Correction of Over-Dosed Insulin in a Type-2-Diabetic Associates With 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 is unknown. Here, we report a case of a chronically over-dosed insulin therapy in conjunction with uncontrolled hypertension.

Case Presentation: A 73-year-old, male diabetic of Caucasian ethnicity was admitted to a neurological intermediate-care unit of a university hospital for progressive weakness due to diabetic polyneuropathy. Besides obesity (body-mass index: 31 kg/m²) and type-2 diabetes, an uncontrolled arterial hypertension was present. Diabetes therapy consisted of fixed-dose insulin (160 units QD). Symptomatic or documented hypoglycemic episodes were not reported. Hemoglobin A1c was 11.2%. Prior to hospitalization, a urapidil (60 mg thrice a day), was added to his antihypertensive medication with valsartan (160 mg BID) and bisoprolol (5mg BID). During hospitalization, metformin, empagliflozin, and dulaglutide (1.5 mg per week) were added to insulin. An intensified conventional therapy with a cumulative daily dose of 46 units was introduced. 22 months after discharge, the medical therapy consisted of metformin (1 g BID), liraglutide (1.8 mg QD), and insulin glargine (26 units QD). The antihypertensive medication was reduced to bisoprolol and valsartan, urapidil was discontinued. The follow-up visit showed Hemoglobin A1c of 6.6%, and a well-controlled blood pressure. The patient's physical activity improved with the patient being able to leave his flat alone for the first time within 6 years.

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

Background

Hypoglycemia represents a life-threatening hazard of insulin therapy, especially in cardiovascular high-risk patients (1, 2). According to a recent consensus recommendation for the therapy of type-2 diabetes, glucagon-like-peptide-1 (GLP-1) agonists and sodium-glucose transporter-2 (SGLT-2) inhibitors are preferred alternatives, when hypoglycemic episodes occur or atherosclerotic vascular disease is present (3). Hypoglycemia unawareness is associated with increased glucose concentrations in the brain most likely due to an up-regulation of insulin-independent glucose-transport mechanisms to the brain (4). 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 (5). 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 (6).

In patients experiencing hypoglycemic episodes, it is unclear whether post-hypoglycemia-induced catecholamine release and/or the activated sympathetic nervous system contribute to the development of arterial hypertension (7). In a small cohort study, the hypoglycemic burden in insulin-treated diabetics with hypertensive crisis or with hypoglycemia as the cause of hospital admission was similar (8).

In general, the average use of insulin per capita of the population is very high in Germany (9) and the adoption of novel therapy guidelines to reduce the risk for hypoglycemia is still challenging (10–12). 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 with decreased muscle reflexes and hypopallesthesia. Electrophysiological investigation showed a sensorimotor axonal and demyelinating peripheral neuropathy. 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. 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. 4 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 (5 mg BID). At admission, 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. At admission, the HbA1c was 11.2% and the kidney function was not impaired. 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, empagliflozin, a sodium-glucose transporter-2 inhibitor (SGLT-2i), and dulaglutide, a subcutaneously applied, once-a-week glucagon-like-peptide-1 (GLP-1) agonist, were added. In follow-up visits during the ensuing 22 months following the discharge (Table 3), diabetes therapy ultimately consisted of metformin (2 g/d), the GLP-1 agonist liraglutide (1.8 mg/d) 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 as shown in Fig. 1 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, coronary angiography was not performed. Transthoracic echocardiography, performed 22 months after discharge, revealed a normal systolic left-ventricular function, moderate left-ventricular hypertrophy and a moderate mitral stenosis. 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. The stroke prevention was changed from Aspirin to Clopidogrel. Holter electrocardiogram showed sinus rhythm and a reduced heart rate variability (standard deviation of normal beats: 64 ms). The patient was discharged with the same diabetic and antihypertensive medication like 22 months after discharge of index hospitalization (Table 3).

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
0.5	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 reduced catecholamine-induced hypertension.

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/d to 46 units/d. 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 (13:14), 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% to 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. As a weakness, no continuous glucose monitoring was performed. Summarily, the introduction of insulin in patients should be conducted cautiously. As the per-capita dose of insulin is very high in Germany (9), more comprehensive management of type-2 diabetes is needed, which includes the correction of possibly over-dosed insulin therapy.

As conclusion, an association of asymptomatic hypoglycemic episodes due to over-dosed insulin therapy and hypertension is suggested. More clinical data using continuous glucose monitoring are needed to substantiate the suspected association between reduction of asymptomatic hypoglycemic episodes and improvement of uncontrolled arterial hypertension.

List Of Abbreviations

ALAT Alanine aminotransferase

ASAT Aspartate *transaminase*

DDD Defined daily dose

eGFR estimated glomerular filtration rate

GGT gamma glutmyltransferase

GLP-1 glucagon-like-peptide-1

HbA1c glycated hemoglobin A1c

m metre

NA Not applicable

NT-pro BNP N-terminal-pro B-type natriuretic peptide

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.

Availability of data and materials

All relevant datasets used and/or analyzed in this case report 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

AB gathered data, gave critical input to the interpretation of data. RUP was the attending physician of this patient, conceived this case report and wrote the manuscript draft. TK added important insights to the neurological diagnostics and treatments. MG provided the resources for publication of the case report. All authors read and approved the final manuscript.

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Figures

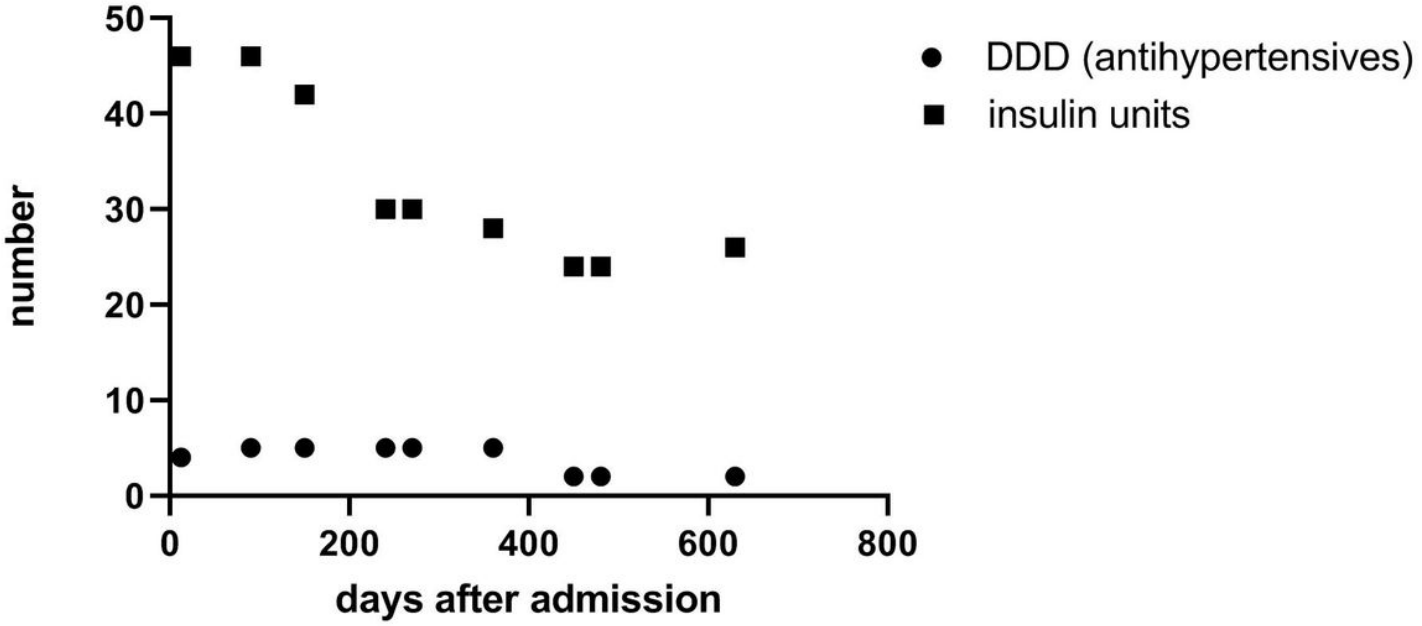

Figure 1

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