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TOPIC HIGHLIGHT

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

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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

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.

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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[1,2]. 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[3-5], challenging a 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)[6].

Patients with diabetes treated with insulin and hypoglycemic drugs are at a greater risk of developing hypoglycemia than patients treated with only diet and exercise[7-9]. Drug-induced hypoglycemia causes substantial morbidity and mortality, and compromises physiological and behavioral defenses against subsequent hypoglycemia, and also precludes the maintenance of glyemic control[10-26].

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*[27] 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[28]. Signorovitch *et al*[29] 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*[30] 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%).

Hsu *et al*[31] showed that the number of insulin and SU user was significantly greater in patients with severe hypoglycemia (24.2% for insulin, 67.8% for SU) than in patients without hypoglycemia (4.35% and 54.95%, respectively).

Holstein *et al*[32] 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*[33] 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*[34], 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%),

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%) Gliclazide (5.4%) Glibenclamide (8.4%)	NPH/RI (38.3%) Premixed (11.1%) Glargine/Detemir (13.1%)	
Tsujimoto *et al*[28]	Type 1 (*n* = 85)	2006-2012	Japan	Retrospective cohort study in one medical center		Insulin (100%)	
	Type 2 (*n* = 305)				SU (42.3%) Others (6.6%)	Insulin (51.1%)	
Signorovitch *et al*[29]	Type 2 not treated with insulin (*n* = 5582)	1998-2010	United States	US-based employer claims database	SU (38.2%) Biguanides (56.3%) a-GI (0.9%) Sitagliptin (1.0%) Incretin mimetics (0.5%) TZD (14.9%)		
Moisan *et al*[30]	Not determined (*n* = 3575)	2000-2008	Canada	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 (2.1%)	Insulin (8.5%)	
Hsu *et al*[31]	Type 2 (*n* = 500)	1998-2009	Taiwan	A nationwide population-based study using the National Health Insurance Research Database	SU (67.8%) Others (61.4%)	Insulin (24.2%)	
Holstein *et al*[32]	Type 1 (*n* = 92)	1997-2000	German	A longitudinal population-based study		Conventional (27.2%) Intensified (69.6%) CSII (3.3%)	
	Type 1 (*n* = 121)	2007-2010				Conventional (6.6%) Intensified (79.3%) CSII (13.2%)	
	Type 2 (*n* = 148)	1997-2000			SU (30.4%)	Conventional (52.7%) Intensified (0%) CSII (0%)	SU + Insulin (16.9%)
	Type 2 (*n* = 225)	2007-2010			SU (29.8%) Metformin (0.9%)	Conventional (40.8%) Intensified (21.8%) CSII (0%)	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%) Glibenclamide (4.7%) Gliclazide (4.7%) Gliquidone (1.3%) Glipizide (0.9%) Others (24.7%)	Insulin (29.1%)	SU + Insulin (5.0%)
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%) Glyburide + Metformin (10.2%)	Insulin (23.2%)	Insulin + Glyburide (13.1%) Insulin + Metformin (2.0%)
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%) Metformin (75.7%) TZD (33.3%) Other oral agents (4.4%)	Insulin (6.0%) Other injectable agents (2.7%)	

Parsaik *et al*[37]	Type 1 (*n* = 210)	2003-2009	United States	Population-based study		Simple insulin (10.0%) MDI (67.0%) CSII(18.0%)	OAD + Insulin (1.0%)
	Type 2 (*n* = 503)				OAD (23.0%)	Simple insulin (27.0%) MDI (37.0%) CSII (1.0%)	OAD + Insulin (11.0%)

a-GI: a-glucosidase inhibitors; CSII: Continuous subcutaneous insulin infusion; DPP-4: Dipeptidyl peptidase-4; GLP-1: Glucagon-like peptide-1; MDI: Multiple daily insulin injection; NPH: Neutral protamine Hagedorn; OAD: Oral anti-diabetic drug; RI: Regular insulin; SU: Sulfonylurea; TZD: Thiazolidinediones.

respectively, of estimated ED visits for insulin-related hypoglycemia.

Ben-Ami *et al*[35] found that the glyburide use as mono-therapy (51.5%) and as combination therapy with metformin was the most frequently used drug in patients with hypoglycemic coma. Quilliam *et al*[36] estimated the rate and costs of hypoglycemia in patients with type 2 diabetes, by using a retrospective cohort design to assess the rate and costs of hypoglycemia among working-age patients in the 2004-2008 MarketScan database. The use of SU (42.3%), metformin (75.7%) and TZD (33.3%) were highly associated with the development of hypoglycemia. In the study among patients with type 1 diabetes by Parsaik *et al*[37], 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[38]. 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[38].

Hypoglycemia occurs due to relative or absolute insulin excess and compromised physiological defenses against decrease in plasma glucose[38-42]. The physiological defenses against decrease in plasma glucose include: reduction of insulin secretion; enhancement of glucagon and epinephrine secretion[39,43,44], which are compromised in patients with type 1 diabetes and also patients with long duration of type 2 diabetes[39,40,45,46]. Defective glucose counter-regulation is associated with the risk of severe hypoglycemia[47,48].

The list of published articles about the underlying clinical factors for hypoglycemia is shown in Table 2. Yaffe *et al*[49] reported that black race and low education level were significantly associated with severe hypoglycemia. Punthakee *et al*[50] also reported that significant associations of race and education level with severe hypoglycemia. Leese *et al*[51] 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*[50]. Yaffe *et al*[49] 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[50,51].

Punthakee *et al*[50] 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*[49], Hsu *et al*[31] and Signorovitch *et al*[29] 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[29,31,50].

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[29,31,50]. Hsu *et al*[31] performed a nationwide cohort study, and suggested that comorbidities such as hypertension and renal disease are associated with hypoglycemic episodes. Signorovitch *et al*[29] 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[50]. In neuropathy, especially, hypoglycemia-associated autonomic failure (HAAF) is significantly associated with the development of severe hypoglycemia[46,52]. 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[39,40,45]. According to "Evaluation and Management of Adult Hypoglycemia Disorders: An Endocrine Society Clinical Practice

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[49]	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
Hsu *et al*[31]	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
Leese *et al*[51]	Age (mean, yr)			
	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)			
	Type 1 treated with insulin	20.7	16.7	0.013
	BMI (mean, kg/m^2)			
	Type 2 treated with insulin	26.7	30.1	< 0.001
Signorovitch *et al*[29]	Mental disorders (%)	15.2	11.4	< 0.001
	Neurological disorders (%)	17.2	10.7	< 0.001
	Cardiovascular disorders (%)	60.4	59.0	0.05
	Renal disorders (%)	16.5	12.3	< 0.001
	Epilepsy (%)	1.2	0.7	< 0.001
	Stroke (%)	4.9	2.9	< 0.001
	CCI [mean (SD)]	1.42 (1.70)	1.3	< 0.001
Punthakee *et al*[50]	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/m^2]	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.

Guideline", risk factors for HAAF include absolute deficiency of endogenous insulin secretion; a history of severe hypoglycemia, and hypoglycemia unawareness[38].

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 3 Summary of the underlying clinical factors for the development of hypoglycemia in patients with diabetes

1 Socioeconomic status (education, race)
2 Aging
3 State of diabetes (duration, HbA1c, body mass index)
4 Cognitive and mental function
5 Comorbidity
6 Failure of organ which influence on clearance of insulin and oral anti-diabetic drugs (Heart, liver, renal failure)
7 Hypoglycemia-associated autonomic failure

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.

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