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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Case report

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Abstract

Background:

An association between hypoglycemia and arterial hypertension has been proposed. Here, for the first time, we report a case of a chronically over-dosed insulin therapy with uncontrolled hypertension, which improved after insulin-dose reduction.

Case Presentation:

A 73-year-old, male type-2 diabetic of Caucasian ethnicity was hospitalized for uncontrolled arterial hypertension and weakness. Prior to hospitalization, a fixed-dose insulin therapy (160 units per day) and antihypertensive medication with urapidile, valsartan and bisoprolol were prescribed. Hemoglobin A1c was 11.2%, symptomatic hypoglycemic episodes were not reported. During hospitalization, metformin, empagliflozin, and dulaglutide (1.5 mg per week) were added to insulin. Conventional insulin therapy was switched to an intensified insulin therapy with a cumulative daily dose of 46 units. 22 months after discharge, the medical therapy consisted of metformin, liraglutide, and insulin glargine (26 units per day), antihypertensive medication was reduced to bisoprolol and valsartan. Blood pressure was well controlled, hemoglobin A1c was 6.6%. As a likely explanation, undocumented, asymptomatic hypoglycemic events with a post-hypoglycemic hormonal stimulation were the cause for the poor glycemic and blood-pressure control. A step-wise reduction of insulin translated into a better glycemic and blood-pressure control.

Conclusions:

Undocumented, asymptomatic hypoglycemic events and post-hypoglycemic hormonal stimulation were the likely cause for the poor glycemic and blood-pressure control prior to index hospitalization. A step-wise reduction of insulin concurrently translated into a better glycemic and blood-pressure control.

Background

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). There, the avoidance of neuroglycopenia during subsequent hypoglycemic episodes seems to be a plausible explanation. An autonomic neuropathy or polyneuropathy does not associate with hypoglycemia unawareness (4). In geriatric diabetes patients on insulin therapy, glycated hemoglobin A1c (HbA1c) does not correlate with less hypoglycemic episodes suggesting that a higher HbA1c goal does not suffice to reduce the risk for hypoglycemia in this cohort (5).

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 (6). In a cohort study of hospitalized insulin-treated diabetics presenting with hypertensive crisis or with hypoglycemia, the hypoglycemic burden was similar (7).

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, the steady reduction of insulin dose over 22 months led to an improved glycemic control and allowed for reduction of antihypertensive medication.

Case Presentation

A 73-year-old male diabetic of Caucasian ethnicity presented with progressive weakness and vertigo for one week at the Neurology Department of the University Hospital Halle. 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. Due to uncontrolled arterial hypertension, urapidil (60 mg thrice a day) was added, before hospitalization, to his known antihypertensive medications with valsartan (160 mg BID) and bisoprolol (5mg BID). At admission, arterial hypertension still was uncontrolled, HbA1c was 11.2%, the kidney function was not impaired. Diabetes therapy consisted of fixed-dose prandial insulin (Actrapid®, 40 units thrice a day) and basal insulin analog (insulin glargine, 40 units QD) with a daily cumulative insulin dose of 160 units. Documented or symptomatic hypoglycemic episodes were not reported by the patient. Intermittent blood-glucose test results during the hospital stay and routine laboratory results at admission are summarized in Tables 1 and 2. The patient was admitted to an Intermediate-Care Unit initially, due to hyperglycemia, based on intermittent blood glucose, and hypertensive crisis. The insulin therapy was switched to intensive conventional therapy resulting in a cumulative insulin dose of 46 units per day after 11 days in the hospital. In addition, metformin (500 mg QD), empagliflozin (10 mg QD), a sodium-glucose transporter-2 inhibitor (SGLT-2i), and dulaglutide (1.5 mg per week), a subcutaneously applied glucagon-like-peptide-1 (GLP-1) agonist, were added. In follow-up visits during the ensuing 22 months (Table 3), diabetes therapy ultimately consisted of metformin (2 g BID), liraglutide (1.8 mg QD), a subcutaneously applied GLP-1 agonist and insulin glargine (26 units QD). The SGLT-2 inhibitor was discontinued due to side effects. The HbA1c was 6.6%, body weight decreased to 94.7 kg (body-mass index: 28.0 kg/m²). Strikingly, the patient was switched from a 3-fold to a 2-fold combination of antihypertensive drugs. 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 follow-up visit, 22 months after discharge. Although the insulin dose was reduced from 160 units/d to 46 units/d during the index hospitalization, further reductions were achieved during the 22 ensuing months during 9 follow-up visits (Fig. 1). The decrease of antihypertensive medication lagged behind insulin reduction and HbA1c normalization considerably. However, an ambulatory blood-pressure recordings over 24 hours after 3 months proved a normal blood pressure (mean day-time systolic blood pressure (mean day-time systolic 131 mmHg, diastolic blood pressure 88 mmHg, reverse dipper). Likewise, the patient's mobility improved for one year following insulin reduction. For the first time in 6 years, the patient was able to leave his flat alone using a

walking aid. Lastly, troponin T elevation at index hospitalization normalized with a period of 10 months following the discharge (troponin T levels dropped to 19.5 ng/L, normal reference: < 14.0). During the observation period in hospital and after discharge, a coronary angiography was not performed. After 22 months, the patient was rehospitalized 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. Transthoracic echocardiography 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. The patient was discharged with the same diabetic and antihypertensive medication like 22 months after discharge of index hospitalization.

Table 1

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			17.0		9.8	12.3		
Day 7		14.9	13.7	8.3		10.4		
Day 8		12.1	11.4	11.0		11.9		
Day 9		12.7	11.3	10.5		11.8		
Day 10		11.4	13.2	10.0		11.0		
Day 11		8.9	10.7					

Table 2

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	2.20	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	73.70
Creatinine	µmol/l	62–106	101	88
Urea	mmol/l	2.76–8.07	7.50	6.00
ASAT	µkat/l	202.3-416.5	0.53	0.43
ALAT	µkat/l	2.0–21.0	0.60	0.45
GGTP	µkat/l	< 5.0	0.67	0.48
Troponin T	ng/l	0.17–0.85	34.0	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 normlalized ratio		0.85–1.15	1.11	1.05

Table 3

Months after hospital admis-sion (n)	Wt (kg)	Hb A1c (%)	Blood pres-sure (mmHg)	Anti-hyper-ten-sive drug classes (n)	Defined Daily Dose of anti-hyper-ten-sive Rx (n)	Daily cumulative dose of antihypertensive Rx (mg)	Daily cumulative dose of non-insulin diabetes Rx (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
9	NA	NA	135/81	3	1 + 2 + 2	Amlodipine (5), Valsartan (320). Metoprolol (96.5)	Metformin (2000), Liraglutide (1.2)	30

Months after hospital admis-sion (n)	Wt (kg)	Hb A1c (%)	Blood pres-sure (mmHg)	Anti-hyper-ten-sive drug classes (n)	Defined Daily Dose of anti-hyper-ten-sive Rx (n)	Daily cumulative dose of antihypertensive Rx (mg)	Daily cumulative dose of non-insulin diabetes Rx (mg)	Insulin units per day (n)
12	95.0	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

Discussion And Conclusions

Undocumented, asymptomatic hypoglycemic events with reactive hyperglycemia within the framework of the Somogyi effect are the presumed cause of poor glycemic control at hospital admission. In this case, a step-wise reduction of exogenous insulin translated into better glycemic control. Hypothetically, the improved control of arterial hypertension and the improved physical activity can be attributed to the reduced catecholamine-induced hypertension following hypoglycemic episodes. Importantly, hypoglycemia-induced hormonal and neural counter-regulatory responses need to be considered as intermittent blood-glucose tests do not rule out hypoglycemia, and hypoglycemia-related symptoms may be lacking. Hypoglycemia unawareness is common among patients with long-standing diabetes mellitus. As a diagnostic hint, hyperglycemia in this patient appeared to be refractory to conventional insulin therapy. Concurrently, arterial

hypertension was uncontrolled, when a high-insulin therapy was established. During the index hospitalization, the hyperglycemic situation was alleviated when insulin therapy was reduced from 160 units per day to 46 units per day. Likewise; the DDD of antihypertensive medication needed to control arterial hypertension was reduced significantly once insulin therapy was deescalated. Here, for the first time, we present an association between high-dose insulin therapy possibly leading to asymptomatic, undocumented hypoglycemic episodes and uncontrolled arterial hypertension. Of note, only the reduction of hypoglycemic episodes necessitating less reactive hyperglycemic responses explains the tremendous reduction of HbA1c. From the literature (8, 9), both metformin added to insulin (HbA1c decrease of 0.6%) and dulaglutide added to insulin (HbA1c decrease of 1.0 to 1.9%) do not explain the absolute reduction of HbA1c by 4.6% during 22 months after discharge (from 11.2–6.6%), while insulin dose was reduced from 160 to 26 units per day concurrently. The weight loss of 10.3 kg does not explain the reduction in antihypertensive medications needed neither (10). As a limitation, no continuous glucose monitoring was performed. Summarily, in diabetes patients, the introduction of insulin should be conducted cautiously.

List Of Abbreviations

ALAT Alanine aminotransferase

ASAT Aspartate transaminase

BID twice daily

DDD Defined daily dose

eGFR estimated glomerular filtration rate

GGT gamma glutmyltransferase

GLP-1 glucagon-like-peptide-1

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.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

RP conceptualized this case report. AA 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. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work. Each author has sufficient knowledge of and participation in this case report that he or she can accept public responsibility for the report.

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Figures

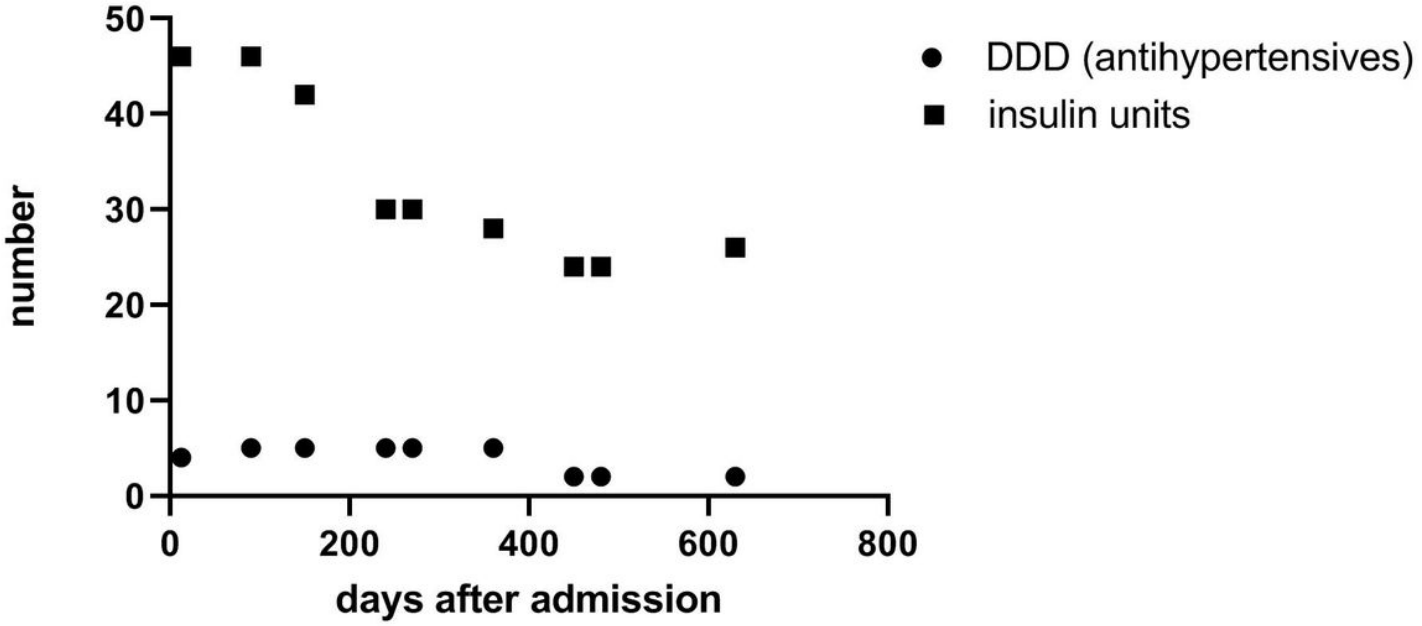

Figure 1

Graph depicting the insulin units and the defined daily dose (DDD) of antihypertensive medications prescribed since discharge of index hospitalization.

Supplementary Files

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