Causative anti-diabetic drugs and the underlying clinical factors for hypoglycemia in patients with diabetes

Hidekatsu Yanai, Hiroki Adachi, Hisayuki Katsuyama, Sumie Moriyama, Hidetaka Hamasaki, Akahito Sako

Abstract
Recent clinical trials indicated that the intensive glycemic control do not reduce cardiovascular disease mortality among diabetic patients, challenging a significance of the strict glycemic control in diabetes management. Furthermore, retrospective analysis of the Action to Control Cardiovascular Risk in Diabetes study demonstrated a significant association between hypoglycemia and mortality. Here, we systematically reviewed the drug-induced hypoglycemia, and also the underlying clinical factors for hypoglycemia in patients with diabetes. The sulfonylurea use is significantly associated with severe hypoglycemia in patients with type 2 diabetes. The use of biguanide (approximately 45%-76%) and thiazolidinediones (approximately 15%-34%) are also highly associated with the development of severe hypoglycemia. In patients treated with insulin, the intensified insulin therapy is more frequently associated with severe hypoglycemia than the conventional insulin therapy and continuous subcutaneous insulin infusion. Among the underlying clinical factors for development of severe hypoglycemia, low socioeconomic status, aging, longer duration of diabetes, high HbA1c and low body mass index, comorbidities are precipitating factors for severe hypoglycemia. Poor cognitive and mental functions are also associated with severe hypoglycemia.

Key words: Comorbidity; Hypoglycemia; Insulin; Oral anti-diabetic drugs

© The Author(s) 2015. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: The use of sulfonylurea is significantly associated with severe hypoglycemia in patients with type 2 diabetes. Biguanide and thiazolidinediones use are also highly associated with severe hypoglycemia. The intensified insulin therapy is more frequently associated with severe hypoglycemia compared with other insulin therapies. Low socioeconomic status, aging, longer duration of diabetes, high HbA1c and low body mass index, comorbidities, poor cognitive and mental function are precipitating factors for severe hypoglycemia.
INTRODUCTION

The Diabetes Controls and Complication Trial and the United Kingdom Prospective Diabetes Study lead us to consider the strict glycemic control to prevent micro- and macro-vascular complications. Recent clinical trials such as Action to Control Cardiovascular Risk in Diabetes (ACCORD) presented that cardiovascular disease mortality did not decrease by the intensive glycemic control in diabetic patients, challenging the significance of the strict glycemic control in diabetes management.

In retrospective analysis of the ACCORD study, the annual mortality among patients in the intensive and standard glucose control arms were significantly higher in patients with severe hypoglycemia (2.8% and 3.7%, respectively) than those with no episodes (1.2% and 1.0%, respectively).

Patients with diabetes treated with insulin and antidiabetic drugs are at a greater risk of developing hypoglycemia than patients treated with only diet and exercise. Drug-induced hypoglycemia causes substantial morbidity and mortality, and compromises physiological and behavioral defenses against subsequent hypoglycemia, and also precludes the maintenance of glycemic control.

Here we systematically reviewed drug-induced hypoglycemia, and the underlying clinical factors for the development in diabetic patients.

CAUSATIVE ANTI-DIABETIC DRUGS FOR HYPOGLYCEMIA

The list of published articles about the drug-induced hypoglycemia is shown in Table 1. Kim et al. analyzed subjects with severe hypoglycemia who were brought to the Emergency Departments (ED) between January 1, 2004 and December 30, 2009. Fifty three percent of subjects were treated by insulin. Among patients with severe hypoglycemia due to sulfonylurea (SU), the glimepiride use increased from 2004 to 2009, while the gliclazide use decreased. Among patients treated with insulin, the treatment by using long-acting insulin analogues and premixed insulin increased, while the treatment by neutral protamine Hagedorn (NPH)-insulin and regular insulin (RI) decreased. According to the accumulated data between 2004 and 2009, glimepiride (24.2%) and NPH/RI (38.3%) use were frequently associated with severe hypoglycemia.

A retrospective cohort study showed that severe hypoglycemia in patients with type 1 diabetes was almost due to insulin, and 42.3% and 51.1% of type 2 diabetic patients were due to SU and insulin, respectively. Signorovitch et al. showed that the use of SU (38.2%), biguanide (56.3%) and thiazolidinediones (TZD) (14.5%) were highly associated with the development of severe hypoglycemia. Although this study did not reveal whether monotherapy or combination therapy by using biguanide induced severe hypoglycemia, this study showed that the number of patients treated with biguanide was greater than those with SU. To understand the burden of severe hypoglycemia among new users of insulin and oral anti-diabetic drugs (OAD), Moisan et al. conducted an inception cohort study using the databases of the Quebec health insurance board and the Quebec registry of hospitalizations between January 1, 2000 and December 31, 2008. A total of 188659 new users of anti-diabetic treatment were included. A total of 3575 (1.9%) individuals had at least 1 hypoglycemia-related ED visit. This study also showed the greater use of metformin (45.0%) as compared with SU (32.1%).

Holstein et al. compared the incidences of severe hypoglycemia between 2007-2010 and 1997-2000. Severe hypoglycemia among all emergency admissions significantly increased from 0.68% in 1997-2000 to 0.83% in 2007-2010, which was associated with the intensification of anti-hyperglycemic therapy. In type 1 diabetes, severe hypoglycemia increased from 11.5/100000 inhabitants to 23.4/100000 inhabitants for ten years, and also increased in type 2 diabetes from 18.5/100000 inhabitants to 32.6/100000 inhabitants. The number of drugs had increased in type 1 and type 2 diabetes. In patients with type 1 diabetes, the number of incidence of severe hypoglycemia due to the intensified insulin therapy (IIT) increased from 64 in 1997-2000 to 96 in 2007-2010, and severe hypoglycemia due to IIT (79.3%) was more frequent compared with the conventional (6.6%) or continuous subcutaneous insulin infusion (CSII) (13.2%), in 2007-2010. In type 2 diabetes, the frequency of IIT significantly increased in 2007-2010 as compared with those in 1997-2000. Severe hypoglycemia due to SU monotherapy increased from 45 cases to 67 cases. Severe hypoglycemia due to glimepiride (n = 65) occurred fourfold more frequently than severe hypoglycemia due to glibenclamide (n = 16). Ha et al. also reported that glimepiride was the most frequently prescribed drug in patients with severe hypoglycemia in South Korea.

In the survey by Geller et al., in an estimated 22.9% of ED visits for insulin-related hypoglycemia, more than 1 type of insulin product was documented. Long-acting (32.9%) and rapid-acting (26.4%) products were the most commonly documented insulin product types. Metformin and SU were the most commonly documented concomitant OAD, identified in 50.9% (95%CI: 47.6%-54.2%) and 39.2% (95%CI: 34.8%-43.6%), respectively.
Table 1  Published articles about the drug-induced hypoglycemia in patients with diabetes

| Ref.          | Subjects                   | Year         | Nation   | Setting                                                                 | OAD                          | Insulin                       | Combination                  |
|---------------|----------------------------|--------------|----------|-------------------------------------------------------------------------|------------------------------|-------------------------------|------------------------------|
| Kim et al[27] | Type 2 (n = 298)           | 2004-2009    | South Korea | The Emergency Department of two general hospitals                       | Glimepiride (24.2%)          | NPH/RI (38.3%)                | Premixed (11.1%)              |
|               |                            |              |          | Retrospective cohort study in one medical center                        | Gliclazide (5.4%)            |                               | Clargine/Detemir (13.1%)      |
|               |                            |              |          |                                                                         | Glibenclamide (8.4%)         |                               | Insulin (100%)                |
| Tsujimoto et al[28] | Type 1 (n = 305) | 2006-2012    | Japan     | SU (42.3%)                                                              | Others (6.6%)                | Insulin (51.1%)               |                              |
|               |                            |              |          |                                                                         | SU (38.2%)                   |                               |                              |
|               |                            |              |          |                                                                         | a-GI (0.9%)                  |                               |                              |
|               |                            |              |          |                                                                         | Sitagliptin (1.0%)           |                               |                              |
|               |                            |              |          |                                                                         | Incretin mimetics (0.5%)     |                               |                              |
|               |                            |              |          |                                                                         | TZD (14.9%)                  |                               |                              |
|               |                            |              |          |                                                                         |                               |                               |                              |
| Sognorovitch et al[29] | Type 2 not treated with insulin (n = 5582) | 1998-2010 | United States | Inception cohort study using the database of the Quebec health insurance board and the Quebec registry of hospitalizations | SU (32.1%)                   | Metformin (45.0%)             | SU + Metformin (12.3%)        |
|               |                            |              |          |                                                                         | Others (21.1%)               |                               |                              |
|               |                            |              |          |                                                                         |                               |                               |                              |
| Moisan et al[30] | Not determined (n = 3575) | 2000-2008 | Canada | SU (30.4%)                                                              | Convention (52.7%)           | SU + Insulin (16.9%)           |                              |
|               |                            |              |          |                                                                         | Intensified (0%)             |                               |                              |
|               |                            |              |          |                                                                         | CSII (0%)                    |                               |                              |
|               |                            |              |          |                                                                         |                               | SU + Insulin (6.7%)            |                              |
| Hsu et al[31]  | Type 2 (n = 500)           | 1998-2009    | Taiwan   | SU (29.8%)                                                              | Conventional (21.8%)         | SU + Insulin (6.7%)            |                              |
|               |                            |              |          |                                                                         | Intensified (8%)             |                               |                              |
|               |                            |              |          |                                                                         | CSII (0%)                    |                               |                              |
|               |                            |              |          |                                                                         |                               |                               |                              |
| Holstein et al[32] | Type 1 (n = 92) | 1997-2000 | German | SU (29.8%)                                                              | Conventional (27.2%)         | SU + Insulin (5.0%)            |                              |
|               |                            |              |          |                                                                         | Intensified (69.6%)          |                               |                              |
|               |                            |              |          |                                                                         | CSII (3.3%)                  |                               |                              |
|               |                            |              |          |                                                                         | Conventional (6.6%)          | SU + Insulin (5.0%)            |                              |
|               |                            |              |          |                                                                         | Intensified (79.3%)          |                               |                              |
|               |                            |              |          |                                                                         | CSII (13.2%)                 |                               |                              |
|               |                            |              |          |                                                                         |                               | SU + Insulin (6.7%)            |                              |
|               |                            |              |          |                                                                         |                               |                               |                              |
| Ha et al[33]   | Not determined (n = 320)   | 2006-2009    | South Korea | Retrospective analysis of hypoglycemic patients presented to emergency room of Uijeongbu St. Mary’s Hospital | Glimepiride (29.7%)          | Insulin (29.1%)               |                              |
|               |                            |              |          |                                                                         | Glibenclamide (4.7%)         |                               |                              |
|               |                            |              |          |                                                                         | Gliclazide (4.7%)            |                               |                              |
|               |                            |              |          |                                                                         | Glipizide (0.9%)             |                               |                              |
|               |                            |              |          |                                                                         | Others (24.7%)               |                               |                              |
| Geller et al[34] | Not determined (n = 8100) | 2007-2011 | United States | Nationally representative public health surveillance of adverse drug events among insulin-treated patients seeking emergency department care | Insulin (83.4%)              |                               |                              |
|               |                            |              |          |                                                                         |                               | Insulin + Biguanide (8.5%)    |                              |
|               |                            |              |          |                                                                         |                               | SU (6.6%)                     |                              |
|               |                            |              |          |                                                                         |                               | TZD (3.6%)                    |                              |
|               |                            |              |          |                                                                         |                               | DPP-4 inhibitors (1.3%)       |                              |
|               |                            |              |          |                                                                         |                               | GLP-1 analogues (0.2%)        |                              |
|               |                            |              |          |                                                                         |                               | Others (0.9%)                 |                              |
| Ben-Ami et al[35] | Type 1 and 2 (n = 99) | 1986-1992 | Israel | Retrospective analysis of the medical record in Rambam Medical Center | Glyburide (51.5%)            | Insulin (23.2%)               |                              |
|               |                            |              |          |                                                                         | Glyburide + Metformin (10.2%) |                               |                              |
| Quilliam et al[36] | Type 2 (n = 536581) | 2004-2008 | United States | Retrospective cohort designed to assess the rate and costs of hypoglycemia among working-age patients with type 2 diabetes in the MarketScan database | SU (42.3%)                   | Insulin (6.0%)                |                              |
|               |                            |              |          |                                                                         | Metformin (75.7%)            |                               |                              |
|               |                            |              |          |                                                                         | TzD (33.3%)                  |                               |                              |
|               |                            |              |          |                                                                         | Other oral agents (4.4%)     |                               |                              |
|               |                            |              |          |                                                                         |                               |                              |                              |
Glucose counter-regulation is associated with the risk of long duration of type 2 diabetes in patients with type 1 diabetes and also patients with epinephrine secretion reduction of insulin secretion; enhancement of glucagon against decrease in plasma glucose.

Insulin excess and compromised physiological defenses sensitivity; decreased insulin clearance endogenous glucose production; increased insulin glucose delivery; increased glucose utilization; decreased ill-timed, or of the wrong type; decreased exogenous risk factors include excessive anti-diabetic drugs doses, causes of hypoglycemia in diabetic patients. Conventional epinephrine; non-islet cell tumor sepsis and inanition; deficiency of cortisol, glucagon and alcohol and drugs other than anti-diabetic agents and to anti-diabetic drugs (insulin or insulin secretagogue), medicated adult individuals include hypoglycemia due Practice Guideline", the causes of hypoglycemia in ill or HYPOGLYCEMIA UNDERLYING CLINICAL FACTORS FOR hypoglycemia. In the study among patients with type 1 diabetes by Parsaik et al, multiple daily insulin injection (MDI) (67.0%) was more frequently associated with severe hypoglycemia as compared with simple insulin (10.0%) and CSII (18.0%). In type 2 diabetes, MDI was also more frequently associated with severe hypoglycemia than simple insulin (27.0%), CSII (1.0%) and combination therapy with OAD (11.0%).

UNDERLYING CLINICAL FACTORS FOR HYPOGLYCEMIA

According to “Evaluation and Management of Adult Hypoglycemia Disorders: An Endocrine Society Clinical Practice Guideline”, the causes of hypoglycemia in ill or medicated adult individuals include hypoglycemia due to anti-diabetic drugs (insulin or insulin secretagogue), alcohol and drugs other than anti-diabetic agents and alcohol; critical illness (hepatic, renal and heart failure), sepsis and inanition; deficiency of cortisol, glucagon and epinephrine; non-islet cell tumor. These can also be the causes of hypoglycemia in diabetic patients. Conventional risk factors include excessive anti-diabetic drugs doses, ill-timed, or of the wrong type; decreased exogenous glucose delivery; increased glucose utilization; decreased endogenous glucose production; increased insulin sensitivity; decreased insulin clearance.

Hypoglycemia occurs due to relative or absolute insulin excess and compromised physiological defenses against decrease in plasma glucose. The physiological defenses against decrease in plasma glucose include: reduction of insulin secretion; enhancement of glucagon and epinephrine secretion, which are compromised in patients with type 1 diabetes and also patients with long duration of type 2 diabetes. Defective glucose counter-regulation is associated with the risk of severe hypoglycemia.

The list of published articles about the underlying clinical factors for hypoglycemia is shown in Table 2. Yaffe et al reported that black race and low education level were significantly associated with severe hypoglycemia. Punthakee et al also reported that significant associations of race and education level with severe hypoglycemia. Leese et al indicated older age, a longer duration of diabetes, and a higher HbA1c as underlying clinical factors for hypoglycemic patients, which was also reported by Punthakee et al. Yaffe et al also suggested a significant association between severe hypoglycemia and a higher HbA1c. A lower body mass index (BMI) was also associated with the development of severe hypoglycemia.

Punthakee et al studied the association between severe hypoglycemia and cognitive function, and showed poor cognitive function is associated with severe hypoglycemia in type 2 diabetic patients. Yaffe et al, Hsu et al and Signorovitch et al also reported a significant association between mental disorders and severe hypoglycemia. Neurological disorders such as stroke and epilepsy which influence mental and cognitive functions were also associated with development of severe hypoglycemia.

Heart, liver and renal functions affect pharmacokinetics and clearance of insulin and OAD. Liver cirrhosis, renal disease including diabetic nephropathy, heart diseases including cardiovascular diseases are significantly associated with severe hypoglycemia. Hsu et al performed a nationwide cohort study, and suggested that comorbidities such as hypertension and renal disease are associated with hypoglycemic episodes. Signorovitch et al also indicated a significant associations of hypoglycemia with comorbidities such as mental disorders and stroke. In their study, patients with hypoglycemia showed a higher Charlson comorbidity index than those without hypoglycemia.

Neuropathy is also associated with hypoglycemia. In neuropathy, especially, hypoglycemia-associated autonomic failure (HAAF) is significantly associated with the development of severe hypoglycemia. In patients with HAAF, in the absence of reduction of insulin secretion and enhancement of glucagon secretion, the defective glucose counter-regulation by epinephrine induces hypoglycemia unawareness by reducing the sympathetic neural activity and neurogenic symptoms. According to “Evaluation and Management of Adult Hypoglycemia Disorders: An Endocrine Society Clinical Practice
Guideline”, risk factors for HAAF include absolute deficiency of endogenous insulin secretion; a history of severe hypoglycemia, and hypoglycemia unawareness.}

**CONCLUSION**

The use of SU is significantly associated with severe hypoglycemia in patients with type 2 diabetes. Especially, the glimepiride-induced severe hypoglycemia (approximately 20%-30%) occurred more frequently as compared with other SU. The use of biguanide (approximately 45%-76%) and TZD (approximately 15%-34%) are also highly associated with the development of severe hypoglycemia. The study that investigated insulin product types and

---

**Table 2: Published articles about the underlying clinical factors for the development of hypoglycemia in patients with diabetes**

| Ref. | Clinical factors | Hypoglycemia | No hypoglycemia | *P* value |
|------|------------------|--------------|-----------------|-----------|
| Yaffe et al. | Black race/ethnicity (%) | 72.1 | 44.9 | < 0.01 |
| | Education (< high school education) (%) | 36.1 | 24.0 | 0.04 |
| | Glycated hemoglobin level (%) | 8.0 | 7.2 | < 0.01 |
| | Prevalent diabetes mellitus (%) | 85.2 | 47.9 | < 0.01 |
| | MMSE score [mean (SD)] | 89.6 (5.7) | 91.5 (5.2) | < 0.01 |
| | Hypertension (%) | 63.6 | 51.2 | < 0.0001 |
| | Liver cirrhosis (%) | 3.0 | 1.3 | 0.0074 |
| | Renal disease (%) | 17.4 | 5.2 | < 0.0001 |
| | Mental disease (%) | 21.4 | 12.5 | < 0.0001 |
| | Cancer (%) | 8.0 | 2.4 | < 0.0001 |
| | Stroke (%) | 15.0 | 4.0 | < 0.0001 |
| | Heart disease (%) | 13.2 | 3.6 | < 0.0001 |
| Hsu et al. | Age (mean, yr) | 72.1 | 36.1 | < 0.0001 |
| | Type 1 treated with insulin | 37.7 | 32.8 | 0.009 |
| | Type 2 treated with insulin | 66.6 | 63.2 | 0.038 |
| | Diabetes duration (mean, years) | 20.7 | 16.7 | 0.013 |
| | Type 1 treated with insulin | 26.7 | 30.1 | < 0.001 |
| | Type 2 treated with insulin | 15.2 | 11.4 | < 0.001 |
| | Mental disorders (%) | 17.2 | 10.7 | < 0.001 |
| | Neurological disorders (%) | 60.4 | 59.0 | 0.05 |
| | Cardiovascular disorders (%) | 16.5 | 12.3 | < 0.001 |
| | Renal disorders (%) | 1.2 | 0.7 | < 0.001 |
| | Stroke (%) | 4.9 | 2.9 | < 0.001 |
| | CCI [mean (SD)] | 1.42 (1.70) | 1.3 | < 0.001 |
| Leese et al. | Age [yr, mean (SD)] | 63.91 (6.41) | 62.41 (5.77) | 0.002 |
| | Female (%) | 55.6 | 46.1 | 0.019 |
| | Race | | | < 0.0001 |
| | Non-Hispanic white (%) | 60.0 | 70.9 | |
| | African American (%) | 30.0 | 15.4 | |
| | Hispanic (%) | 6.3 | 7.1 | |
| | Others (%) | 3.8 | 6.6 | |
| | Education | | | 0.01 |
| | Less than high school (%) | 16.3 | 12.8 | |
| | High school graduate (%) | 35.0 | 25.2 | |
| | Some college (%) | 26.9 | 35.1 | |
| | College graduate (%) | 21.9 | 26.9 | |
| | BMI [mean (SD), kg/m²] | 32.08 (5.64) | 33.03 (5.33) | 0.029 |
| | Diabetes duration [mean (SD) of years] | 14.13 (8.74) | 10.18 (7.22) | < 0.0001 |
| | HbA1c (%) | 8.46 (1.06) | 8.27 (1.05) | 0.021 |
| | History of stroke (%) | 11.3 | 4.6 | 0.0002 |
| | History of cardiovascular disease (%) | 41.9 | 28.4 | 0.0003 |
| | Neuropathy score [mean (SD)] | 0.53 (0.50) | 0.45 (0.50) | 0.049 |
| | UACR (mg/mmol) | | | < 0.0001 |
| | < 30 (%) | 58.8 | 72.4 | |
| | 30-300 (%) | 27.5 | 21.9 | |
| | > 300 (%) | 13.8 | 5.7 | |
| | DSST score [mean (SD)] | 46.45 (17.01) | 52.89 (15.76) | < 0.0001 |
| | RAVLT score [mean (SD)] | 6.90 (2.72) | 7.55 (2.53) | 0.002 |
| | Stroop score [mean (SD)] | 37.69 (22.02) | 31.66 (16.25) | < 0.0001 |
| | MMSE score [mean (SD)] | 26.83 (2.80) | 27.45 (2.49) | 0.002 |

BMI: Body mass index; CCI: Charlson comorbidity index; DSST: Digit Symbol Substitution Test; MMSE: Mini-Mental Status Exam; RAVLT: Rey Auditory Verbal Learning Test; UACR: Urinary albumin creatinine ratio.
hypoglycemia is very limited. In one study in Korea, NPH/RI was more frequently associated with severe hypoglycemia as compared with premixed insulin and glargine/detemir. In diabetic patients treated with insulin, IIT is more frequently associated with severe hypoglycemia compared with conventional insulin therapy and CSII.

Summary of the underlying clinical factors for hypoglycemia is shown in Table 3. Low socioeconomic status, aging, longer duration of diabetes, high HbA1c and low BMI are precipitating factors for severe hypoglycemia. Poor cognitive and mental functions are also associated with the development of severe hypoglycemia. Comorbidities including heart, liver, renal failures are likely to induce severe hypoglycemia. We should also pay attention to HAAF which leads to very serious hypoglycemia.

REFERENCES

1. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med 1993; 329: 977-986 [PMID: 8366922 DOI: 10.1056/NEJM19930903291401]

2. UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study Group. Lancet 1998; 352: 837-853 [PMID: 9742976 DOI: 10.1016/S0140-6736(98)07019-6]

3. Duckworth W, Abriria C, Moritz T, Reda D, Emanuele N, Reaven PD, Zieve FJ, Marks J, Davis SN, Hayward WG, Huang GD. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009; 360: 129-139 [PMID: 19092145 DOI: 10.1056/NEJMoa0802987]

4. Gerstein HC, Miller ME, Byington RP, Goff DC, Bigger JT, Buse JB, Cushman WC, Gennuth S, Ismail-Beigi F, Grimm RH, Probstfield JL, Simons-Morton DG, Freedwald WT. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008; 358: 2545-2559 [PMID: 18539917 DOI: 10.1056/NEJMoa0802743]

5. Patel A, MacMahon S, Chalmers J, Neil B, Billot L, Woodward M, Marre M, Cooper M, Glasspoor P, Grobbbee D, Hamet P, Harrap S, Heller S, Liu L, Mancia G, Mogensen CE, Pan C, Poulter N, Rodgers A, Williams B, Bompoin S, de Galan BE, Joshi R, Travers F. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008; 358: 2560-2572 [PMID: 18539916 DOI: 10.1056/NEJMoa0829867]

6. Bonds DE, Miller ME, Bergenstal RM, Buse JB, Byington RP, Cutler JA, Dand JJ, Ismail-Beigi F, Kimel AB, Hoogwerf BJ, Horowitz KR, Savage PJ, Seagust ET, Simmons DL, Sivitz WI, Sperli-Hillen JM, Sweeney ME. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. BMJ 2010; 340: b409 [PMID: 20061358 DOI: 10.1136/bmj.b409]

7. Gale EA, Tattersall RB. Unrecognised nocturnal hypoglycaemia in insulin-treated diabetics. Lancet 1979; 1: 1049-1052 [PMID: 86775 DOI: 10.1016/0140-6736(79)92950-7]

8. Unger RH. Nocturnal hypoglycemia in aggressively controlled diabetes. N Engl J Med 1982; 306: 1294 [PMID: 7040970 DOI: 10.1056/NEJM198205273062113]

9. Poulter N, Rodgers A, Williams B, Bompoint S, de Galan BE, Joshi R, Travert F. Intensive blood glucose control and vascular complications in patients treated with insulin. Br Med J (Clin Res Ed) 1985; 291: 376-379 [PMID: 3926200 DOI: 10.1136/bmj.291.6492.376]

10. Cryer PE. The barrier of hypoglycemia in diabetes. Diabetes 2008; 57: 3169-3176 [PMID: 19033403 DOI: 10.2337/db08-1084]

11. Harris EL. Adverse reactions to oral antidiabetic agents. Br Med J 1971; 3: 29-30 [PMID: 5091891 DOI: 10.1136/bmj.3.5765.29]

12. Seltzer HS. Drug-induced hypoglycaemia. A review based on 473 cases. Diabetes 1972; 21: 955-966 [PMID: 4626706 DOI: 10.2337/diab.21.9.955]

13. Deckert T, Poulsen JE, Larsen M. Prognosis of diabetes with diabetes onset before the age of thirty-one. I. Survival, causes of death, and complications. Diabetologia 1978; 14: 363-370 [PMID: 669100]

14. Goldstein DE, England JD, Hess R, Rawlings SS, Walker B. A prospective study of symptomatic hypoglycemia in young diabetic patients. Diabetes Care 1981; 4: 601-605 [PMID: 6751735 DOI: 10.2337/diabetes.4.6.601]

15. Salans LB. NIH plans study of diabetes control and complications. N Engl J Med 1982; 307: 1527-1528 [PMID: 7144825]

16. Goldwicht C, Slama G, Papos L, Tchobroutsky G. Hypoglycaemic reactions in 172 Type 1 (insulin-dependent) diabetic patients. Diabetologia 1983; 24: 95-99 [PMID: 6541141 DOI: 10.1007/BF00297389]

17. Asplund K, Wilholm BE, Lithner F. Glibenclamide-induced hypoglycaemia: a report on 57 cases. Diabetologia 1983; 24: 412-417 [PMID: 6411511 DOI: 10.1007/BF00257338]

18. Casparie ALF, Elving LD. Severe hypoglycaemia in diabetic patients: frequency, causes, prevention. Diabetes Care 1985; 8: 141-145 [PMID: 3885635 DOI: 10.2337/diabetes.8.2.141]

19. Wallis WE, Donaldson I, Scott RS, Wilson J. Hypoglycemia masquerading as cerebrovascular disease (hypoglycemic hemiplegia). Ann Neurol 1985; 18: 510-512 [PMID: 4073444 DOI: 10.1002/ana.410180415]

20. Malouf R, Brust JC. Hypoglycaemia: causes, neurological manifestations, and outcome. Ann Neurol 1985; 17: 421-430 [PMID: 4004130 DOI: 10.1002/ana.410170502]

21. Nexo RW, Phillips RT. Asymptomatic myocardial ischemia in diabetic patients. Am J Med 1986; 80: 40-47 [PMID: 3706356 DOI: 10.1016/0002-9343(86)90451-1]

22. Jennings AM, Wilson RM, Ward JD. Symptomatic hypoglycemia in NIDDM patients treated with oral hypoglycemic agents. Diabetes Care 1989; 12: 203-208 [PMID: 2702912 DOI: 10.2337/diabetes.12.2.203]

23. Seltzer HS. Drug-induced hypoglycaemia. A review of 1418 cases. Endocr Med Clin North Am 1989; 18: 163-183 [PMID: 2645125]

24. Hepburn DA, Steel JM, Frier BM. Hypoglycaemic convulsions cause serious musculoskeletal injuries in patients with IDDM. Diabetes Care 1989; 12: 32-34 [PMID: 2653747 DOI: 10.2337/diabetes.12.1.32]

25. Pladziewicz DS, Nexo RW. Hypoglycaemia-induced silent myocardial ischemia. Am J Cardiol 1989; 63: 1531-1532 [PMID: 2658533 DOI: 10.1016/0002-9149(89)90025-8]

26. Patrick AW, Campbell IW. Fatal hypoglycaemia in insulin-treated diabetes mellitus: clinical features and neuropathological changes. Diabet Med 1990; 7: 349-354 [PMID: 2140089 DOI: 10.1002/ana.410180415]
Yanai H et al. Underlying clinical factors for hypoglycemia in patients

10.1111/j.1444-5490.1991.tb01403.x

27 Kim JT, Oh TJ, Lee YA, Bae JH, Kim HJ, Jung HS, Cho YM, Park KS, Lim S, Jang HC, Lee HK. Increasing trend in the number of severe hypoglycemia patients in Korea. Diabetes Metab J 2011; 35: 166-172 [PMID: 21738899 DOI: 10.4033/dmj.2011.35.2.166]

28 Tsujimoto T, Yamamoto-Honda R, Kajio H, Kishimoto M, Noto H, Hachiya R, Kimura A, Kakei M, Noda M. Vital signs, QT prolongation, and newly diagnosed cardiovascular disease during severe hypoglycemia in type 1 and type 2 diabetic patients. Diabetes Care 2014; 37: 217-225 [PMID: 23939540 DOI: 10.2337/dc13-0701]

29 Signorovitch JE, Macaulay D, Diener M, Yan Y, Wu EQ, Gruenberger JB, Frier BM. Hypoglycemia and accident risk in people with type 2 diabetes mellitus treated with non-insulin antidiabetes drugs. Diabetes Obes Metab 2013; 15: 335-341 [PMID: 23121373 DOI: 10.1111/dom.12031]

30 Moisan J, Breton MC, Villeneuve J, Grégoire JP. Hypoglycemia-related emergency department visits and hypoglycemia-related hospitalizations among new users of antidiabetes treatments. Can J Diabetes 2013; 37: 143-149 [PMID: 24070806 DOI: 10.1016/j.jcjd.2013.02.039]

31 Hsu PF, Sung SH, Cheng HM, Yeh JS, Liu WL, Chan WL, Chen CH, Chou P, Chuang SY. Association of clinical symptoms with cardiovascular events and total mortality in type 2 diabetes: a nationwide population-based study. Diabetes Care 2013; 36: 894-900 [PMID: 23223349 DOI: 10.2337/dc12-0916]

32 Holstein A, Patzer OM, Machalke K, Holstein JD, Stumvoll M, Kovacs P. Substantial increase in incidence of severe hypoglycemia between 1997-2000 and 2007-2010: a German longitudinal population-based study. Diabetes Care 2012; 35: 972-975 [PMID: 22418017 DOI: 10.2337/dc11-1470]

33 Ha WC, Oh SJ, Kim JH, Lee JM, Chang SA, Sohn TS, Son HS. Severe hypoglycemia is a serious complication and becoming an economic burden in diabetes. Diabetes Metab J 2012; 36: 280-284 [PMID: 22950659 DOI: 10.4093/dmj.2012.36.4.280]

34 Geller AI, Shehab N, Lovegrove MC, Kegler SR, Weidenbach B. A novel, reliable and reproducible test for adequate glucose counterregulation and reproducible test for adequate glucose counterregulation and reproducible test for adequate glucose counterregulation and reproducible test for adequate glucose counterregulation and reproducible test for adequate glucose counterregulation and reproducible test for adequate glucose counterregulation. JAMA Intern Med 2014; 174: 678-686 [PMID: 24615164 DOI: 10.1001/jamainternmed.2014.136]

35 Ben-Ami H, Nagachandran P, Mendelson A, Edoute Y. Drug-induced hypoglycemic coma in 102 diabetic patients. Arch Intern Med 1999; 159: 261-284 [PMID: 99889540 DOI: 10.1001/archinte.159.3.281]

36 Quillin BJ, Simeone JC, Ozbay AB, Kogut SJ. The incidence and costs of hypoglycemia in type 2 diabetes. Am J Manag Care 2011; 17: 673-680 [PMID: 22106460]

37 Parsaik AK, Carter RE, Pattan V, Myers LA, Kumar H, Smith SA, Russi CS, Levine JA, Basu A, Kudva YC. Population-based study of severe hypoglycemia requiring emergency medical service assistance reveals unique findings. J Diabetes Sci Technol 2012; 6: 65-73 [PMID: 22401324 DOI: 10.1177/1932968120360109]

38 Cryer PE, Axelrod L, Grossman AB, Heller SR, Montori VM, Seakin ER, Service FJ. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2009; 94: 709-728 [PMID: 19088135 DOI: 10.1210/jc.2008-1410]

39 Cryer P. Glucose homeostasis and hypoglycemia. In: Kronenberg H, Melmed S, Polonsky K, Larsen P, editors. Williams textbook of endocrinology, 11th ed. Philadelphia: Saunders, an imprint of Elsevier, Inc., 2008: 1503-1533

40 Cryer PE. Diverse causes of hypoglycemia-associated autonomic failure in diabetes. N Engl J Med 2004; 350: 2272-2279 [PMID: 15163777 DOI: 10.1056/NEJMoa035154]

41 Cryer PE. Hypoglycemia: the limiting factor in the glycaemic management of Type 1 and Type II diabetes. Diabetesologia 2002; 45: 937-948 [PMID: 12136392 DOI: 10.1007/s00125-002-0822-9]

42 Cryer PE, Davis SN, Shamoan H. Hypoglycemia in diabetes. Diabetes Care 2003; 26: 1902-1912 [PMID: 12766131 DOI: 10.2337/diacare.26.6.1902]

43 Cryer PE. Hypoglycemia, functional brain failure, and brain death. J Clin Invest 2007; 117: 868-870 [PMID: 17404614 DOI: 10.1172/JCI131669]

44 Cryer P. The prevention and correction of hypoglycemia. In: Jefferson L, Cherrington A, Goodman H, editors. Handbook of physiology; Section 7, the endocrine system. Volume II. The endocrine pancreas and regulation of metabolism. New York: Oxford University Press, 2001: 1057-1092

45 Dagogo-Jack SE, Craft S, Cryer PE. Hypoglycemia-associated autonomic failure in insulin-dependent diabetes mellitus. Recent antecedent hypoglycemia reduces autonomic responses to, symptoms of, and defense against subsequent hypoglycemia. J Clin Invest 1993; 91: 819-828 [PMID: 8450063 DOI: 10.1172/JCI16302]

46 Segel SA, Paramore DS, Cryer PE. Hypoglycemia-associated autonomic failure in advanced type 2 diabetes. Diabetes 2002; 51: 724-733 [PMID: 11872673 DOI: 10.2337/diabetes.51.3.724]

47 White NH, Skor DA, Cryer PE, Levandoski LA, Bier DM, Santiago JV. Identification of type I diabetic patients at increased risk for hypoglycemia during intensive therapy. N Engl J Med 1983; 308: 485-491 [PMID: 6337335 DOI: 10.1056/NEJM1983030809030]

48 Bolli GB, De Feo P, De Cosmo S, Perriello G, Ventura MM, Benedetti MM, Santusianio F, Gerich JE, Brunetti P. A reliable and reproducible test for adequate glucose counterregulation and reproducible test for adequate glucose counterregulation and reproducible test for adequate glucose counterregulation and reproducible test for adequate glucose counterregulation and reproducible test for adequate glucose counterregulation and reproducible test for adequate glucose counterregulation. JAMA Intern Med 2013; 173: 1300-1306 [PMID: 23753199 DOI: 10.1001/jamainternmed.2013.6176]

49 Puntakee Z, Miller ME, Launer LJ, Williamson JD, Lazar RM, Cukierman-Yaffe T, Seaqurist ER, Ismail-Beigi F, Sullivan MD, Lovato LC, Bergerst RL, Gerstein HC. Poor cognitive function and risk of severe hypoglycemia in type 2 diabetes: post hoc epidemiologic analysis of the ACCORD trial. Diabetes Care 2012; 35: 787-793 [PMID: 22374637 DOI: 10.2337/diabetes.33.8.723]

50 Leese GP, Wang J, Broomhall J, Kelly P, Marsden A, Morrison W, Frier BM, Morris AD. Frequency of severe hypoglycemia requiring emergency treatment in type 1 and type 2 diabetes: a population-based study of health service resource use. Diabetes Care 2013; 36: 2176-2180 [PMID: 2363593 DOI: 10.2337/dc12-1855]

51 Davis MR, Mellow M, Shamoan H. Further defects in counterregulatory responses induced by recurrent hypoglycemia in IDDM. Diabetes 1992; 41: 1335-1340 [PMID: 1397708 DOI: 10.2337/diabetes.41.10.1335]

P- Reviewer: Schuurman HJ | S- Editor: Tian YL | L- Editor: A E- Editor: Lu Y
