Acute In-Hospital Random Hyperglycemia And Post-Discharge Clinical Outcomes Among Non-Critically Ill In-Patients

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Citation

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Abstract

Background: Among non-critically in-patients, observational studies have shown that random hyperglycemia during hospitalization is related to adverse outcomes until discharge, especially in those with specific conditions such as myocardial infarction, stroke or pneumonia. Whether the adverse effects of acute in-hospital random hyperglycemia (AIRH) occurs among all non-critically ill in-patients admitted to the general wards and if the effects continue in the immediate post-discharge period remains unclear. Methods: A prospective cohort study was conducted on adult in-patients in a New York City hospital in 2007-09, comparing those with AIRH (random blood glucose > 200 mg/dl) to a control group (< 200 mg/dl). Composite adverse outcome of deaths during index admission and re-admissions up to 90 days follow-up after discharge was analyzed using multivariate generalized linear models including demographic, co-morbidity and treatment variables. Relative risk (RR) and 95% confidence intervals (CI) were calculated. Results: Of the 1149 subjects enrolled, 726 (63%) subjects completed 90-day follow-up. 325 (44.8%) were women; 489 were (67.3%) Latinos, 222 (30.6%) African Americans, and 242 (33.3%) had pre-existing diabetes mellitus. 258 (35.5%) had AIRH, 468 (64.5%) were controls and 154 (21.2%) had hypoglycemia (< 80 mg/dL). Twelve (1.6%) subjects died, 179 (24.6%) were readmitted and 188 (25.9%) died or were re-admitted. Adjusted multivariate analysis showed no association between AIRH and composite outcome (RR 1.19, 95% CI 0.86-1.64, p=0.329). Hypoglycemia had increased mortality risk (RR 3.75, 95% CI 1.25-11.28, p= 0.019). Conclusion: Among general ward in-patients, there was no direct correlation between AIRH, readmissions or death at 90 days of follow-up post-discharge, adjusting for potential confounders. Mortality risk was greater among these in-patients with hypoglycemia. Randomized trials are needed to confirm these findings to guide management of in-hospital hyperglycemia and avoid hypoglycemia in this clinical setting.

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BACKGROUND

Random hyperglycemia is common among hospitalized in-patients, regardless of their diabetic status. (1) Studies have linked random hyperglycemia to adverse clinical outcomes among critically ill patients. (2-4) However, scientific evidence in recent years has shown that tight control of random hyperglycemia towards normal blood sugar range targets does not improve mortality or morbidity, but rather increases hypoglycemia related mortality. (5) Two recently conducted studies in critically ill patients were stopped prematurely because of lack of efficacy of glucose control and increased risk of hypoglycemia. (6, 7) A meta-analysis including 34 randomized trials on critically-ill patients also showed that tight glycemic control does not significantly improve hospital mortality and was related to increased risk of hypoglycemia. (8) These studies have led to a debate regarding the safest glycemic range among critically ill subjects. (9)

Further, clinical evidence on the effects of acute hyperglycemia and optimal blood sugar control in non-critically ill general ward patients is limited to specific populations such as myocardial infarction. (10, 11) One observational study (12) has evaluated admission hyperglycemia and, another study (13) has analyzed in-hospital hyperglycemia and mortality during hospitalization in the general wards. Hyperglycemia related adverse effects during hospitalization have been studied among specific

conditions such as pneumonia, myocardial infarction and stroke. (14-16) Current guidelines from the Endocrine Society of North America and the American Diabetes association recommend glucose control during hospitalization in the general ward settings (17,18), but whether tight blood sugar control would show sustainable clinical benefit in these patients after discharge is not clear. A recent evidenced-based guideline published by the American College of Physicians discouraged tight control of blood sugar during hospitalization in view of lack of benefit in studies among general ward subjects and due to the mortality risk related to hypoglycemia. (19)

This study prospectively investigated the clinical outcomes related to acute in-hospital random hyperglycemia among general ward in-patients of minority background up to 90 days after discharge in a university-affiliated high volume inner-city hospital setting in New York City (NYC).

METHODS

A prospective observational cohort study was conducted in 2007-09 on consecutively eligible consenting adult patients hospitalized in the general in-patient wards at Lincoln Medical and Mental Health Center (LMMHC) Bronx, NYC. Exclusion criteria were: a) blood glucose levels not available, b) age <18 years, c) terminal disease where death is expected within 90 days, d) admission and discharge within <24 hours, e) critical care unit admission directly from the emergency room and f) refusal or inability to consent. The study was approved by the local institutional research review board. Data on demographics, clinical features, laboratory results and outcomes were collected from medical records at the time of enrollment, and during hospitalization. Follow-up data on death, re-admissions and emergency room (ER) visits were collected by chart review and through a direct phone interview at 90 days after discharge.

Study patients were divided into two cohorts, acute random in-hospital hyperglycemia cohort group (defined as random glucose level of equal to or greater than 200 mg/dL at any time during hospitalization), and control cohort group (random glucose level less than 200 mg/dL during hospitalization) at the time of index hospitalization. In the primary analysis, a composite outcome including death and readmissions within 90 days after index hospitalization was studied. Secondary analyses of death, readmissions and emergency room (ER) visits individually were also conducted. ER visits were not included in the composite outcome as recent estimates show that a significant proportion (> 40%) of ER visits among New Yorkers are due to avoidable non-emergent visits. (20)

Baseline demographics and clinical characteristics between the two groups were compared. Stepwise multivariate general linear model (GLM) regression for Poisson probability distribution and robust error variance was utilized to analyze the effects of confounders on the outcomes. (21) P value of <0.05 was considered significant. Variables associated with $p < 0.1$ on univariate analysis were selected for multivariate analyses. For comparison of outcomes, relative risk ratios were calculated and 95% CI are reported. Assuming a 2-sided alpha error of 0.05, the study had 87% power to detect an 11% clinically relevant difference between the study and control groups with respect to the composite outcome variable of death and re-admissions, with an estimate of 22% clinical occurrence of the composite outcome events in the control group within the 90 day follow-up after discharge.

RESULTS

A total of 1149 subjects were enrolled at the time of index hospitalization. Of these, 726 patients (63.2%) completed the study at 90 days follow-up. Among these study subjects who completed follow-up, mean age was 56 years, 401 (55.2%) were men. About two thirds of the study subjects (67.3%) were Hispanics and 222 (30.6%) were African Americans.

Two hundred and fifty eight patients (35.5%) were found to have at least one episode of random in-hospital hyperglycemia and 468 patients (64.5%) had random glucose values less than 200 mg/dL (controls). One third (33.3%) of all subjects had pre-existing diabetes mellitus (DM). One hundred and eighty three AIRH patients (70.8%), and 59 (12.6%) of the controls had history of DM.

The median length of stay of all study patients was 2 days (Inter-quartile range (IQR) 1-3 days). In the AIRH group, 4 (1.5%) patients died, 82 (31.7%) were re-admitted within 90 days after index hospitalization and 70 (27%) had emergency room (ER) visits for various conditions within 90 days. Among the controls, 8 patients died, 97 (20.1%) had re-admissions and 122 (26.1%) had ER visits within 90 days. Of the 468, 103 (22%) controls had a composite outcome event of either death or were re-admitted within 90 days of discharge, whereas 85/258 (33%) of the AIRH group died or were re-admitted.

As shown in Table 1, selective differences in demographic, clinical, laboratory and composite outcomes data were noted between the random hyperglycemia and control groups. AIRH group subjects were found to be significantly older, obese, diabetic, had more cardiovascular, renal co-morbidity, greater re-admissions alone or composite outcome events compared to controls.

Adjusted multivariate GLM regression analyses did not confirm an independent association of hyperglycemia with composite outcomes (RR 1.19, 95% CI 0.86-1.64, p=0.329), after adjusting for significant independent confounder variables. Pre-existing diabetes mellitus was noted among a third of all hospitalized subjects (33.3%), greater among AIRH (70.9% versus 12.6%, p= 0.000) than among the control group, but did not have an independent impact on the composite outcomes (RR 1.00, 95% CI 0.66-1.50, p = 0.988) in the multivariate analysis. Additional factors that were significantly associated with composite outcomes were advanced age and systemic steroid therapy during index hospitalization.

In the secondary analyses of individual outcomes (death or re-admissions or ER visits), random hyperglycemia was not associated with any individual outcomes after adjusting for other confounder variables (Tables 3-5). Advanced age (RR 1.01, 95% CI 1.00-1.02, p= 0.024), neurologic disease (RR 1.38, 95% CI 1.03-1.84, p=0.030) and use of systemic steroid therapy (RR 1.57, 95% CI 1.20-2.04, p=0.001) during the index hospitalization were associated with greater re-admissions. Gastro-intestinal illness (RR 1.44, 95% CI 1.07-1.94, p= 0.017) and intravenous glucose infusion (RR 2.12, 95% CI 1.19-3.78, p=0.01) during index hospitalization were associated subsequently with more ER visits.

Hypoglycemia defined as random glucose level less than 80 mg/dL anytime during hospitalization, was noted to be independently associated with increased mortality (RR 3.75, 95% CI 1.25-11.28, p= 0.019). (Table 3)

Figure 1

Table 1: Comparison of baseline characteristics in random hyperglycemia & control subjects

Variable	Non-hyperglycemia (n=468)	Hyperglycemia(n=258)	P value
Demographics			
Age, mean (SD) yrs	54.1(17.4)	59.8(15.3)	<0.0001
Women, n (%)	213 (45.6)	112 (43.2)	0.640
Hispanic, n (%)	314 (67.1)	175 (67.8)	0.869
Insurance, no. (%)	443 (94.7)	240 (93.0)	0.412
Family and personal history			
Family h/o diabetes, no. (%)	77 (16.5)	29 (11.2)	0.062
Tobacco use, n (%)	218 (46.7)	109 (42)	0.244
Alcohol use, n (%)	74 (15.9)	22 (8.49)	0.006
Illicit substance use, n (%)	82 (17.6)	32 (12.4)	0.071
Co-morbidity			
*BMI kg/m2, median	28.9	32.9	0.05
DM, n (%)	59 (12.6)	183 (70.9%)	< 0.0001
Cardiovascular, n (%)	305 (65.0)	211 (81.8)	< 0.0001
Respiratory, n (%)	162 (34.6)	91 (35.)	0.871
Neurologic, n (%)	75 (16.0)	55 (21.3)	0.085
Gastrointestinal-hepatic, n (%)	66 (14.1)	29 (11.2)	0.302
Renal, n (%)	60 (12.8)	61 (23.6)	< 0.0001
Hematologic, n (%)	71 (15.2)	39 (15.1)	1.000
Oncologic, n (%)	20 (4.3)	15 (5.8)	0.369
Rheumatologic, n (%)	60 (12.8)	31 (12.0)	0.815
Infections, n (%)	79 (16.9)	30 (11.6)	0.065
Surgical, n (%)	33 (7.0)	23 (8.9)	0.385
Psychiatric, n (%)	66 (14.1)	29 (11.1)	0.302
Obstetric, n (%)	6 (1.3)	2 (0.8)	0.719
Gynecologic, n (%)	17 (3.6)	7 (2.7)	0.665
Lab & treatment data			
Rx with oral DM or Insulin therapy in hospital, n (%)	55 (11.8)	170 (67.1)	<0.0001
Steroid use, n (%)	99 (21.2)	58 (22.5)	0.707
*HbA1c, mean (SD)	6.58(1.17)	8.46(2.52)	0.0012
Clinical Outcomes			
LOS, median (IQR)	2 (1-3)	2 (1-4)	0.0001
ER visits, n (%)	122 (26.1)	70 (27.1)	0.792
Readmissions, n (%)	97 (20.77)	82 (31.8)	0.001
Death, n (%)	8 (1.7)	4 (1.5)	1.000
Death or re-admissions, n (%)	103 (22.01)	85 (32.95)	0.001

* not available in all patients

Figure 2

Table 2: Multi-variate GLM regression analysis of composite outcomes (Death or Re-admissions)

*Variables	Relative risk ratio (95% Confidence Interval)	P value
Demographics-		
• Age	1.01 (1.00-1.02)	0.037
• Insurance status	1.58 (0.75-3.33)	0.228
Co-morbidity-		
• Neurologic	1.28 (0.96-1.71)	0.093
• Renal	1.32 (0.97-1.78)	0.073
• Oncologic	1.33 (0.82-2.18)	0.252
• Diabetes Mellitus	1.00 (0.66-1.50)	0.988
Treatment during hospitalization-		
• Systemic steroid therapy	1.46 (1.12-1.89)	0.005
• Insulin therapy	1.22 (0.82-1.80)	0.329
• Glucose infusion	1.56 (0.86-2.84)	0.145
Blood sugar levels-		
• Hyperglycemia	1.19 (0.86-1.64)	0.329

Figure 3

Table 3: Adjusted GLM regression analysis of individual outcome- death

*Variables	Relative risk ratio (95% Confidence Interval)	P value
Blood sugar levels-		
• Hyperglycemia	3.75 (1.25-11.28)	0.019
• Hypoglycemia	0.84 (0.26-2.70)	0.771

Figure 4

Table 4: Adjusted GLM regression analysis of individual outcomes- re-admissions

*Variables	Relative risk ratio (95% Confidence Interval)	P value
Age	1.01 (1.00-1.02)	0.024
Co-morbidity-		
• Neurologic	1.38 (1.03-1.84)	0.030
• Renal	1.31 (0.96-1.78)	0.088
• Oncologic	1.28 (0.77-2.14)	0.339
• Diabetes	1.07 (0.71-1.62)	0.748
Random Hyperglycemia	1.17 (0.85-1.63)	0.334
Treatment during hospitalization-		
• Systemic steroids	1.57 (1.20-2.04)	0.001
• Insulin therapy	1.18 (0.79-1.75)	0.419
• Glucose infusion	1.58 (0.88-2.83)	0.124

Figure 5

Table 5: Adjusted GLM regression analysis of individual outcomes - ER visits

*Variables	Relative risk ratio (95% Confidence Interval)	P value
Insurance	1.76 (0.85-3.62)	0.125
Illicit drug use	1.28 (0.93-1.76)	0.134
Alcohol abuse	1.16 (0.82-1.65)	0.409
Co-morbidity-		
• Respiratory	1.14 (0.86-1.50)	0.369
• Gastro-intestinal	1.44 (1.07-1.94)	0.017
• Hematologic	1.29 (0.97-1.74)	0.083
Treatment during hospitalization-		
• Systemic steroids	1.35 (1.00-1.83)	0.054
• Glucose infusion	2.12 (1.19-3.78)	0.01
Random hyperglycemia	1.07 (0.83-1.38)	0.58

* Only confounder variables associated with p < 0.1 in univariate analyses were included in the multi-variate analysis and shown here.

DISCUSSION

This first observational cohort study that does not demonstrate an association of high blood sugar levels during hospitalization, death or re-admissions and ER visits up to 90-day follow-up after discharge among non-critically ill minority in-patients. Pre-existing diabetes mellitus was noted among a high percentage (33%) of these hospitalized United States minority subjects when compared to national hospital discharge survey estimates, where the percentage of discharges reported with diabetes is about 15%. (22, 23) Although diabetic minority individuals had significant random hyperglycemia during hospitalization, it did not contribute to excessive morbidity or mortality in this study population.

Regardless of diabetes status, intra-cellular patho-physiologic response mechanisms explain the range of the effects of acute random hyperglycemia including serious internal metabolic derangements encountered in prolonged or critical illness leading to severe adverse and organ dysfunction, or the occurrence of relatively mild metabolic derangements among in-patients on the general wards associated with minimal or no systemic inflammatory response and mild adverse effects.

The human body responds to acute stress by increasing counter-regulatory hormones such as cortisol, epinephrine to increase serum glucose level to produce more adenosine tri-phosphate (ATP) and thus creating a hyperglycemia stress response. As in this study, general ward patients have brief acute illnesses that require short in-patient treatment. Therefore, the initial metabolic response leading to acute hyperglycemia is short lived and maybe associated with fewer adverse events.

However in critically ill patients in the ICU, persistent or severe illness may lead to a series of complex metabolic derangements and systemic inflammatory responses such as increase in cytosolic calcium level and decrease ATP production, causing cellular and leukocyte dysfunction, decreased fibrinolytic activity, increased platelet activation causing more thrombosis, increased cytokine, causing more inflammation and endothelial dysfunction. It also causes increased oxidative stress, by increasing reactive oxygen species to the amount that our body cannot metabolize, causing direct tissue injury including beta cell dysfunction, relative insulin deficiency, aggravating hyperglycemia, triggering a vicious cycle and leading to permanent organ dysfunction eventually. (1) Corroborating the impact of such sustained cellular mechanisms of injury on clinical outcomes in critically ill patients who were seriously ill and required treatment in intensive care unit for more than 3 days, was a land mark study on glucose control in critically ill patients, which showed that the overall benefits was significantly greater in only among long stay ICU patients. (24)

The use of steroid therapy during index hospitalization that was found to be associated with increased re-admissions in this study could be related to acute severe asthma or chronic obstructive pulmonary disease (COPD) exacerbations requiring re-admissions among inner city New Yorkers. (25) In this study, respiratory co-morbidity includes asthma/COPD and did not independently contribute significantly to the composite outcomes. Studies on COPD patients have shown that systemic steroid use is related to risk of re-admissions and mortality. (26) Interestingly, glucose infusions administered during index hospitalization was also noted to be associated with a significant increase in subsequent ER visits. Whether this could have led to the worsening of metabolic milieu is unclear from the data. As noted earlier, non-emergent ER visits are higher in this inner city population, thereby potentially confounding data related

to ER visits.

Hypoglycemia, as defined by serum glucose less than 40 mg/dl, is an important risk factor for mortality in the setting of hyperglycemia control. (4, 8, 27) This study shows that among inner city minority subjects, hypoglycemia at serum glucose level less than 80 mg/dl can also be associated with increased mortality. Whether hypoglycemia is the direct cause of increased mortality cannot be concluded from the observational data. However, recent reports have suggested even mild hypoglycemia as one of the possible reason for increased mortality during tight glycemic control. (27) Our results indirectly supports this evidence and underscores the importance of avoiding even mild hypoglycemia during attempts to improve glycemic control among hospitalized in-patients with short length of stay and relatively less severe illnesses in an inner city population regardless of their diabetes disease burden.

There are limitations to our study. First, this is an observational study within a single center setting serving a predominantly minority population. Second, patients were selected regardless of the knowledge of their diabetic status pre-admission. Considering the studies showing higher mortality among patients with newly diagnosed hyperglycemia, further studies will be needed comparing the effect of newly diagnosed diabetes on outcome. In this study, diabetes did not have a direct impact on outcomes in this study. Third, data on nutritional intake during hospitalization and how blood sugar control was sustained post-discharge could not be taken into consideration. Lastly, whether sustaining blood sugar levels within a specific blood sugar range will lead to better and safe outcomes could not be decisively established in this observational clinical study setting.

Nevertheless, the results of this study serves as a sounding board of caution to in-patient physicians treating in-patients, with respect to attempts at aggressive blood sugar control especially during short lengths of hospitalization in general wards for brief acute illnesses that could potentially lead to hypoglycemia related effects. Randomized clinical trials are required to validate or refute the results within inner city minority populations.

CONCLUSION

In summary, random acute hyperglycemia of > 200 mg/ dL among non-critically ill in-patients of predominantly minority background has no impact on readmissions or mortality and emergency room visits within 90 days of discharge, regardless of diabetes status. This finding could be explained on the basis of a relatively mild and brief metabolic derangement resulting in reactive hyperglycemia to non-critical illness. On the other hand, hypoglycemia is associated with increased mortality. Avoidance of hypoglycemia during hospitalization is an important consideration during treatment of non-critically ill patients.

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