

# Substantial Increase in Incidence of Severe Hypoglycemia Between 1997–2000 and 2007–2010

A German longitudinal population-based study

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**OBJECTIVE**—To compare the incidences of severe hypoglycemia and corresponding clinical circumstances in a German population between 2007–2010 and 1997–2000.

**RESEARCH DESIGN AND METHODS**—A screening for severe hypoglycemia was performed in the Lippe-Detmold area in Germany to sensitively detect severe hypoglycemia. This was defined as a symptomatic event requiring treatment with intravenous glucose and being confirmed by a blood glucose measurement of <50 mg/dL.

**RESULTS**—Severe hypoglycemia increased considerably from 264 events in 1997–2000 to 495 events in 2007–2010, which translated into an increase in frequency of severe hypoglycemia among all emergency admissions from 0.68 to 0.83% ( $P = 0.015$ ). This was mostly related to intensification of antihyperglycemic therapy, particularly in the increasingly morbid group of hypoglycemic patients with type 2 diabetes indicated by lower HbA<sub>1c</sub>, more comedication (3.3 vs. 7.7 drugs), and more concomitant diseases (3.6 vs. 4.4) (all  $P$  values <0.001).

**CONCLUSIONS**—Within a 10-year period, there was an intensification of antihyperglycemic therapy in increasingly comorbid subjects, leading to a considerably higher incidence of severe hypoglycemia.

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Severe hypoglycemia remains the limiting factor in successful metabolic control of diabetes mellitus. In patients with long-standing and complicated diabetes mellitus, severe hypoglycemia may even increase cardiovascular and all-cause mortality (1). In the current study, we compared the incidence rates of severe hypoglycemia and corresponding clinical circumstances between the years 2007–2010 and 1997–2000 in a German population.

## RESEARCH DESIGN AND

**METHODS**—In this prospective population-based study, the incidences of severe hypoglycemia and its clinical characteristics were longitudinally compared

over two 4-year periods between 1 January 2007 and 31 December 2010 vs. 1 January 1997 and 31 December 2000. All patients with severe hypoglycemia were recruited at the medical department of the Lippe-Detmold Hospital. This large tertiary-care hospital in East Westphalia, Germany, covers all emergency patients in an urban-rural region with a population of ~200,000 inhabitants, which remained approximately constant between the two periods. Results from the period 1997–2000 have previously been published (2).

Using the same method of hypoglycemia detection in both periods, our study provided a possibility for longitudinal assessment. Blood glucose testing was

systematically performed in every emergency patient irrespective of the presenting condition, either in the prehospital situation at the emergency site or immediately after arrival at the emergency department. Deaths and resuscitations were excluded from blood glucose determination at the emergency site. The entire emergency team underwent continuing education related to diagnosis and therapy of hypoglycemia (3).

Severe hypoglycemia was defined as a symptomatic event requiring treatment with intravenous glucose and was confirmed by a blood glucose measurement of <50 mg/dL (<2.8 mmol/L). Renal impairment was defined as a creatinine clearance of <60 mL/min (Cockcroft-Gault equation [4]).

**RESULTS**—Throughout both observational periods, 85 and 86.3% of all emergency patients, respectively, received a blood glucose measurement. From 1997–2000, a total of 264 cases of severe hypoglycemia were registered among the 30,768 patients who attended the emergency department of the Lippe-Detmold Hospital and among 7,804 patients who were treated by the emergency medical service. By comparison, in the period from 2007 to 2010, we found a total of 495 episodes of severe hypoglycemia occurring in 46,700 subjects attending the emergency department and among 13,290 patients treated by the emergency medical service. This translated into an increase in frequency of severe hypoglycemia among all emergency admissions from 0.68% in 1997–2000 to 0.83% in 2007–2010 ( $P = 0.015$ ,  $\chi^2$  test). Expressed per 100,000 inhabitants, the overall incidence of severe hypoglycemia increased from 33 to 62 in 10 years. In patients with type 1 diabetes mellitus (T1DM), the incidence of severe hypoglycemia rose from 11.5 to 23.4 and in subjects with type 2 diabetes mellitus (T2DM) from 18.5 to 32.6. In both periods, more severe hypoglycemia occurred in patients with T2DM (56 and 53%) than in T1DM (35 and 38%) (Supplementary Table 1). In 2007–2010 (Table 1), concomitant

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**Table 1—Basic characteristics of patients with severe hypoglycemia in 1997–2000 vs. 2007–2010**

	Type 1 diabetes		P	Type 2 diabetes		P
	1997–2000	2007–2010		1997–2000	2007–2010	
<i>n</i>	92	121		148	225	
<b>Anthropometric characteristics</b>						
% female	35% (32/92)	46% (56/121)	0.09	64% (95/148)	59% (133/225)	0.33
Age (years)	44 ± 17 (4–81)	47 ± 19 (6–91)	0.23	76 ± 12 (44–95)	77 ± 10 (38–97)	0.38
BMI (kg/m <sup>2</sup> )	23.5 ± 3.7 (13.2–30.3)	24.5 ± 4.2 (15.7–34.7)	0.09	25.7 ± 4.8 (15.8–39.7)	26.8 ± 5.3 (12.5–48.2)	0.06
Initial blood glucose prior to treatment (mg/dL)	33 ± 15 (0–49)	33 ± 12 (10–43)	1.00	34 ± 16 (0–49)	34 ± 12 (7–48)	1.00
<b>Diabetes</b>						
Diabetes duration (years)	23 ± 14 (0–46)	23 ± 16 (0–60)	1.00	17 ± 11 (0–40)	14 ± 9 (1–46)	<b>0.01</b>
HbA <sub>1c</sub> (1997–2000: nondiabetic range 3.4–4.9%, 2007–2010: nondiabetic range 4.0–6.4%)	6.9 ± 1.7 (4.2–10.1)	7.6 ± 1.4 (5.6–12.1)	<b>0.002</b>	6.2 ± 1.8 (3.9–15.5)	6.6 ± 1.7 (5.0–14.5)	<b>0.03</b>
HbA <sub>1c</sub> (adjusted to reference <5.0%)	6.9 ± 1.7	5.8 ± 1.1	<b>&lt;0.001</b>	6.2 ± 1.8	5.1 ± 1.3	<b>&lt;0.001</b>
<b>Comorbidity</b>						
Renal impairment (creatinine clearance <60 mL/min)	15% (11/72)	23% (22/94)	0.19	54% (80/148)	76% (122/160)	<b>&lt;0.001</b>
Comorbidity (number of concomitant diseases)	1.1 ± 1.5 (0–7)	2.2 ± 1.9 (0–7)	<b>&lt;0.001</b>	3.6 ± 2.6 (0–7)	4.4 ± 1.7 (0–8)	<b>&lt;0.001</b>
Comedication (number of different drugs)	1.0 ± 2.2 (0–14)	3.8 ± 3.5 (0–12)	<b>&lt;0.001</b>	3.3 ± 3.0 (0–18)	7.7 ± 3.4 (0–17)	<b>&lt;0.001</b>
Patients living in nursing homes (or cared for by a home nursing service)	0	8% (10/121)	<b>0.005</b>	34% (50/148)	30% (68/225)	0.52
Ambulant treatment of severe hypoglycemia	22% (20/92)	43% (52/121)	<b>0.001</b>	0	14% (32/225)	<b>&lt;0.001</b>
<b>Diabetes therapy (<i>n</i> patients)</b>						
Conventional insulin therapy	25	8	<b>&lt;0.001</b>	78	92	<b>0.03</b>
ICT	64	96	0.10	—	49	<b>&lt;0.001</b>
Insulin pump (CSII)	3	16	<b>0.01</b>	—	—	—
Sulfonylurea monotherapy	—	—	—	45	67	0.90
Sulfonylurea plus insulin	—	1	1.00	25	15	<b>0.002</b>
Metformin monotherapy	—	—	—	—	2	0.52

Data are % (*n/n*) or means ± SD (range) unless otherwise indicated. Owing to ambulatory treatment, HbA<sub>1c</sub> and creatinine clearance were not ascertainable in all patients. CSII, continuous subcutaneous insulin infusion. Boldface data indicate a statistical significance of *P* < 0.05.

diseases, in particular renal insufficiency, and number of drugs had increased in both types of diabetes mellitus. Especially in hypoglycemic subjects with T2DM and comorbid conditions, comedication not related to diabetes had increased from 3.3 drugs in 1997–2000 to 7.7 drugs in 2007–2010. Notably, the prevalence of renal insufficiency in this group had increased significantly from 54 to 76%.

HbA<sub>1c</sub> adjusted to the reference range of <5.0% was significantly lower in 2007–2010 than in 1997–2000 for both types of diabetes mellitus. Significantly more patients with T1DM were on intensified insulin therapy (ICT), either conventional or continuous subcutaneous insulin infusion, in 2007–2010. In addition, in subjects with T2DM we observed a significant increase of ICT in 2007–2010 compared with the period 10 years earlier. The incidence of severe hypoglycemia associated with sulfonylureas increased from 8.8 to 10.3. Correlating with the higher prescribing frequency of glimepiride, severe hypoglycemia associated with glimepiride occurred fourfold more frequently than severe hypoglycemia associated with glibenclamide (65 vs. 16 episodes; 1 event concerned gliquidone) (5) (Supplementary Fig. 1). Severe hypoglycemia in subjects without diabetes was related to advanced stage malignancies, liver failure, and alcohol intoxication.

Supplementary Tables 1 and 2 provide detailed information about comparison of severe hypoglycemia in the two periods and patients' metabolic control during the period 2007–2010. In particular, the inappropriate low HbA<sub>1c</sub> values (<6.0 to <6.5%) in a large proportion of patients with T2DM are highlighted (Supplementary Table 2).

**CONCLUSIONS**—Corresponding with a substantial overall increase of emergency treatments, a 22% increase occurred in the total number of severe hypoglycemia cases between 2007 and 2010 versus between 1997 and 2000.

In face of gradually changing circumstances in Germany concerning epidemiological factors, diabetes guidelines, and the health care system, these unexpected results should be interpreted with caution. Firstly, the growing incidence of diabetes might have substantially contributed to our findings. Based on a large sample from a Statutory Health Insurance, a recent estimate revealed a marked increase of T2DM prevalence in Germany. Between 2000 and 2007, the official prevalence of

treated diabetes rose continuously from 6.5 to 8.9% (an increase of 36.8%). The number of patients treated with insulin or insulin plus oral antidiabetic agents increased by 54.7 and 61.7%, respectively (6). Moreover, the incidence of T1DM increased on average by 2.5–3% per year worldwide (7). Thus, in 2007–2010, considerably more people in our area were affected by diabetes and received antihyperglycemic therapy, with the potential risk of severe hypoglycemia.

Furthermore, the significant increase of severe hypoglycemia in 2007–2010 correlated with the implementation of stringent goals for metabolic control by the German Diabetes Association. As of 2003, the German Diabetes Association defined a target HbA<sub>1c</sub> of <6.5% for T2DM and HbA<sub>1c</sub> values as low as possible for T1DM but explicitly avoiding severe hypoglycemia (8,9). In addition, the nationwide Disease Management Program (DMP)-Diabetes for T2DM and T1DM was progressively implemented from 2003 onward to optimize diabetes therapy (10). Within the DMP, participating general practitioners were requested to refer to diabetes specialists every patient with T1DM and patients with T2DM who did not reach target HbA<sub>1c</sub>. Thus, intensification of therapy by diabetologists was preprogrammed. Our findings support a cumulative effect by the shift toward more stringent glycemic goals and the implementation of the DMP. Apart from a significant decrease in HbA<sub>1c</sub>, there were also increasing comorbidities including renal insufficiency and concomitant drug use in hypoglycemic patients with T1DM and in particular in those with T2DM in the period from 2007 to 2010.

Consistent with previously published rates in other larger studies (11,12), we observed the highest incidences for severe hypoglycemia in patients with long-standing insulin treatment irrespective of T1DM or T2DM. Severe hypoglycemia associated with long-acting sulfonylureas not only continued to be a problem but even increased in incidence. In both periods but more so in 2007–2010, the overwhelming proportion of our hypoglycemic subjects with T2DM were characterized by advanced age, long-standing diabetes, comorbidities, and extensive comedication. Their low HbA<sub>1c</sub> of 6.6% seems to be an indicator for recurrent but possibly unnoticed severe hypoglycemia and raises the question of dangerous overtreatment and adequate targets in elderly patients. Consequently, the National Institute for Health and Clinical

Excellence (NICE) guidelines for T2DM recommend a less stringent HbA<sub>1c</sub> target (7.5%) for individuals with longer duration of diabetes and those who require third-line therapy (two or more medications) (13).

Our data, determined under the conditions of real life, revealed a substantial increase of severe hypoglycemia also in subjects with T1DM. By contrast, a controlled trial in patients with T1DM and suboptimal glycemic control showed that the use of a sensor-augmented insulin pump was associated with significant improvement in HbA<sub>1c</sub> without increasing the rate of severe hypoglycemia compared with a regimen of multiple daily injections (14).

Given the limitations of an observational study and covering a relatively small region represented by a single-center experience, local specifics could have confounded our results. Nevertheless, our study provides a sensitive prospective screening for severe hypoglycemia in an unselected population.

In conclusion, our study demonstrated a considerably increased incidence of severe hypoglycemia in 2007–2010 compared with 1997–2000. Apart from the increasing prevalence of diabetes, stricter goals for metabolic control and the implementation of the DMP could have contributed to this development. In the course of time, there was a clear shift toward intensification of antihyperglycemic therapy in increasingly older and morbid subjects with T1DM and in particular in those with T2DM. A critical definition of the metabolic target tailored to individual circumstances will be vital for minimizing the risk of hypoglycemia as a potentially life-threatening condition.

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A.H. conceived and designed the study, collected and assembled data, analyzed and interpreted data, wrote the manuscript, contributed to discussion, reviewed and edited the manuscript, and provided final approval of the manuscript. O.M.P. collected and assembled data and contributed to discussion, and the data of this study were obtained within the framework of O.M.P.'s dissertation. K.M. and J.D.H. collected and assembled data. M.S. contributed to discussion, reviewed and edited the manuscript, and provided final approval of the manuscript. P.K. analyzed and interpreted data, contributed to discussion, reviewed and edited the manuscript, and provided final approval of the manuscript. A.H. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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