Hypoglycemia as a Predictor of Mortality in Hospitalized Elderly Patients

Nadya Kagansky, MD; Shmuel Levy, MD; Ephraim Rimon, MD; Lutzy Cojocaru, PhD; Alla Fridman, MD; Zinaida Ozer, MD; Hilla Knobler, MD

Background: Hypoglycemia during hospitalization occurs in patients with and without diabetes. The aims of this study were to determine the incidence, associated risk factors, and short- and long-term outcome of hypoglycemia among hospitalized elderly patients.

Methods: This is a case-control study conducted at geriatric and medicine departments. All patients 70 years or older with documented hypoglycemia hospitalized within 1 year (n=281) were compared with a nonhypoglycemic group of 281 elderly, randomly selected patients from the same hospitalized population.

Results: Among 5404 patients 70 years or older, 281 (5.2%) had documented hypoglycemia. Compared with the nonhypoglycemic group, we found the following characteristics to be true in the hypoglycemic group: there were more women than men (58% vs 44%, P=.001); sepsis was 10 times more common (P<.001); malignancy was 2.8 times more common (P=.04); the mean serum albumin level was lower (2.8 g/dL vs 3.4 g/dL, P<.001); and the mean serum creatinine and alkaline phosphatase levels were higher (P<.001 for both). Diabetes was known in 42% of the hypoglycemic group and in 31% of the nonhypoglycemic group (P=.03); 70 patients in the hypoglycemic group were taking sulfonylureas or insulin. Multivariate logistic analysis showed that sepsis, albumin level, malignancy, sulfonylurea and insulin treatment, alkaline phosphatase level, female sex, and creatinine level were all independent predictors of developing hypoglycemia. In-hospital mortality and 3-month mortality were about twice as high in the hypoglycemic group (P<.001). Multivariate analysis of mortality found that sepsis, low albumin level, and malignancy were independent predictors, while hypoglycemia was not.

Conclusions: Hypoglycemia was common in elderly hospitalized patients and predicted increased in-hospital 3- and 6-month cumulative mortality. However, in a multivariate analysis, hypoglycemia was not an independent predictor for mortality, implying that it is only a marker.

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agree for alkaline phosphatase. Multivariate analysis was performed with forward stepwise logistic regression. Odds ratio and their 95% CIs were calculated. All statistical computations were 2-tailed.

### RESULTS

#### CLINICAL AND LABORATORY CHARACTERISTICS

Among 5404 patients 70 years or older admitted during the 1-year period, we identified 281 (5.2%) who had documented hypoglycemia. We compared the hypoglycemic group with 281 elderly patients without hypoglycemia (nonhypoglycemic group) hospitalized in the same wards during the same period. The clinical characteristics are summarized in Table 1. The mean age in the hypoglycemic group was 80.5 years, which was not statistically different from that of the nonhypoglycemic group (80.9 years). There were also no significant differences found in specific age subgroups (70–79, 80–89, and ≥90 years). There was a female preponderance in the hypoglycemic group (38% women and 42% men) and a reversed ratio in the nonhypoglycemic group (44% women and 56% men) (*P* = .001).

The most common cause of hospitalization in the 2 groups was infections: 34% of patients in the hypoglycemic group and 28% of patients in the nonhypoglycemic group were admitted to the hospital because of infections; the difference between the 2 groups was not significant. However, in the hypoglycemic patients, sepsis was 10 times more common than in the nonhypoglycemic group: it was diagnosed in 50 patients (18%) vs 5 patients (1.8%) (*P* < .001). Malignancy as the reason for hospitalization was also more common in the hypoglycemic group: 28 patients (10%) in the hypoglycemic group and 10 (3.5%) in nonhypoglycemic group (*P* = .04). On the other hand, hospitalization for stroke was more prevalent in the nonhypoglycemic group. There was no significant difference in the number of patients admitted for congestive heart failure.

Patients with known DM represented 42% (n = 118) of the patients in the hypoglycemic group and 31% (n = 87) of the patients in the nonhypoglycemic group (*P* = .03). Of the other previously known illnesses on admission, we found that the following illnesses were more common in the hypoglycemic group than in the nonhypoglycemic group: dementia, 24% vs 16% (*P* = .04); malignancy, 21% vs 13.5% (*P* = .03); and known chronic renal failure, 20% vs 11% (*P* = .01). Chronic liver disease was known prior to hospitalization in only a small number of patients, 16 in the hypoglycemic group and 14 in the nonhypoglycemic group. In none of the cases was hypoglycemia the reason for hospitalization.

Detailed evaluation of concomitant medications revealed that 63 patients in the hypoglycemic group and 43 patients in the nonhypoglycemic group received sulfonylureas, but only a small number of patients in both groups received insulin either alone or in combination with sulfonylureas (9 and 8 patients, respectively). Therefore, we combined sulfonylureas and insulin treatment into 1 group: insulin secretagogues and insulin treatment (ISIT). In the hypoglycemic group, 70 patients (25%)

### Table 1. Clinical Characteristics of Hypoglycemic and Nonhypoglycemic Elderly Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hypoglycemic (n = 281)</th>
<th>Nonhypoglycemic (n = 281)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (95% CI), y</td>
<td>80.5 (79.7-81.2)</td>
<td>80.9 (80.1-81.7)</td>
<td>.72</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>118/163</td>
<td>157/124</td>
<td>.001</td>
</tr>
<tr>
<td>Causes of hospitalization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>96 (34.1)</td>
<td>79 (28.1)</td>
<td>.20</td>
</tr>
<tr>
<td>Sepsis</td>
<td>50 (17.8)</td>
<td>5 (1.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Malignancy</td>
<td>28 (10)</td>
<td>10 (3.5)</td>
<td>.04</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>11 (3.9)</td>
<td>15 (5.3)</td>
<td>.43</td>
</tr>
<tr>
<td>Stroke</td>
<td>13 (4.6)</td>
<td>35 (12.4)</td>
<td>.001</td>
</tr>
<tr>
<td>Others</td>
<td>83 (29.5)</td>
<td>135 (48.4)</td>
<td></td>
</tr>
<tr>
<td>Previously known diseases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>118 (42)</td>
<td>87 (30.9)</td>
<td>.03</td>
</tr>
<tr>
<td>Dementia</td>
<td>67 (23.8)</td>
<td>45 (16)</td>
<td>.04</td>
</tr>
<tr>
<td>Malignancy</td>
<td>59 (21)</td>
<td>38 (13.5)</td>
<td>.03</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>55 (19.6)</td>
<td>32 (11.3)</td>
<td>.01</td>
</tr>
<tr>
<td>DM treatment†</td>
<td>70 (25)</td>
<td>48 (17)</td>
<td>.03</td>
</tr>
</tbody>
</table>

*Abbreviations: CI, confidence interval; DM, diabetes mellitus.

†Insulin secretagogues or insulin treatment.

Data were expressed as means±SDs or as means (95% confidence intervals [CIs]). Comparison between groups was done with the t test for continuous variables and the χ² test for categorical variables. A logarithmic transformation (ln) was applied for alkaline phosphatase. Multivariate analysis was performed with forward stepwise logistic regression. Odds ratio and their 95% CIs were calculated. All statistical computations were 2-tailed.

#### LABORATORY METHODS

Blood tests were done at the hospital clinical chemistry laboratory. Glucose was measured by the glucose oxidase method, and all biochemical determinations were performed on a Roche-Hitachi analyzer (Mannheim, Germany).

#### STATISTICAL ANALYSIS

Data were expressed as means±SDs or as means (95% confidence intervals [CIs]). Comparison between groups was done with the t test for continuous variables and the χ² test for categorical variables. A logarithmic transformation (ln) was applied for alkaline phosphatase. Multivariate analysis was performed with forward stepwise logistic regression. Odds ratio and their 95% CIs were calculated. All statistical computations were 2-tailed.

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received ISIT compared with 48 (17%) in the nonhypoglycemic group (P = .03). Twenty-five patients in each group received metformin. The differences in the usage of β-blockers, diuretics, antidepressants, antipsychotic agents, and angiotensin-converting enzyme inhibitors were not significant (data not shown).

Laboratory characteristics of patients in the 2 groups are summarized in Table 2. As noted, mean albumin levels were significantly lower in the hypoglycemic group than in the nonhypoglycemic group (2.8 g/dL vs 3.4 g/dL; P < .001). Patients in the hypoglycemic group also had significantly higher mean creatinine levels compared with the nonhypoglycemic group (1.7 mg/dL [150.3 µmol/L] vs 1.3 mg/dL [114.9 µmol/L]; P < .001). Patients in the hypoglycemic group had significantly higher mean levels of alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase; higher white blood cell count; and significantly lower hemoglobin levels.

Evaluation of mobility status prior to hospitalization is a routine procedure in geriatric patients in our hospital. A significantly higher number of patients in the hypoglycemic group were classified as bedridden: 48% of the hypoglycemic group compared with 29% in the nonhypoglycemic group (P < .001).

RISK FACTORS FOR DEVELOPING HYPOGLYCEMIA

To determine risk factors for developing hypoglycemia, a multivariate logistic regression analysis was performed (Table 3). As shown, sepsis was associated with an odds ratio (OR) of 6.4 (95% CI, 2.3-17.3) for development of hypoglycemia. Malignancy was associated with an OR of 2.6 (95% CI, 1.1-6.2) and a decrease in serum albumin level by 1 g/dL was associated with an OR of 4.3 (95% CI, 2.9-6.5) for developing hypoglycemia. Other risk factors found to contribute significantly to developing hypoglycemia were ISIT, alkaline phosphatase level, creatinine level, and female sex.

We compared patients with and without DM. The mean age of patients with DM was significantly lower (79.2 vs 81.5 years; P < .001). However, there were no statistically significant differences in sex, sepsis, malignancy, hypoalbuminemia, or elevated alkaline phosphatase level. Renal failure (defined as creatinine levels >1.4 mg/dL [123.8 µmol/L]) was more common in patients with DM than in those without (40% vs 30%; P = .02). More patients in the DM group received treatment with angiotensin-converting enzyme inhibitors (54.6% vs 31.3%; P < .001).

SHORT- AND LONG-TERM MORTALITY

Mortality rates are presented in the Figure. Regarding in-hospital mortality, 72 patients (26%) in the hypoglycemic group and 38 (14%) in the nonhypoglycemic group died (P < .001). Three months after discharge, an additional 71 patients died in the hypoglycemic group and 32 in the nonhypoglycemic group, with a cumulative number of deaths reaching 143 and 70, respectively (P < .001). During the next 3 months, the number of deaths was relatively small: 12 patients in the hypoglycemic group and 9 in the nonhypoglycemic group died. We did not find a correlation between the degree of hypoglycemia and mortality.
There were no statistically significant differences in in-hospital mortality or 6-month mortality between patients with DM and those without. Interestingly, ISIT was associated with lower mortality in the hypoglycemic group. Only 8 (11%) of the 70 patients in the hypoglycemic group who received ISIT died, compared with 64 (30%) of the 211 in the hypoglycemic group who did not receive ISIT (P = .001). Thus, hypoglycemia in patients who underwent ISIT was associated with lower mortality than in patients who had no ISIT.

Since our data showed that hypoglycemia was associated with a high in-hospital mortality rate, we wanted to determine whether risk factors for developing hypoglycemia were also predictors of mortality. A multivariate logistic regression analysis of the whole study population (hypoglycemic and nonhypoglycemic patients) was performed, including the occurrence of hypoglycemia as well as all the clinical variables associated with hypoglycemia (Table 4). Sepsis, malignancy, and low albumin levels, which were predictors of developing hypoglycemia, were also found to be strong predictors of in-hospital mortality. Interestingly, ISIT was associated with lower mortality. It is also noteworthy that hypoglycemia was not found to be an independent risk factor for in-hospital mortality in the multivariate analysis.

### Table 4. Risk Factors for In-Hospital Mortality in 562 Elderly Patients

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis</td>
<td>9.9 (5.1-19.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Albumin &lt;3.0 g/L</td>
<td>2.9 (1.7-4.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Malignancy</td>
<td>4.7 (2.2-9.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ISIT</td>
<td>0.5 (0.2-0.9)</td>
<td>.03</td>
</tr>
</tbody>
</table>

*Multiple regression analysis included the following variables: age, sex, causes of hospitalization, insulin secretagogues or insulin treatment (ISIT), albumin, creatinine, alkaline phosphatase, and occurrence of hypoglycemia.

Older age can increase the risk of developing hypoglycemia because of the higher rate of comorbidities such as renal failure, malnutrition, malignant diseases, and dementia, which were found to be risk factors for hypoglycemia in the present study and in previous studies. Older hospitalized patients often experience failure of regulatory mechanisms, especially in stress situations, such as reduced release of glucagon and epinephrine in response to hypoglycemia. Hypoglycemia was found in the present study to be more common in women, which may be related to sex differences in counterregulatory responses to hypoglycemia. Cognitive impairment with communication difficulties, frailty, polypharmacy, and possibly less attention from medical staff can add to the increased risk observed.

In the present study, multivariate regression analysis found sepsis to be a strong predictor for developing hypoglycemia (OR, 6.4; 95% CI, 2.3-17.3) and for mortality (OR, 9.9; 95% CI, 5.1-19.3). The association found in the present study between sepsis, hypoglycemia, and increased mortality is in accordance with 2 previous studies. In one of these studies, among patients with hypoglycemia who died, 50% had sepsis compared with 14% of those who remained alive. However, in a previous study focusing on hypoglycemia in the elderly, sepsis was common in hypoglycemic patients, but it was not a statistically significant risk factor for hypoglycemia or mortality in a multivariate analysis. One proposed mechanism for hypoglycemia during sepsis is decreased liver and renal gluconeogenesis.

A low albumin level in our study was also a strong predictor for hypoglycemia (OR, 4.3; 95% CI, 2.9-6.5) and for mortality (OR, 2.9; 95% CI, 1.7-4.7). Low serum albumin has been shown by several studies to indicate higher rates of mortality and complications. There are several medical conditions predisposing to low levels of albumin: chronic liver disease, nephrotic syndrome, malnutrition, and decreased production of albumin associated with increased levels of cytokines. In our study population, previous diagnosis of chronic liver disease was relatively rare, possibly owing to lower rates of alcohol-induced liver disease in the Israeli population. Liver function test disturbances that were more common in the hypoglycemic group were probably related to the effects of sepsis or malnutrition on the liver. We had no data on albuminuria, but renal failure was a significant predictor only for hypoglycemia and not for mortality. Therefore, the association between hypoalbuminemia and mortality can be explained by either malnutrition or by long-standing comorbidities. Hypoalbuminemia can therefore be regarded as an indicator of poor health.

Renal insufficiency was found to be a risk factor for hypoglycemia in our study as well as by Fisher et al, but not for mortality. The association between hypoglycemia and renal insufficiency in patients without diabetes has already been reported with several proposed mechanisms. Under normal conditions, renal glucose release has been shown to account for about 40% of overall gluconeogenesis and in conditions such as fasting and hypoglycemia can increase 2- to 3-fold. In patients with renal insufficiency, decreased renal gluconeogenesis, lack of gluconeogenic substrates with decreased food intake

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**COMMENT**

The present study dealing exclusively with hospitalized subjects 70 years or older shows that hypoglycemia is a common complication in this age group associated with 2-fold increased mortality during hospitalization and during 3 months of follow-up. The incidence of 5.2% found in our study is significantly higher than the 0.5% to 1.5% found in previous studies dealing with hypoglycemia during hospitalization. This high incidence can be attributed to differences in study groups: 2 of the studies, reporting an incidence of 1.2% and 1.5%, included middle-aged patients, and the third, although focusing on the elderly population, included a relatively broad range of ages, 65 to 98 years, and also excluded patients with diabetes. In addition, the criterion for hypoglycemia in the present study of serum glucose levels lower than 60 mg/dL was higher than the criterion used in the previous studies (<50 mg/dL). Another possible explanation for differences between the findings is differences in the frequency of blood sampling; hypoglycemia, especially in the elderly, is often unsuspected clinically.
or malnutrition that often accompanies renal failure, decreased renal degradation and excretion of insulin, and impairment of counterregulatory hormonal responses can all lead to hypoglycemia. In a large study of 1545 admissions of patients with end-stage renal failure, 3.6% were admitted with hypoglycemia. 25 In this study, mortality was high when hypoglycemia was associated with either sepsis or malnutrition.

The finding in the present study that malignancy was a strong predictor not only for mortality but also for hypoglycemia is intriguing. In the past, malignancy-associated hypoglycemia was mainly attributed to secretion of insulinlike growth factor by non-β-cell tumors such as large mesenchymal tumors. 24 Recently, another factor named proteolysis-inducing factor, was found to affect carbohydrate metabolism in addition to causing a profound depression of body weight. 25

Patients with DM constituted fewer than half (42%) of the patients with hypoglycemia in the present study compared with 31% in the nonhypoglycemic group (P = 0.03). These results are in accordance with 2 previous studies that found that 45% and 26% of patients with hypoglycemia also had diabetes. 5, 6 Therefore, most cases of hypoglycemia occurred in patients without DM. Use of sulfonylureas that are insulin secretagogues or insulin was associated with a 2-fold increase in hypoglycemia. However, ISIT was an independent predictor not only for mortality but also for hypoglycemia. In the present study. This finding is not surprising, considering that previous studies have shown a high incidence of hypoglycemia associated with these treatment modalities, which further increases with advancing age and polypharmacy. 8 Interestingly, ISIT was associated with a significantly lower mortality rate not only in the hypoglycemic group but was also found to be an independent predictor for lower mortality in the whole study group. This unexpected finding may be explained by possible better surveillance of patients receiving antidiabetic treatment and earlier recognition of clinical deterioration. Recent data also suggest that insulin exerts an anti-inflammatory effect compared with glucocorticoids. 26 Because hospitalized diabetic patients in unstable condition routinely receive insulin, this anti-inflammatory effect of insulin may be relevant. Further studies are needed to confirm this finding.

The present study evaluated not only in-hospital mortality but also 3- and 6-month mortality, and it is the first study to show that hypoglycemia is a marker for short- and long-term poor outcome. However, a multivariate analysis for in-hospital mortality revealed that hypoglycemia did not remain an independent predictor. The risk factors that predicted increased mortality in this model were sepsis, low albumin level, and malignancy. These findings point out that hypoglycemia is only a marker for poor health and general deterioration associated with higher mortality rates. One previous study found hypoglycemia to be a risk factor for mortality in the elderly in a multivariate analysis, 8 although in this study as well as in others, hypoglycemia was not a direct cause of mortality. 3, 7

In conclusion, hypoglycemia was a common finding in elderly hospitalized patients, predicting in-hospital as well as 3-month and 6-month higher mortality rates. Female sex, sepsis, malignancy, renal failure, serum albumin level, alkaline phosphatase level, and ISIT for DM were predictors for developing hypoglycemia. Multivariate analysis revealed that sepsis, hypoalbuminemia, and malignancy were predictors for in-hospital mortality. However, hypoglycemia was not a predictor in this analysis, implying that hypoglycemia is a marker of poor health without a direct effect on survival. Frequent blood sampling in elderly patients and detecting asymptomatic hypoglycemia can therefore serve as a useful indicator for prognosis.

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