient. A copy of the consent form is available for review by the Editor of this journal.

Availability of data and Materials

The datasets analyzed during the current case report are not publicly available due to the data-protection policy of the hospital (Universitätsklinikum Halle) but are available from the corresponding author on reasonable request.

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Authors' Contributions

RP conceptualized this case report. AA and MG gave critical input in all parts of this case report. TK added significant input on neurological aspects of this case report. RP wrote the manuscript draft, all authors critically revised the case report. All authors contributed to data acquisition and interpreted the data. All authors approved the final version to be published.

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