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ORIGINAL ARTICLE

Outcomes of Community-Dwelling Adults without Diabetes Mellitus Who Require Ambulance Services for Hypoglycemia

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Abstract

Objective:

We evaluate the prevalence, etiology, and outcomes of hypoglycemia requiring emergency medical services (EMS) in patients without diabetes mellitus (non-DM).

Methods:

We reviewed medical records of all ambulance calls for non-DM with blood glucose <70 mg/dl in Olmsted County, Minnesota, between January 1, 2003, and December 31, 2009.

Results:

A total of 131 patients (age 51 ± 19 years; 54 % females) made 142 EMS calls, while 10 patients made repeated calls. Causes of hypoglycemia were critical illness (42; 32%), alcohol and polysubstance use (36; 27.5 %), insulinoma/bariatric surgery (10; 8%), restricted oral intake (7; 5%), and multiple factors (3; 27.5 %). Patients with alcohol and polysubstance abuse were younger (p = .002). A total of 54 patients had additional hypoglycemia predisposing comorbidities/factors [adrenal insufficiency (2), end-stage renal disease (11) and chronic liver disease (7), beta blockers use (34), and pentamidine use (1)]. Repeated calls and emergency room transportation were similar, but hospitalization varied across the etiologies, with the lowest proportion in the multiple-factor-related hypoglycemia group (p = .01). Duration of follow-up was 1.28 (interquartile range 0.13–2.70) years. A total of 38 patients died, and age-adjusted mortality varied across different etiologies (p < .001), with highest among critically ill. Cancer caused the highest number of deaths (7/38; 18%), while 1 death was due to hypoglycemia.

Conclusions:

There were multiple etiologies for hypoglycemic episodes in community-dwelling non-DM that required EMS. Critical illness, multifactorial causes, and alcohol/polysubstance abuse were common causes. Hospitalization and mortality were higher with critical illnesses.

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Abbreviations: (AI) adrenal insufficiency, (CLD) chronic liver disease, (DM) diabetes mellitus, (EMS) emergency medical services, (ERT) emergency room transportation, (ESRD) end-stage renal disease, (IQR) interquartile range, (non-DM) patients without diabetes mellitus

Keywords: emergency medical services, emergency room, hypoglycemia, non-diabetes

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Introduction

Hypoglycemia is a common complication in diabetes mellitus (DM), but it can also occur in patients without diabetes mellitus (non-DM). Hypoglycemia in non-DM may not be promptly diagnosed because it is not always suspected as a cause of clinical manifestations in non-DM. Hypoglycemia has been reported in hospitalized patients with severe underlying illness and is associated with poor outcomes.[1] Hypoglycemia may occur in ambulatory care because of different reasons. Outpatients experiencing hypoglycemia may be critically ill or in relatively stable ambulatory state. Possible causes of hypoglycemia in non-DM are adrenal insufficiency (AI); end-stage renal disease (ESRD); chronic liver disease (CLD); post-bariatric surgery; insulinoma; use of certain medications; alcohol intoxication, especially on an empty stomach; hypopituitary state; cancers cachexia; prolonged fasting or starvation; malnutrition; inborn errors of carbohydrate, fat, amino acid, or organic acid metabolism; and alterations of metabolism associated with infection or failure of various organ systems.[2–4]

Postprandial hypoglycemia caused by abnormal insulin secretion after a large meal of carbohydrate can occur in obese people after bariatric surgeries, though the frequency is unknown.[5,6] Insulin secretagogues, alcohol, and medications such as cibenzoline, gatifloxacin, pentamidine, quinine, and indomethacin have been reported to cause hypoglycemia with moderate quality of evidence.[7] Similarly, many other drugs have been reported to cause hypoglycemia with a low quality of evidence.[7] Even though many causes of hypoglycemia have been reported in non-DM, epidemiology of hypoglycemia requiring emergency medical services (EMS) in a population-based cohort has not been reported previously.

We have reported that hypoglycemic episodes requiring EMS for revival are not uncommon in non-DM, and such episodes have poor long-term outcomes compared with the DM population.[8] The higher rate of such outcomes, including emergency room transportation (ERT), hospitalization, and mortality, could be due to the severe nature of underlying illness or the more severe presentation of hypoglycemia in such patients or both. Higher mortality among hospitalized myocardial ischemia patients have been reported after iatrogenic hypoglycemia, but irrespective of DM status.[1] Also, such data are lacking for non-DM who experience hypoglycemia in ambulatory settings. The main objectives of our study were to elaborate on the underlying causes of hypoglycemia requiring EMS in a population-based cohort of non-DM and to analyze the long-term morbidity and mortality associated with such hypoglycemic episodes. This report provides the contemporary prevalence of such events associated with different etiologies, and long-term outcomes.

Methods

This study was approved by the Mayo Clinic Institutional Review Board.

Study Group

We retrospectively searched the Gold Cross Ambulance database from January 1, 2003, to December 31, 2009, and captured all ambulance calls made by non-DM in Olmsted County with reflectance meter glucose levels of less than 70 mg/dl at the time of call. Gold Cross Ambulance personnel check reflectance meter glucose in all subjects who present with coma, loss of consciousness, confusion, disorientation, and dizziness or critically ill patients irrespective of clinical presentations. Accuracy of reflectance meters are tested once in a month by measuring the plasma glucose level for quality control and reliability of the instrument. Patients are treated at the site and then transported to the emergency room based on their general health condition and wishes. Our cohort included patients above 18 years of age who authorized the use of their medical records for research.

We reviewed medical records to retrieve baseline demographics such as age, gender, plasma glucose concentration, mode of revival, and risk factors such as medication use, alcohol intoxication, drug overdose, polysubstance abuse, CLD, ESRD, and AI. We also analyzed outcomes, including ERT, hospitalization, hospital stay, endocrinology referral, hypoglycemia recurrence, and mortality. Medication overdose, polysubstance abuse, and alcohol intoxication were confirmed with blood and urine drug screen tests. Previously published methods were used to ascertain CLD, ESRD, and AI.[9–11] Patients were categorized as critically ill if they had acute hepatic, acute renal, cardiac, or multiorgan failure or sepsis or inanition or multisystem involvement with poor general condition.

Mortality

Mortality data, including date of death and mortality causes, were obtained from Mayo Clinic records and social security death master file. Whenever available, autopsy reports were also reviewed.

Analysis

Continuous variable summaries are reported as mean ± standard deviation or median and interquartile range (IQR; Q1–Q3), and categorical variable summaries are reported as counts and percentages. Baseline factors and outcomes among different risk factors were tested with chi-square or analysis of variance methods. Mortality risk associated with different risk factors was estimated using a Cox proportional hazards model adjusted for age. Early and late mortality groups were compared for different outcomes using chi-square or Fisher test as appropriate. All statistical analyses were done with JMP 8 and SAS 9 (SAS institute, Cary, NC).

Results

A total of 148 patients experienced hypoglycemia, but only 131 were included for further analysis, while the rest were excluded because of incomplete data. A total of 131 patients made 142 ambulance calls during the study period, while 10 patients made more than 1 ambulance call. These calls represent 0.45% of the total (31,540) EMS calls made during the study period. Of 148 patients, 96 were from Olmsted County, and 48 were from other places and temporarily staying in Olmsted County, with residency status unknown for remaining 4 patients. The population of Olmsted County aged 18 or above in 2003 was estimated to be 96,528 as per 2000 census,[12] thus resulting in 0.14% prevalence of hypoglycemia among non-DM during the study period. Median reflectance meter glucose concentration at scene was 52 (IQR 41–61) mg/dl. Most of the patients were revived with intravenous dextrose (93%), with the remaining requiring oral glucose, oral glucose + glucagon, or intravenous dextrose + glucagon (**Table 1**). Baseline demographics are described in **Table 1**. Mean age was 51 ± 19 years, with 54% females. Patients in the alcohol or medication intoxication group were younger than others [41 (IQR 33.3–48) versus 56 (IQR 39–71) years; $p = .002$].

Hypoglycemia Predisposing Comorbidities and Drugs

A total of 54 patients had additional hypoglycemia predisposing comorbidities/factors [AI (2), ESRD (11), and CLD (7) and medications causing hypoglycemia (35)], with 1 patient having both ESRD and CLD. All except 1 patient on hypoglycemia-causing medications were on beta blockers. None of the patients were on gatifloxacin, clinafloxacin, quinine, cibenzoline, and indomethacin, medications known to have moderate association with hypoglycemia.[7]

Table 1.
Baseline Demographics for Patients without Diabetes Mellitus Who Required Emergency Medical Services for Hypoglycemia in Olmsted County 2003–2009 (n = 131)

Age (standard deviation), years	51 (19)
Females (%)	71 (54)
Patients with single hypoglycemic call (%)	121 (92)
Patients with repeated hypoglycemic calls (%) Beta-blockers use Comorbidities Insulinoma	(8) 2 1 3
CLD (%)	7 (5)
ESRD (%)	11 (8)
Adrenal insufficiency (%)	2 (1.5)
Drugs predisposing to hypoglycemia Beta blockers (%) Pentamidine (%)	 34 (26) 1 (1)
Plasma blood level (mg/dl) at the time of ambulance arrival	52 (IQR 41–61)
Revival Intravenous dextrose (%) Intravenous dextrose + glucagon (%) Oral glucose (%) Oral glucose + glucagon (%)	 122 (93.1) 6 (4.6) 1 (0.8) 2 (1.5)

Causes Of Hypoglycemia and Clinical Presentation

Details about hypoglycemia causes and clinical presentation are described in **Table 2**. The cohort was divided into five groups for further analysis, based on the underlying causes of hypoglycemia: critical illness, poor oral intake, alcohol or medication intoxication, insulinoma or bariatric surgery, and multiple factors. Alcohol or medication intoxication (antidepressants, tramadol, benzodiazepine, amphetamine, methamphetamine, opioids, and salicylate) was confirmed with laboratory values in 34/36 (95%) patients. Mean alcohol level was 2736 ± 1069 μg/dl.

Outcomes

Repeated calls, ERT, and endocrinology consultation were similar between the groups ($p = .28$, .67, and .29, respectively; **Table 3**). Emergency room transportation was also similar between patients with or without chronic organ failure (CLD, ESRD, AI; 89% versus 84%; $p = 1.00$). Hospitalization varied across the different groups, with the lowest rate among patients with hypoglycemia due to multiple factors (**Table 3**). However, duration of hospital stay did not vary between the groups. Hospitalization was higher among patients with chronic organ failure compared with those without chronic organ failure (72% versus 46%; $p = .04$).

Total duration of follow-up was 1.28 (IQR 0.13–2.70) years. Thirty-eight patients died during follow-up. Age-adjusted mortality varied across the five groups ($p < .001$) and the highest rate was among the patients with hypoglycemia due to critical illnesses. No patient died in the insulinoma or bariatric surgery group (**Table 3**). After adjusting for age and hypoglycemia-causing etiologies, mortality risk was not different between those who required ERT versus no ERT, hospitalization versus no hospitalization ($p = .46$ and .44, respectively), and chronic organ failure versus no chronic organ failure ($p = .06$).

Of 38, 21 (55%) had autopsy confirmation. Different causes for mortality are described in **Table 4**. Cancer caused maximum deaths (18%). One death due to hypoglycemia was associated with cardiac arrhythmia. An underlying cause of mortality could not be defined in 3 patients. Twenty-five patients (66%) died within 1 year, with highest mortality among critical illness group (80%), followed by patients with alcohol or drugs intoxication (12%) and multiple factorial etiologies (8%). Twenty patients (53%; 16 critical illness, 3 alcohol or drugs intoxication, 1 multiple factors) died within 30 days, while 16 patients (42%) died during the same hospitalization. Early mortality (with in 1 year) did not differ by gender ($p = .31$), repeated calls ($p = .16$), ERT ($p = 1.00$), and hospitalization ($p = 1.00$) from late mortality (after 1 year).

Table 2.
Causes and Clinical Presentations of Hypoglycemia

Causes of hypoglycemia	
Underlying critical illness	42 (32.1%)
Multifactorial	36 (27.5%)
Alcohol intoxication	22 (16.8%)
Polysubstance abuse	14 (10.7%)
Gastric bypass	6 (4.6%)
Insulinoma	4 (3.1%)
Acute gastroenteritis and vomiting with decreased oral intake	4 (3.1%)
Religious fasting	1 (0.8%)
Eating disorder	1 (0.8%)
Functional dyspepsia with decreased oral intake	1 (0.8%)
Clinical symptoms	
Coma/loss of consciousness	43 (32.8%)
Confusion and aggressiveness	32 (24.4%)
Anxiety, nervousness, and palpitation	27 (20.6%)
Seizure	8 (6.1 %)
Lightheadedness/dizziness	6 (4.6%)
Weakness	4 (3.1%)
Drowsiness	4 (3.1 %)
Pain and weakness	3 (2.3%)
Nausea and vomiting	2 (1.5%)
Headache	1 (0.8%)
Slurred speech	1 (0.8%)

Discussion

We retrospectively retrieved all EMS calls made by non-DM for hypoglycemia in a community-based cohort between January 2003 and December 2009. We have previously reported that hypoglycemia requiring EMS

Table 4.
Mortality Causes

Primary causes	Total subjects (38)	Autopsy confirmation (21)
Infection	4 (11%)	4 (19%)
Cardiovascular	4 (11%)	2 (10%)
Respiratory	5 (13 %)	5 (24%)
Hepatic	2 (5%)	2 (10%)
Renal	3 (8%)	0 (0%)
Cancers	7 (18%)	3 (14%)
Neurologic/cerebrovascular	5 (13%)	3 (14%)
Hypoglycemia	1 (3%)	0 (0%)
Other causes (e.g., multiorgan failure, acidosis, hemorrhage)	4 (11%)	2 (10%)
Unknown	3 (8%)	0 (0%)

Table 3.
Outcomes among Different Etiologies of Hypoglycemia ($n = 131$)

	Critical illness ($n = 42$)	Poor oral intake ($n = 7$)	Alcohol or drugs intoxication ($n = 36$)	Insulinoma or bariatric surgery ($n = 10$)	Multiple factors ($n = 36$)	p value
Repeated calls	4 (10%)	0 (0%)	0 (0%)	3 (30%)	3 (8%)	0.28
ERT	33 (83%)	6 (86%)	33 (92%)	9 (90%)	29 (81%)	0.67
Hospitalization	25 (61%)	5 (71%)	21 (58%)	5 (50%)	9 (25%)	0.01
Duration of hospital stay (standard deviation), days	4 (5.1)	6.5 (9.4)	3.2 (3.6)	5.4 (6.2)	4.2 (4.7)	0.67
Endocrinology consultation	17 (41%)	1 (14%)	14 (39%)	6 (60%)	11 (31%)	0.29
Mortality	27 (71%)	2 (5%)	7 (19%)	0 (0%)	2 (5%)	<0.001

among patients with DM and non-DM constituted 5% of such calls in Olmsted County, MN.[8] Even though EMS calls for hypoglycemia among non-DM were low (<1% of total EMS calls), they were clinically important given the poor outcomes associated with iatrogenic hypoglycemia and hypoglycemia related to underlying medical conditions.[1] Most of the mild hypoglycemic episodes in non-DM are not recognized because of low suspicion for hypoglycemia. Also, hypoglycemic symptoms in these patients may be interpreted as related to underlying illnesses. Therefore, plasma glucose is not routinely checked in these patients. Because of these reasons, we included only those non-DM patients who required EMS for hypoglycemia. Also, ambulance utilization is associated with significant burden on medical resources utilization and cost.[13,14] To the best of our knowledge, hypoglycemia in ambulatory non-DM requiring EMS has not been reported before, and our report fills this significant knowledge gap. We have elaborated the major etiologies causing hypoglycemia in non-DM, which required EMS, and analyzed the outcomes among different etiologies after such events, including short- and long-term mortality.

Underlying critical illness was the most common cause of hypoglycemia in non-DM, followed by alcohol intoxication and polysubstance abuse. Critical illnesses, including septic shock, acute renal insufficiency, cardiac or hepatic failure, and inanition, along with severity of illness, are independent risk factors for developing hypoglycemia.[2,15] Patients with severe hypoglycemia have been associated with poor long-term outcomes compared with others.[1,15] However, all these previous studies have been performed in hospitalized patients. Our study evaluated the population burden of hypoglycemia requiring EMS and highlights, for the first time, the importance of prompt diagnosis. Whether prompt intervention would change outcomes needs to be tested in randomized control trials. Approaches that could be tested include (I) EMS protocol to routinely check the blood glucose in high-risk populations versus all EMS patients, (II) critical pathway development for hypoglycemia in non-DM that would include prompt diagnostic evaluation and stepwise intervention, and (III) point-of-care videoconferencing with endocrinology services.

Eating disorders and religious fasting can also cause severe hypoglycemia that may require EMS for revival.[16] Religious fasting is practiced by Muslims during Ramadan, Greek Orthodox Christians, certain Christians groups (Bible-based Daniel fast), and Asian Hindus.[17] Patients who experienced severe hypoglycemia due to fasting and eating disorders and subsequently required EMS for revival constituted a very small fraction of our cohort. Hypoglycemia due to decreased oral intake was also observed in few patients with acute gastroenteritis, vomiting, and functional dyspepsia. Hypoglycemia has been reported in children with acute gastroenteritis,[18] but such data are missing in literature for adults. Educating high-risk groups, especially religious people and patients with eating disorders, on how to recognize hypoglycemic symptoms early can help in timely action and prevention of severe episodes.

Acute alcohol intoxication and medication overdose with substance abuse resulted in 27% of the hypoglycemic episodes in our cohort. These patients were younger than others. Thus hypoglycemia caused by alcohol and drug abuse seems to be common among young population, which is expected because of the higher rate of alcohol intoxication and recreational substance use among younger generations. Correlation between different medications, hypoglycemia, and glucose homeostasis has been reported before, but underlying mechanisms need to be better understood.[19–22] After alcohol intoxication, hypoglycemia may be associated with inadequate food intake, but many other factors might be involved.[23,24] Similarly, polysubstance abuse may cause hypoglycemia due to poor oral intake or may be associated with hypoglycemia by itself.[7,25]

Insulinoma contributed to 3% of the hypoglycemic episodes, and most of the patients experienced repeated attacks. All four patients with insulinoma were from other states and temporarily staying in Olmsted County because of the nature of our institutional referral practice. Hypoglycemia due to insulinoma is primarily due to reduced hepatic glucose output rather than increased glucose utilization, and symptoms mainly occur during fasting but may also occur during the postprandial state.[26] Early diagnosis and surgical removal of insulinoma may prevent recurrent severe hypoglycemic episodes and associated morbidities. Medical therapy should be considered for insulinoma in patients who are not candidates for or refuse surgery or have unresectable metastatic disease.

Bariatric surgery caused 4% of hypoglycemia. Pancreatic nesidioblastosis and, rarely, insulinomas cause severe hypoglycemia after bariatric surgery.[6,27] Most of the patients respond to dietary modification with a low carbohydrate diet.[28] However, patients with hypoglycemia refractory to such measures may obtain relief with laparoscopic restoration of gastric restriction and, rarely, pancreatic resection.[29]

Multiple factors may act together to cause hypoglycemia in non-DM. More than one-fourth of the patients in our cohort experienced hypoglycemia due to multiple underlying etiologies. Clinical presentation of hypoglycemia was mostly neuroglycopenic symptoms, with coma and loss of consciousness being the most common (one-third of the patients). This could be because of failure to recognize early autonomic symptoms due to low hypoglycemia suspicion among non-DM or rapid fall in blood glucose level. A variety of other symptoms were also reported by patients without any dominant symptom pattern.

Repeated calls were not frequent among non-DM (8%). Repeated calls were predominantly seen among patients with insulinoma, underlying critical illness, or multifactorial etiologies. Chronic organ failure resulting in hypoglycemia was present only in two such patients, while one patient was on beta-blocker therapy. Most of the patients were revived with intravenous dextrose either because of the severe nature of hypoglycemia or inability to take orally.

Beta-blocker usage, which has moderate quality of evidence for association with hypoglycemia, was seen in one-third of the patients.[7] One patient was on pentamidine, while none of the other drugs with moderate quality of hypoglycemia evidence were identified in our cohort. Beta blockers can suppress the adrenergic defense symptoms of hypoglycemia, thus leading to severe neuroglycopenic symptoms.[30,31]

Hospitalization was higher among patients with poor oral intake, critical illness, and chronic organ failure. Thus hypoglycemia associated with reduced oral intake due to fasting or eating disorder and underlying critical illness with chronic organ failures seems to be more complex and requires special attention. Mortality was higher among patients with underlying critical illnesses, with shorter duration to death post-EMS-requiring hypoglycemia, as expected. None of the deaths were observed in patients with insulinoma and bariatric surgery. Cancer was the most common cause of death, while hypoglycemia caused one death. Death occurred suddenly in this patient due to cardiac arrhythmia with no other significant underlying cause identified.

Our study is limited by the small sample size, small number of events in each subgroup, limited follow-up time, and retrospective study design.

In summary, hypoglycemia in non-DM requiring ambulance services is not uncommon. A multitude of factors can predispose to hypoglycemia with underlying critical illnesses, multifactorial causes, and alcohol and polysubstance abuse being the most common. Hospitalization and mortality was higher among patients with critical illnesses but not different between other causes. Outcomes could be improved by managing such episodes with a critical clinical pathway with special attention given to those with critical illness and hypoglycemia predisposing comorbidities. Besides raising the plasma glucose concentration to normal range, identification and treatment of underlying causes is important in improving the long-term outcomes of such patients. Plasma glucose should be routinely checked in each patient requiring EMS for early recognition of hypoglycemia in non-DM to reduce frequency and morbidities associated with severe episodes.

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