Original Article

Hypoglycemia: Adverse Cardiovascular Outcomes in Non-Critically Ill People with Type 2 Diabetes

Parisa Akhavan MD[1], Rokhsareh Aghili MD[1], Mojtaba Malek MD[1], Ameneh Ebrahim Valojerdi BSc[1], Mohammad Ebrahim Khamseh MD•[1]

Abstract

Background: Hypoglycemia is associated with adverse health outcomes and can result in vascular events in diabetic patients. The impact of hypoglycemia on cardiovascular outcomes in non-critically ill people with diabetes is not well-determined. So, we examined short-term cardiovascular outcomes of hypoglycemic events in people with type 2 diabetes treated with insulin during routine clinical care.

Methods: This study was conducted in Tehran, Iran from January 2012 to January 2013. One hundred and twenty non-critically ill people with type 2 diabetes on oral glucose lowering drugs were enrolled. Insulin therapy was initiated for uncontrolled diabetes. The patients were educated to perform self-monitoring of blood glucose on a daily basis. Furthermore, they were asked to record the results if they experienced any symptom indicative of hypoglycemia during the 24 weeks of the study. The occurrence of any major cardiovascular event including unstable angina, fatal or non-fatal myocardial infarction, fatal and non-fatal stroke, or death from cardiovascular cause was also evaluated based on the patients' hospital records.

Results: There were 210 hypoglycemic episodes and 31 major cardiovascular events. Forty four percent of patients with documented hypoglycemic episodes developed cardiovascular events compared to 15.6% of those who did not experience any hypoglycemia ($P = 0.001$). The odds ratio for occurrence of major cardiovascular events related to hypoglycemia was 7.41 (CI = 2.15–25.47) with a risk ratio of 2.66.

Conclusion: Hypoglycemia is a major risk factor for occurrence of the first major cardiovascular event in non-critically ill people with type 2 diabetes initiating insulin therapy.

Keywords: Cardiovascular event, hypoglycemia, insulin, Type 2 diabetes

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Introduction

Macrovascular disease is more common in people with diabetes, and diabetes is considered a major risk factor for cardiovascular disease and death.[1,2] It is now clear that atherosclerosis and cardiovascular disease have an inflammatory pathogenesis from the very early stages of development.[3]

Hypoglycemia is a well-recognized side effect of glucose lowering therapies. Although episodes of hypoglycemia occur much less frequently in people with type 2 diabetes compared to type 1,[4–6] hypoglycemia may adversely affect the vasculature which has already become compromised by atherosclerosis.

Major vascular events can be precipitated by severe hypoglycemia. This might be due to hemodynamic changes on myocardial perfusion, or electrolyte disturbances on cardiac conduction.[7–9] A low level of glucose in blood is associated with a surge of sympathetic activity, catecholamine secretion, and inflammatory alterations, which may potentially cause endothelial damage and contribute to the development or progression of vascular disease.[10–12]

The results of the four major trials comparing different intensities of glucose-lowering therapies in people with type 2 diabetes suggest that the risk of myocardial infarction is reduced by glucose lowering approaches that increase the risk of severe hypoglycemia. However, the effect on cardiovascular death varied among the studies.[13]

With regards to the association of hypoglycemia and cardiovascular events, the bulk of evidence comes from glucose lowering therapy trials or trials of insulin therapy in hospitalized patients with critical illness and dysglycemia.

A meta-analysis of 26 trials of insulin therapy and mortality in hospitalized critically ill patients suggests that despite a 6-fold higher risk of hypoglycemic episodes, there was no increase in mortality. However, for the subgroup of diabetic people, the risks of hypoglycemia and mortality were not reported.[14]

Less attention has been paid to the glycemic management outside the critical care setting. It would now be considered dangerous and unethical to induce hypoglycemia in patients who have established coronary heart disease or considered to be at high risk of developing vascular disease. Moreover, documentation of hypoglycemic episodes is a very important issue. The aim of this study was to explore short term cardiovascular outcomes in relation to hypoglycemic events in non-critically ill people with type 2 diabetes switching to insulin therapy in their routine clinical care setting.

Patients and Materials

Study population

One hundred and twenty non-critically ill people with uncontrolled type 2 diabetes who were on oral glucose lowering drugs

Authors' affiliation: [1]Endocrine Research Center, Institute of Endocrinology and Metabolism, Iran University of Medical Sciences, Tehran, Iran.
•**Corresponding author and reprints:** Mohammad Ebrahim Khamseh MD, Firouzgar Alley, Valadi St., Behafarin St., Karimkhan Ave., Vali-asr Sq., Tehran, Iran. Tel: +98-21-88945172, Fax: +98-21-88945173, E-mail: khamseh.m@iums.ac.ir
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were enrolled in this study. They had not achieved the recommended glycated hemoglobin level of less than 7% and were considered eligible to initiate insulin therapy according to ADA/EASD guidelines.[15] No upper threshold for the level of blood glucose or glycated hemoglobin was set for inclusion in the study. Ethical approval was obtained from the ethics committee of Tehran University of Medical Sciences. All participants signed a written informed consent.

People with a documented history of any major cardiovascular event and those who experienced hypoglycemic episodes within the past six months prior to the enrollment were excluded from the study. This study was conducted in Tehran, Iran from January 2012 to January 2013.

Treatment Protocol

All participants initiated insulin therapy in an inpatient care setting. This was a routine clinical practice in Iran when insulin analogues were not available yet. Split-mixed insulin regimen (NPH/Regular insulin) was started and titrated according to the local protocols. All patients were allowed to continue biguanides and/or thiazolidinedione. However, sulfonylureas were discontinued at the time of insulin initiation. Titration was performed in accordance with the glucose monitoring data and all participants were discharged from the hospital in good medical condition.

Study follow-up

Insulin titration was done during hospitalization. At the time of discharge, all participants were educated to perform self-monitoring of blood glucose (SMBG) on a daily basis considering fasting, pre-meal and bedtime blood sugar levels. They were also asked to check and record their blood sugar when they had any symptoms referable to hypoglycemia (such as blurred vision, weakness, sweating, and shakiness). In addition to their routine follow-up care, they were contacted by telephone at weeks 12 and 24 after insulin initiation. The patients were asked about any hypoglycemia events and the occurrence of any major cardiovascular event. The diagnosis of cardiovascular events was confirmed based on hospital records.

Definition of hypoglycemia

Clinical symptomatic hypoglycemia was defined as a blood glucose level of less than 3.8 mmol per liter (70 mg/dL).[16] Patients with transient dysfunction of the central nervous system, who were unable to treat themselves and required help from others, were considered to have severe hypoglycemia. Patients with transient dysfunction of central nervous system who were able to treat themselves were considered to have minor hypoglycemia. Nocturnal hypoglycemia was defined as any hypoglycemic episode occurring during the night.

Clinical outcomes

The primary clinical outcome was the occurrence of the first major cardiovascular events (fatal and nonfatal myocardial infarction, death from cardiovascular cause, unstable angina, fatal or nonfatal stroke) leading to hospital admission or requiring medical intervention.

Statistical analysis

Analyses were performed for all participants. IBM SPSS for Windows Version 19 (IBM Corp., Armonk, NY, USA) was applied for statistical analysis. The data were analyzed anonymously. Descriptive statistics (means and SDs) were used to describe clinical and demographic characteristics. Categorical data and proportions were compared with χ^2-test and Spearman's rho. Histogram and Kolmogorov-Smirnov statistic test were used to assess the normality of continuous variables. For normally distributed variables, independent sample *t*-test was used to determine whether there was a statistically significant difference between groups. Mann-Whitney U was used for not normally distributed variables. Binary logistic regression analysis was also done considering the occurrence of the first major cardiovascular event as a dependent variable and hypoglycemia and systolic blood pressure as independent variables.

Results

We enrolled 120 people with type 2 diabetes in this study. The mean age of the participants was 58.23 ± 12.81 years and the mean duration of diabetes was 10.62 ± 5.64 years. Seventy eight percent of the participants were female.

Table 1 illustrates the demographic and biochemical variables of the study participants in relation to occurrence of the first major cardiovascular event during the follow-up period. There were not any significant differences regarding cardiovascular risk factors namely, hyperlipidemia, diastolic blood pressure, and prior CVD in patients who experienced more CV events. However, systolic blood pressure was significantly higher in this group.

During the follow-up, 43 (36%) patients reported to have hypoglycemia, 19 of whom experienced a major cardiovascular event. No episode of severe hypoglycemia was reported (Table 2). The mean HbA1c was 8.74% in patients who experienced hypoglycemia while it was 8.51% in those who did not experience hypoglycemic events ($P = 0.88$).

The rate of hypoglycemia in patients who experienced a major cardiovascular event was 5.29 event/patient/year which was higher than those who did not experience any cardiovascular event (2.88 events/patient/year). Furthermore, nocturnal hypoglycemia was more frequent in patients with major cardiovascular events (Table 3).

In a binary logistic regression analysis considering the occurrence of the first major cardiovascular event as a dependent variable, only occurrence of any hypoglycemic episode after initiation of insulin therapy was significantly correlated to the major cardiovascular event (Table 4).

The odds ratio for occurrence of the first major cardiovascular event relating to hypoglycemia was 7.41, CI = 2.15–25.47. The calculated risk ratio was 2.66, using the equation:

$$RR=\frac{OR}{(1-Pref)+(Pref\times OR)}\Big/\frac{OR}{(1-Pref)+(Pref\times OR)},$$

Where Pref is the incidence outcome in unexposed group.

Discussion

We found that symptomatic hypoglycemia is the only risk factor for occurrence of the first major cardiovascular event in non-critically ill people with type 2 diabetes initiating insulin therapy.

Improvements in glycemic control are usually associated with an increased risk of hypoglycemia.[17] It has been shown that acute hypoglycemia provokes activity of the sympathetic nervous

Table 1. Demographic and biochemical variables of the study population.

	All patients	Major Cardiovascular Event		*P*-value
		Yes	No	
	N = 120	N = 31	N = 89	
Age (yrs.)	58.23 ± 12.81	60.29 ± 12.49	57.51 ± 12.91	0.31
Female, *n* (%)	78 (65)	18 (58)	60 (67)	0.35
Diabetes duration (yrs.)	10.62 ± 5.64	11.58 ± 4.79	10.28 ± 5.90	0.27
Prior CVD, *n* (%)	34 (28.3%)	12 (39%)	22 (25%)	0.09
BMI	27.05 ± 4.44	26.33 ± 3.24	27.32 ± 4.81	0.43
HbA1c	8.71 ± 1.28	8.52 ± 1.19	8.76 ± 1.31	0.62
Systolic BP (mmHg)	123.81 ± 14.83	130.48 ± 15.29	121.32 ± 13.95	0.006
Diastolic BP (mmHg)	75.92 ± 8.30	76.61 ± 8.98	75.66 ± 8.07	0.41
Total cholesterol (mg/dL)	171.83 ± 43.93	182.21 ± 28.60	169.10 ± 46.96	0.14
Triglyceride (mg/dL)	188.61 ± 88.27	197.53 ± 88.18	182.49 ± 83.18	0.49
LDL (mg/dL)	93.94 ± 41.13	98.58 ± 32.43	92.66 ± 43.34	0.58
HDL (mg/dL)	45.13 ± 12.48	44.39 ± 12.79	45.31 ± 12.48	0.76
Insulin dose (dose/Kg)	0.84 ± 0.37	0.83 ± 0.31	0.85 ± 0.45	0.81

Table 2. Episodes of any type of hypoglycemia in all study participants and according to the occurrence of major cardiovascular event.

	All patients	Major Cardiovascular Event		*P*-value
		Yes	No	
	N = 120	N = 31	N = 89	
Total hypoglycemic events	210	82	128	
Patients, *n* (%)	43 (36)	19 (61)	24 (27)	0.001
One event (no. of people)	17	7	10	0.87
Two events (no. of people)	8	5	3	
Three or more events (no. of people)	18	7	11	
Rate (per person per year)	3.50	5.29	2.88	

Table 3. Episodes of nocturnal hypoglycemia in all study participants and according to the occurrence of major cardiovascular event.

	All patients	Major Cardiovascular Event		*P*-value
		Yes	No	
	N = 120	N = 31	N = 89	
Total nocturnal hypoglycemia events	95	47	53	
Patients, *n* (%)	23 (19.2)	11 (35.5)	12 (13.5)	0.007
One event (no. of people)	8	4	4	0.82
Two events (no. of people)	6	3	3	
Three or more events (no. of people)	9	4	5	
Rate (per person per year)	1.58	2.84	1.15	

Table 4. Binary logistic regression analysis for the occurrence of first major cardiovascular event.

	B	SE	*P*-value	Odds ratio	CI for odds ratio	
Systolic BP (mmHg)	0.021	0.024	0.368	1.022	0.975	1.070
Any hypoglycemia	2.003	0.630	0.001	7.410	2.155	25.477
Cholesterol	0.007	0.007	0.279	1.007	0.994	1.021
Prior CVD	0.966	0.721	0.180	2.627	0.640	10.785
Constant	-6.428	3.329	0.053	0.002		

BP = blood pressure; CVD = cardiovascular disease.

system and increases the secretion of potent vasoconstrictors,[12] thereby promoting destabilization of atherosclerotic plaques.[10] In addition, hypoglycemia has profound effects on cardiac function and significantly increases stroke volume and cardiac output.[18] It also promotes platelet aggregation that might precipitate cardiac and cerebral ischemic events in people with type 2 diabetes.[19,20]

Three large clinical trials investigate the risk of cardiovascular outcomes after in-hospital hypoglycemic episodes in patients with coronary artery disease or acute myocardial infarction. In the 2nd Diabetes Glucose and Acute Myocardial Infarction (DIGAMI) trial,[21] the risk of cardiovascular death was greater in people who experienced a hypoglycemic episode during the 2-year follow-up compared with individuals who did not. However, the risk was no longer present after adjustment for baseline characteristics (HR = 1.20, 95% CI: 0.69–2.0). Similar findings were reported from the other 2 clinical trials in people with diabetes who were admitted with acute MI.[22]

On the other hand, the risk of death in an ambulatory environment has been reported to be higher in people who experienced a minor or major hypoglycemic episode.[23,24] However, the participants either had documented coronary artery disease or cardiovascular risk factors.

The 4 large trials conducted in people with type 2 diabetes compared different intensities of glucose lowering therapies and allocated people to more versus less intensive glucose lowering. The risk of severe hypoglycemia in the intensive therapy arms versus standard arms varied from 1.9-fold in the Action in Diabetes and Vascular disease: Preterax Diamicrone MR Controlled Evaluation (ADVANCE) to 3.0-fold in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) and the UKPDS trials.[25] Despite this increase in the risk of severe hypoglycemia in intensive therapy arms, the overall risk of the first occurrence of major cardiovascular events has been reported to diminish modestly with intensive approach. However, it is possible that the impact of hypoglycemia was underestimated due to un-recorded episodes. On the other hand, it has been suggested that hypoglycemia might be confounded by other risk factors for adverse health related outcomes. The possible coexisting factors include renal disease, hepatic disease, cancer, cognitive decline, and other chronic diseases.[13]

The previous studies investigating the relationship between hypoglycemia and future cardiovascular events were based on patients recruited during hospitalization.[26,27] Recently, a nation-wide population based study found that even mild symptomatic hypoglycemia is associated with an increased risk of cardiovascular events.[28] The participants were recruited from real-world outpatient clinical practice. However, the patients who were prone to hypoglycemic episodes were more likely to have comorbidities such as heart disease, stroke, renal disease, hypertension, and liver disease.

In our study, the risk of the first major cardiovascular event was significantly higher in people who experienced symptomatic hypoglycemia in an ambulatory setting after adjusting for other major cardiovascular risk factors including age, sex, diabetes duration, hemoglobin A1c (HbA1c), blood pressure, lipid profile, and history of previous cardiovascular disease (CVD).

The occurrence of hypoglycemic episodes was confirmed by SMBG records. Furthermore, none of the participants had coexisting chronic morbidities. In addition, the rate of previous CVD was similar in those who experienced a major cardiovascular event with those who did not.

The strengths of this study include investigating the risk of cardiovascular events in non-critically ill people with type 2 diabetes during their routine management environment. In addition, the hypoglycemic episodes were recorded and reported by the participants. Moreover, none of the participants had coexisting risk factors such as hepatic or renal diseases. However, we could not record the duration of time for hypoglycemia to resolve, and the temporal relationship between hypoglycemia and the cardiovascular events. In addition, the markers of inflammation were not measured in this study.

In conclusion, the results support the notion that even mild hypoglycemia could be strongly associated with the occurrence of major cardiovascular events in non-critically ill people initiating insulin therapy in their real world during routine management of diabetes. Therefore, more attention should be paid in order to prevent hypoglycemia after initiation of insulin therapy in people with type 2 diabetes.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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References

1. Deckert T, Poulsen JE, Larsen M. Prognosis of diabetics with diabetes onset before the age of thirty-one. Ii. Factors influencing the prognosis. *Diabetologia*. 1978; 14(6): 371 – 377.
2. Morrish NJ, Wang SL, Stevens LK, Fuller JH, Keen H. Mortality and causes of death in the who multinational study of vascular disease in diabetes. *Diabetologia*. 2001; 44(2): S14 – S21.
3. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation*. 2002; 105(9): 1135 – 1143.
4. Pedersen-Bjergaard U, Pramming S, Heller SR, Wallace TM, Rasmussen AK, Jorgensen HV, et al. Severe hypoglycaemia in 1076 adult patients with type 1 diabetes: Influence of risk markers and selection. *Diabetes Metab Res Rev*. 2004; 20(6): 479 – 486.
5. UK Hypoglycaemia Study Group. Risk of hypoglycaemia in types 1 and 2 diabetes: Effects of treatment modalities and their duration. *Diabetologia*. 2007; 50(6): 1140 – 1147.
6. Frier BM. How hypoglycaemia can affect the life of a person with diabetes. *Diabetes Metab Res Rev*. 2008; 24(2): 87 – 92.
7. Fisher M, Heller SR. Mortality, cardiovascular morbidity and possible effects of hypoglycaemia on diabetic complications. *Hypoglycaemia in Clinical Diabetes*. United State: John Wiley & Sons, Ltd; 2007: 265 – 283.
8. Tattersall RB, Gill GV. Unexplained deaths of type 1 diabetic patients. *Diabet Med*. 1991; 8(1): 49 – 58.
9. Ewing DJ, Boland O, Neilson JM, Cho CG, Clarke BF. Autonomic neuropathy, qt interval lengthening, and unexpected deaths in male diabetic patients. *Diabetologia*. 1991; 34(3): 182 – 185.
10. DeFronzo RA, Hendler R, Christensen N. Stimulation of counterregulatory hormonal responses in diabetic man by a fall in glucose concentration. *Diabetes*. 1980; 29(2): 125 – 131.
11. Robinson RT, Harris ND, Ireland RH, Lindholm A, Heller SR. Comparative effect of human soluble insulin and insulin aspart upon hypoglycaemia-induced alterations in cardiac repolarization. *Br J Clin Pharmacol*. 2003; 55(3): 246 – 251.
12. Wright RJ, Frier BM. Vascular disease and diabetes: Is hypoglycaemia an aggravating factor? *Diabetes Metab Res Rev*. 2008; 24(5): 353 – 363.
13. Yakubovich N, Gerstein HC. Serious cardiovascular outcomes in diabetes: The role of hypoglycemia. *Circulation*. 2011; 123(3): 342 – 348.
14. Griesdale DE, de Souza RJ, van Dam RM, Heyland DK, Cook DJ, Malhotra A, et al. Intensive insulin therapy and mortality among critically ill patients: A meta-analysis including nice-sugar study data. *CMAJ*. 2009; 180(8): 821 – 827.
15. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes: A patient-centered approach: Position statement of the american diabetes association (ada) and the european association for the study of diabetes (easd). *Diabetes Care*. 2012; 35(6): 1364 – 1379.
16. American Diabetes Association. Standards of medical care in diabetes--2012. *Diabetes Care*. 2012; 35(1): S11 – S63.
17. 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 (ukpds) group. *Lancet*. 1998; 352(9131): 837 – 853.
18. Hilsted J, Bonde-Petersen F, Norgaard MB, Greniman M, Christensen NJ, Parving HH, et al. Haemodynamic changes in insulin-induced hypoglycaemia in normal man. *Diabetologia*. 1984; 26(5): 328 – 332.
19. Hutton RA, Mikhailidis D, Dormandy KM, Ginsburg J. Platelet aggregation studies during transient hypoglycaemia: A potential method for evaluating platelet function. *J Clin Pathol*. 1979; 32(5): 434 – 438.
20. Frier BM, Corrall RJ, Davidson NM, Webber RG, Dewar A, French EB. Peripheral blood cell changes in response to acute hypoglycaemia in man. *Eur J Clin Invest*. 1983; 13(1): 33 – 39.
21. Malmberg K, Ryden L, Wedel H, Birkeland K, Bootsma A, Dickstein K, et al. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (digami 2): Effects on mortality and morbidity. *Eur Heart J*. 2005; 26(7): 650 – 661.
22. Goyal A, Mehta SR, Diaz R, Gerstein HC, Afzal R, Xavier D, et al.

Differential clinical outcomes associated with hypoglycemia and hyperglycemia in acute myocardial infarction. *Circulation*. 2009; 120(24): 2429 – 2437.
23. Fisman EZ, Motro M, Tenenbaum A, Leor J, Boyko V, Mandelzweig L, et al. Is hypoglycaemia a marker for increased long-term mortality risk in patients with coronary artery disease? An 8-year follow-up. *Eur J Cardiovasc Prev Rehabil*. 2004; 11(2): 135 – 143.
24. Bonds DE, Miller ME, Bergenstal RM, Buse JB, Byington RP, Cutler JA, et al. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the accord study. *BMJ*. 2010; 340: b4909.
25. Turnbull FM, Abraira C, Anderson RJ, Byington RP, Chalmers JP, Duckworth WC, et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. *Diabetologia*. 2009; 52(11): 2288 – 2298.
26. Svensson AM, McGuire DK, Abrahamsson P, Dellborg M. Association between hyper- and hypoglycaemia and 2 year all-cause mortality risk in diabetic patients with acute coronary events. *Eur Heart J*. 2005; 26(13): 1255 – 1261.
27. Kosiborod M, Inzucchi SE, Krumholz HM, Xiao L, Jones PG, Fiske S, et al. Glucometrics in patients hospitalized with acute myocardial infarction: Defining the optimal outcomes-based measure of risk. *Circulation*. 2008; 117(8): 1018 – 1027.
28. Hsu PF, Sung SH, Cheng HM, Yeh JS, Liu WL, Chan WL, et al. Association of clinical symptomatic hypoglycemia with cardiovascular events and total mortality in type 2 diabetes: a nationwide population-based study. *Diabetes Care*. 2013; 36(4): 894 – 900.