

# Clinical characteristics and outcomes of symptomatic and asymptomatic hypoglycemia in hospitalized patients with diabetes

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## ABSTRACT

**Importance** The frequency and impact of asymptomatic hypoglycemia in hospitalized patients with diabetes is not known.

**Objective** We determined the clinical characteristics and hospital outcomes of general medicine and surgery patients with symptomatic and asymptomatic hypoglycemia.

**Research design and methods** Prospective observational study in adult patients with diabetes and blood glucose (BG) <70 mg/dL. Participants were interviewed about signs and symptoms of hypoglycemia using a standardized questionnaire. Precipitating causes, demographics, insulin regimen, and complications data during admission was collected.

**Results** Among 250 patients with hypoglycemia, 112 (44.8%) patients were asymptomatic and 138 (55.2%) had symptomatic hypoglycemia. Patients with asymptomatic hypoglycemia were older (59±11 years vs 54.8±13 years, p=0.003), predominantly males (63% vs 48%, p=0.014), and had lower admission glycosylated hemoglobin (8.2%±2.6% vs 9.1±2.9%, p=0.006) compared with symptomatic patients. Compared with symptomatic patients, those with asymptomatic hypoglycemia had higher mean BG during the episode (60.0±8 mg/dL vs 53.8±11 mg/dL, p<0.001). In multivariate analysis, male gender (OR 2.08, 95% CI 1.13 to 3.83, p=0.02) and age >65 years (OR 4.01, 95% CI 1.62 to 9.92, p=0.02) were independent predictors of asymptomatic hypoglycemia. There were no differences in clinical outcome, composite of hospital complications (27% vs 22%, p=0.41) or in-hospital length of stay (8 days (IQR 4–14) vs 7 days (IQR 5–15), p=0.92) between groups.

**Conclusions** Asymptomatic hypoglycemia was common among insulin-treated patients with diabetes but was not associated with worse clinical outcome compared with patients with symptomatic hypoglycemia. Older age and male gender were independent risk factors for asymptomatic hypoglycemia.

## INTRODUCTION

Clinical guidelines for the management of hospitalized patients with diabetes define hypoglycemia as blood glucose lower than 70

## Significance of this study

### What is already known about this subject?

▶ Hypoglycemia is a common complication in hospitalized patients, reported in up to one-third of general medicine and surgery patients treated with insulin. Inpatient hypoglycemia has been associated with increased morbidity and mortality.

### What are the new findings?

▶ In this prospective observational study, we found that 45% of insulin-treated patients with blood glucose <70 mg/dL had asymptomatic hypoglycemia.  
▶ In multivariate analysis, older age and male gender were associated with higher risk of asymptomatic hypoglycemia.

### How might these results change the focus of research or clinical practice?

▶ Our results support current guideline recommendations on the need for blood glucose monitoring in insulin-treated patients in general wards.  
▶ Clinicians should be aware of the high incidence of hypoglycemia, which has been associated with increased incidence of hospital complications compared with patients without hypoglycemia.

mg/dL.<sup>1,2</sup> Hypoglycemia is the most common complication of intensified insulin treatment and represents a major barrier to satisfactory long-term glycemic control.<sup>3,4</sup> In randomized clinical trials, the reported incidence of hypoglycemia in the intensive care unit (ICU) has ranged between 5% and 28%,<sup>5–8</sup> and a similar prevalence has been reported in the non-ICU settings, where 5%–32% of patients treated with insulin develop hypoglycemia.<sup>4,9–13</sup> A large body of evidence indicates a strong association between the development of hypoglycemia and poor clinical outcomes.<sup>14–17</sup> Turchin *et al* reported that patients with inpatient hypoglycemia experienced a 66%

increased risk of death within 1 year and spent 2.8 days longer in hospital compared with those without hypoglycemia.<sup>15</sup> In addition, numerous retrospective and intervention studies in the general medicine and surgery services reported that hypoglycemia was associated with increased length of stay (LOS), need for ICU admission, and hospital mortality.<sup>15 16 18–21</sup>

Bedside capillary point of care (POC) testing is recommended as the preferred method for glucose monitoring and for guiding glycemic management of patients in non-ICU settings.<sup>22</sup> POC testing is usually performed before meals and at bedtime for patients who are eating or every 4–6 hours for patients who are not eating or receiving continuous enteral nutrition.<sup>17</sup> Recent studies using continuous glucose monitoring in the hospital have reported that the current practice of measuring POC testing frequently misses episodes of hypoglycemia<sup>23–26</sup> and that over a quarter of episodes 26.3% of hypoglycemia events were asymptomatic and not recognized by POC testing.<sup>23 27</sup>

To investigate the clinical characteristics of hospitalized patients with asymptomatic and symptomatic hypoglycemia and its impact on clinical outcome, we designed an alert system of hypoglycemic events to prospectively interview patients with BG <70 mg/dL about signs and symptoms of hypoglycemia using a standardized and validated questionnaire.

## SUBJECTS AND METHODS

This was a single-center, prospective study in 250 general medicine and surgery patients with diabetes who experienced hypoglycemia during the hospital stay. Patients with a known history of type 1 or type 2 diabetes and age between 18 years and 80 years were recruited from general medicine and surgery services at Grady Memorial Hospital and Emory University Hospital in Atlanta, Georgia, between April 2015 and August 2016. Patients without a known history of diabetes, pregnancy, and those unable to provide consent or understand the questionnaire questions were excluded.

The nursing staff and laboratory personnel were instructed to immediately notify our research team for all patients with a BG <70 mg/dL during weekdays, by either laboratory value or by POC testing. The study team approached patients after reviewing medical records and confirming the diagnosis of diabetes and treatment regimen. After providing written informed consent, patients were asked about the presence of symptoms and signs of hypoglycemia using a standardized questionnaire adapted from studies by Cox *et al*,<sup>28</sup> as well as information on potential precipitating cause(s) and hospital insulin regimen. Most patients were seen within 2 hours of the event and all patients within 4 hours of detection of blood glucose values. Symptoms were collected only during the first hypoglycemia episode, and no information was collected during subsequent events. Symptoms were categorized as neurogenic/adrenergic or neuroglycopenic.

The study team collected information on: (1) admission service, admitting diagnosis and demographic information, (2) hyperglycemia treatment, (3) number of hypoglycemic episodes by point-of-care testing or laboratory during hospital stay following indexed event, (4) history of hypoglycemia before admission in the ambulatory setting, (5) glycosylated hemoglobin (HbA1c) on admission or within the last 3 months prior to admission, (6) outpatient diabetes treatment, (7) treatment of indexed hypoglycemia episode, (8) value of POC glucose testing following the event, and (9) risk factors for hypoglycemia including impaired kidney and liver function, presence of infection, and use of antibiotics or beta-blockers. The study team also examined patients' hospital outcomes including: LOS, mortality, cardiovascular events (myocardial infarction and arrhythmias), nosocomial infections, pneumonia, bacteremia, respiratory failure, and acute kidney injury (defined as increase in serum creatinine by 50% or more from baseline). We report a composite of complications, including: cardiovascular events, infections, respiratory failure, and acute kidney injury, need for surgical reintervention, stroke, gastrointestinal bleeding, and blood transfusions.

## Statistical analysis

We quantified demographics and clinical characteristics of patients with hypoglycemia with and without symptoms. For continuous variables, depending on normality of data, Student's t-tests or non-parametric Wilcoxon tests were used to assess the differences between those with symptomatic and asymptomatic hypoglycemia. For discrete variables,  $\chi^2$  tests or Fisher's exact tests was used to examine differences between those with symptomatic and asymptomatic hypoglycemia. We used logistic regression to identify predictors of asymptomatic hypoglycemia. The following covariates were included: age, gender, HbA1c, estimated glomerular filtration rate, body mass index (BMI), and blood glucose level at time of event. All tests were two sided, with statistical significance set at  $p < 0.05$ . Statistical analyses were conducted using SAS, V.9.3.

## RESULTS

### Baseline demographic and clinical characteristics

The study cohort consisted of 250 patients with diabetes who developed hypoglycemia during hospitalization. The baseline demographic and clinical characteristics of the overall cohort are shown in [table 1](#). The population consisted of middle-age adults (mean age 56.7±12 years), mostly African-Americans (81%) and male gender (55%). Most patients had type 2 diabetes (93%), a mean duration of diabetes of 13.9±9 years, 85% of patients were admitted to medicine services and the mean admission HbA1c was 8.7%±2.8. The LOS was 8 days (IQR: 4–15). The mean admission BG was 236±173 mg/dL. The average BG on the day before the hypoglycemic event was 154±66 mg/dL. The average BG during the hypoglycemia event for

**Table 1** Demographic and clinical characteristic of patients with hypoglycemia

Characteristics	Symptomatic 138 (55%)	Asymptomatic 112 (45%)	P values
Age, years	54.8±12.7	59.0±10.6	0.003
Gender			0.014
Female	72 (52)	41 (37)	
Male	66 (48)	71 (63)	
Race			0.37
African-American	110 (80)	90 (81)	
Hispanic	7 (5)	6 (5)	
White	19 (14)	11 (10)	
Other	1 (1)	4 (4)	
Admission HbA1c, %	9.1±2.9	8.2±2.6	0.006
Duration of diabetes, years	13.8±9.1	14±9.3	0.79
Diabetes (DM) type			
DM type 1	11(8)	6 (5)	0.46
DM type 2	127 (92)	106 (95)	
# Hypo events, median	2.0 (1.0, 4.0)	2.0 (1.0, 3.0)	0.009
Admission BG, mg/dL	248.2±183	220.7±159	0.43
Outpatient diabetes treatment			0.24
No treatment	6 (4)	6 (5)	
Diet only	8 (6)	14 (13)	
Insulin only	80 (58)	51 (46)	
OAD/GLP1 only	21 (15)	20 (18)	
OAD/GLP1+insulin	23 (17)	20 (18)	
Hospital diabetes treatment			
Basal+SSI	45 (33)	26 (23)	0.10
Basal+bolus	61 (44)	48 (43)	0.83
Basal+bolus+OAD	0 (0)	2 (2)	0.20
SSI only	18 (13)	16 (14)	0.78
OAD+basal insulin	2 (1)	8 (7)	0.046
OAD+SSI	3 (2)	0 (0)	0.26
GLP1+SSI	0 (0)	1 (1)	0.44
No treatment	9 (7)	11 (10)	0.36
Blood glucose during hypoglycemia episode			
Mean BG during hypoglycemia, mg/dL	53.8±11.4	60.0±8.3	<0.001
BG values between 60 mg/dL and 69 mg/dL, n (%)	58 (42)	73 (65)	
BG values between 40 mg/dL and 59 mg/dL, n (%)	63 (46)	37 (33)	
BG values <54 mg/dL, n (%)	60 (43)	22 (20)	
BG values <40 mg/dL, n (%)	17 (12)	2 (2)	

Data are n (%), mean±SD or median (IQR).

To convert HbA1c value in % to mmol/mol= $10.93 \times \% \text{HbA1c value} - 23.5$ , BG value in mg/dL to mmol/L= $\text{BG mg/dL value} / 18$ .

DM, diabetes mellitus; BG, blood glucose; GLP-1, Glucagon-like peptide 1; OAD, Oral antidiabetic drug; SSI, sliding scale insulin.

the entire cohort was 56.6±10.6 mg/dL. A total of 131 (52%) had a BG between 60 mg/dL and 69 mg/dL, 82 (33%) had a BG <54 mg/dL, and 19 (8%) had a BG <40 mg/dL.

There were no differences in baseline clinical characteristics between patients with or without hypoglycemic symptoms including BMI, race, previous antidiabetic treatment, type of diabetes, diabetes duration, admission

service, renal failure, liver failure, heart failure, beta-blockers or antibiotics use or oral intake status; the median number of hypoglycemia episodes was statistically significant ( $p=0.009$ ) but not of clinical significance (tables 1–2).

Patients with asymptomatic hypoglycemia were older (59±10.6 years vs 54.8±12.7 years,  $p=0.003$ ), more likely to be male (63% vs 37%,  $p=0.014$ ) and had lower admission

**Table 2** Risk factors and hospital complications in patients with symptomatic and asymptomatic hypoglycemia

	Symptomatic hypoglycemia	Asymptomatic hypoglycemia	P values
<b>Risk factors</b>			
Reduced oral intake	49 (39)	48 (48)	0.15
eGFR <60 at time of episode	69 (51)	62 (56)	0.42
Liver disease	7 (5)	3 (3)	0.52
Heart failure	29 (21)	16 (14)	0.17
Infection	50 (36)	33 (31)	0.33
<b>Other medications</b>			
Antibiotics	45 (33)	35 (31)	0.82
Beta blockers	47 (34)	45 (40)	0.32
History of previous hypoglycemia episodes	0.2±0.4	0.1±0.4	0.44
<b>Complications</b>			
Inpatient complications	30 (22)	29 (27)	0.41
Cardiovascular event	4 (3)	6 (5)	0.35
Nosocomial infection	4 (3)	6 (5)	0.35
Respiratory failure	0 (0)	6 (5)	0.0075
Acute kidney injury	16 (12)	16 (14)	0.53
Stroke	0 (0)	2 (2)	0.20
Gastrointestinal bleed	1 (1)	2 (2)	0.59
Transfusion	0 (0)	3 (3)	0.09

Data are n (%).

eGFR, estimated glomerular rate filtration.

HbA1c (8.2%±2.6 vs 9.1%±2.9,  $p=0.006$ ), compared with patients with symptomatic hypoglycemia (table 2). The glucose level during the hypoglycemia episode was higher in patients with asymptomatic hypoglycemia compared with patients with symptomatic hypoglycemia (60±8.3 vs 53.8±11.4 mg/dL,  $p<0.001$ ). Among patients with symptomatic hypoglycemia, most commonly reported symptoms were adrenergic symptoms such as sweating (61%), trembling (55%), and anxiety (52%), followed by confusion or difficulty in concentration (52%), and dry mouth (44%), table 3.

A total of 59 patients (24%) experienced ≥1 hospital complications during the hospital stay. There were no differences in complications (27% vs 22%,  $p=0.41$ ), table 3 or in the hospital LOS (8 days (IQR 4–14) vs 7 days (IQR 5–15),  $p=0.92$ ) between patients with asymptomatic and symptomatic hypoglycemia. There were no differences in the hospital treatment or type of insulin regimen between groups except for hospital treatment with oral agents and insulin ( $p=0.0461$ ).

### Hypoglycemia risk factors

A total of 131 (53%) patients with hypoglycemia had a glomerular filtration rate <60 mL/min at time of the hypoglycemic episode, 97 patients (43%) had poor oral intake or were nil per os (NPO) at some point during the admission, other risk factors and concomitant medications are described in table 2. Patients were treated in the hospital with basal-bolus insulin regimen, basal plus

correctional insulin per sliding scale (SSI), or combination of insulin and oral agents, or with sliding-insulin scale alone (table 1).

In multivariate analysis for predictors of asymptomatic hypoglycemia including age, gender, renal function, blood glucose, BMI and HbA1c value, we found that

**Table 3** Frequency of hypoglycemic symptoms

	n (%)
<b>Adrenergic symptoms</b>	
Sweating	79 (61)
Anxiety	70 (52)
Trembling	72 (55)
Dry mouth	57 (44)
Hand coldness	46 (35)
Heart pounding	38 (29)
Hunger	13 (9)
Nausea	9 (7)
<b>Neurological symptoms</b>	
Confusion/low concentration	70 (52)
Blurred vision	53 (40)
Slurred speech	39 (30)
Numbness around lips	21 (16)
Headache	11 (8)

**Table 4** Predictors of asymptomatic hypoglycemia

	OR	(95% CI)
HbA1C	0.94	(0.84 to 1.05)
Age <50 years	1 (ref)	
50–58 years	1.73	(0.76 to 3.96)
59–64 years	2.55	(1.11 to 5.84)
≥65 years	4.01	(1.62 to 9.92)
BG level during hypoglycemic event	1.07	(1.04 to 1.1)
Male gender	2.08	(1.13 to 3.83)
GFR ≥60 versus GFR <60	0.70	(0.39 to 1.26)
BMI	0.99	(0.95 to 1.02)

BG, blood glucose; BMI, body mass index; GFR, glomerular filtration rate; HbA1C, glycosylated hemoglobin.

older age and male gender were independent predictors of asymptomatic hypoglycemia, with men having two times higher odds than women (OR 2.08, CI 1.13 to 3.83,  $p=0.02$ ) (table 4). These relationships were independent of glucose levels at the time of the indexed event. In multivariate analysis adjusted for age, gender, renal function, LOS, and race, we found no significant association between a composite of complications and asymptomatic hypoglycemia ( $p=0.7$ ).

## DISCUSSION

The results of this prospective observational study indicate that asymptomatic hypoglycemia is observed in almost half of insulin-treated general medicine and surgery patients with diabetes. Age and male gender were identified as independent predictors of asymptomatic hypoglycemia, with males having two-times higher odds than females, and older patients ≥65 years having fourfold higher odds of asymptomatic hypoglycemia compared with younger patients. There were no differences in hospital-related complications or duration in LOS between patients with or without hypoglycemia symptoms.

According to Endocrine Society and the American Diabetes Association guidelines,<sup>29</sup> inpatient hypoglycemia is defined as a BG ≤70 mg/dL, which may be independent of the presence of adrenergic or neurological symptoms. The threshold at which patients experience symptoms varies from person to person and depends primarily on the severity of hypoglycemia. In our study, we observed that the average BG in patients with symptomatic hypoglycemia was 53.8±11 mg/dL, and asymptomatic event had a BG of 60.0±8 mg/dL and that most patients with glucose values above 50 mg/dL had asymptomatic events. These results support the recent International Hypoglycemia Study Group report, which recommended a glucose concentrations of less than 3.0 mmol/L (54 mg/dL) to be considered as clinical significant hypoglycemic event and that a blood glucose level of <70 mg/dL should only be considered an alert value and

may be used as a threshold for further titration of insulin regimen.<sup>30 31</sup>

Previous studies have reported that increasing age is an independent risk factor for the development of hypoglycemia in insulin-treated patients with type 2 diabetes.<sup>4</sup> It has also been shown that elderly patients frequently fail to communicate symptoms of hypoglycemia to hospital staff<sup>32</sup> and develop hypoglycemic symptoms at a significantly lower glucose concentration compared with younger patients.<sup>33</sup> These factors often lead to more prolonged and more severe hypoglycemia in the elderly. In agreement with these reports, older patients were more likely to have asymptomatic events and that age of 65 years (OR 4.08, 95% CI 1.65 to 10.07,  $p=0.01$ ) was an independent predictor of asymptomatic hypoglycemia. Implementing the strategies to reduce hypoglycemia, either by avoidance of intensive glycemic control or using agents associated with lower rates of hypoglycemia,<sup>17 34</sup> can lead to significant reduction in hypoglycemia rates, improvement in patient's safety and overall quality of care in elderly population.

Our study has several of strengths. This is the first prospective study aimed to determine the frequency of asymptomatic hypoglycemia in insulin-treated hospitalized patients in general wards. We used a validated outpatient instrument to score symptoms of hypoglycemia<sup>28</sup> with patients seen shortly after the episode of hypoglycemia. We recognize, however, several limitations including a selected population from a single academic institution, with a large population of African-Americans with type 2 diabetes. We limited POC testing to our standard of care before meals and bedtime. Newer technologies such as continuous glucose monitoring has been shown to provide a more comprehensive 24-hour glycemic evaluation and has been shown to be better than POC testing in recognizing episodes of hypoglycemia in insulin-treated patients in the hospital.<sup>23</sup> In addition, we did not collect information to determine if asymptomatic individuals had hypoglycemia unawareness. Future studies using continuous glucose monitoring may help to identify a larger number and durations of asymptomatic events.<sup>23 29</sup>

## CONCLUSION

In summary, the results of this prospective study indicate asymptomatic hypoglycemia is common and is present in about half of insulin-treated patients with diabetes in general wards. In multivariate analysis, male gender and age ≥65 years were independent predictors of asymptomatic hypoglycemia. There were no differences in clinical outcome, composite of hospital complications or in hospital LOS between patients with asymptomatic hypoglycemia compared with patients with symptomatic presentation.

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**Contributors** GEU 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. GEU wrote the initial research proposal. PCG, SC, and GEU wrote the manuscript. FJP, RJG, PV, IA, CR, MAU, JSH and MF reviewed/edited the research proposal and manuscript and contributed to the discussion. HW conducted the statistical analysis.

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