So Much Insulin, So Much Hypoglycemia

Sei J. Lee, MD

University of California, San Francisco and San Francisco VA Medical Center

Hypoglycemia is the most common and serious adverse event caused by insulin treatment. Besides the well-known potential for hypoglycemia to cause immediate injury, coma or even death, there is evidence that hypoglycemia may increase the risk of dementia many years later.[1] Despite its importance, remarkably little is known about the epidemiology of insulin-related hypoglycemia. Thus, the article by Geller and colleagues is an important addition to our knowledge base.[2]

Geller and colleagues used 2 nationally representative surveys to estimate the rate of ED visits for patients taking insulin. First, they utilized the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance (NEISS-CADES) project to estimate the total number of ED visits due to insulin. Then, they utilized the National Health Interview Survey (NHIS) to estimate the total numbers of Americans using insulin. Combining these estimates, the authors calculated the number of ED visits for 1000 persons taking insulin, stratifying the results by age category and concurrent use of oral medications.

The authors report several striking results. First, across all age groups, patients taking only insulin were several times more likely to have an emergency department (ED) visit for hypoglycemia than patients taking insulin with oral glucose-lowering medications. Second, older adults greater than age 80 are at nearly twice the risk for hypoglycemia as younger adults. Finally, insulin-related hypoglycemia is remarkably common.

There are several potential explanations for the finding that using insulin alone leads to greater hypoglycemia than using insulin with oral glucose-lowering medications. First, patients with type 1 diabetes are likely highly overrepresented in the insulin only group and are known to be at 3-4 times higher risk for hypoglycemia than insulin-treated patients with type 2 diabetes.[3] However, since type 1 diabetes accounts for <10% of all patients with diabetes, this segregation of type 1 and type 2 patients is unlikely to fully account for the results. Second, previous studies suggest that continuing oral medications when starting insulin leads to lower total insulin requirements. Lower doses of insulin may lead to lower risk of hypoglycemia. Future research should directly address the question whether concurrent oral glucose-lowering medications with insulin leads to lower hypoglycemia rates than insulin alone in patients with type 2 diabetes.

Requests for reprint should be addressed to: Sei J. Lee, MD MAS Assoc Professor, UCSF Division of Geriatrics 4150 Clement Street Bldg 1, Rm 220F San Francisco, CA 94121 415-221-4810 x4543 415-750-6669 (fax) Sei.lee@ucsf.edu.

The finding that older patients are at especially high risk for hypoglycemia is not new. Shorr and colleagues examined Tennessee Medicaid enrollees age 65 and older between 1985 – 1989 and found that for 1000 person-years of insulin use, there were 27.6 episodes of hospitalization, ED use or death. Further, Shorr found that age >80 (compared to age 65-70) conferred an 80% increased risk of hypoglycemia.[4] The similar results from these 2 studies suggests that the current study's results represent actual rates of insulin-related hypoglycemia.

Beyond the findings that patients >80 years of age and patients taking only insulin are at higher hypoglycemia risk, it is important to recognize the absolute magnitude of the hypoglycemia epidemic. There are nearly 100,000 ED visits for insulin-related hypoglycemia annually, compared to 715,000 myocardial infarctions.[5] Unlike heart attacks, the vast majority of hypoglycemia is caused by the healthcare system. Given the magnitude of the insulin-related hypoglycemia epidemic and our role in this epidemic as healthcare providers, we must examine the causes of this epidemic to develop effective strategies to decrease hypoglycemia in the future.

The pharmaceutical industry has shaped the current widespread belief in tight glycemic control that has led to aggressive prescribing of glucose lowering agents including insulin. From 2002, Aventis (maker of glargine insulin) and public relations firm Burson-Marsteller effectively marshalled many organizations including the American Diabetes Association (ADA) and the National Committee for Quality Assurance (NCQA) to encourage more intensive glycemic treatment. Slogans such as "Aim, Believe, Achieve" and "A1c<7% by 2007" encouraged both patients and providers to push for more intensive glycemic control.[6] In 2006, the NCQA included a Hemoglobin A1c target of <7% in its HEDIS (Healthcare Effectiveness Data and Information Set) quality indicators, despite the fact that the Technical Expert Panel unanimously rejected this measure.[6] In 2008, the ACCORD study showed that intensive glycemic control caused increased mortality, leading NCQA to drop A1c<7 measure. However, the ADA has continued to recommend a goal of A1c<7% for most patients, contributing to the ongoing widespread belief among patients and providers that tighter control is almost always better.[7] Thus, the 50% increase in insulin use in the past decade noted by Geller and colleagues and the resultant epidemic of insulin-related hypoglycemia documented in this report is due in part to the all-too-effective efforts by Aventis to encourage patients and providers to intensify glycemic treatment.

To mitigate these harms in the future, I propose 3 changes to current practice and guidelines.

First, glycemic targets should be a range rather than "less than 7%." By recommending a target that is <7%, proponents are sending a subtle but powerful message that lower is better. For many, a target of <7% suggest that the 6% is better than 7% and that 5% is better still. However, the ACCORD trial showed that when we treat to an overly aggressive A1c target (average A1c 6.4), increased mortality may result. Recommending a target range of A1c (e.g. 6.5 – 7.0%) rather a "less than" target (e.g. <7%) would immediately send the message that too low can be dangerous and a happy medium is best.

Second, quality indicators for glycemic overtreatment must be developed and reported.[8] Currently, nearly all quality indicators for diabetes care encourage healthcare providers to do more. HEDIS measures for 2013 encourage providers to achieve A1c<8%, blood pressure <140/80 and LDL cholesterol <100. Thus, a provider who aggressively treats to these targets would be identified as a "good doctor" even if the patient has hypoglycemia, has orthostatic hypotension with syncope and myalgias. Quality indicators that highlight overtreatment are needed so that providers are encouraged to treat without overtreating. Potential measures for glycemic overtreatment include reporting episodes of hypoglycemia or A1c<7% for adults older than 65 at high risk for hypoglycemia.[9]

Third, insulin should be avoided in most non-hospitalized adults over age 80. Most patients over 80 have significant comorbidities, functional limitations and limited life expectancy. Since the benefits of tight glycemic control are not seen for many years, patients with limited life expectancy are exposed to the immediate hypoglycemia risks with little chance that they would benefit.[10] Although there are 80 year olds who are especially healthy and may benefit from insulin, most are more likely to be harmed. Thus, the default decision should be to avoid insulin in older adults >80 and elect to control sugars less tightly using oral medications.

The occasional episode of hypoglycemia has long been accepted as the price of good glycemic control. However, this research shows that insulin-related hypoglycemia is far too common to be an acceptable price for treatment. In 1980, many accepted the 53,200 fatalities from motor vehicle accidents as the price of living in a mobile society. Through a combination of measures including regulations (e.g. seat belts and air bags) and improvements in vehicles and roads, the number of fatalities in 2008 decreased to 39,000, despite 75% more cars. We should not accept the current rates of hypoglycemia as inevitable. Rather, we should embark on a multi-pronged approach to decrease the overuse of insulin to minimize hypoglycemia.

Acknowledgments

References

1. Whitmer RA, Karter AJ, Yaffe K, Quesenberry CP Jr. Selby JV. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. JAMA : the journal of the American Medical Association. Apr 15; 2009 301(15):1565–1572. [PubMed: 19366776]

2. Geller AISN, Lovegrove MC, Kegler SR, Weidenbach KN, Ryan GJ, Budnitz DS. National Estimates of Insulin-Related Hypoglycemia and Other Misadventures Leading to Emergency Department Visits and Hospitalizations. JAMA Internal Medicine. 2013

3. Donnelly LA, Morris AD, Frier BM, et al. Frequency and predictors of hypoglycaemia in Type 1 and insulin-treated Type 2 diabetes: a population-based study. Diabetic medicine : a journal of the British Diabetic Association. Jun; 2005 22(6):749–755. [PubMed: 15910627]

4. Shorr RI, Ray WA, Daugherty JR, Griffin MR. Incidence and risk factors for serious hypoglycemia in older persons using insulin or sulfonylureas. Archives of internal medicine. Aug 11-25; 1997 157(15):1681–1686. [PubMed: 9250229]

5. Go AS, Mozaffarian D, Roger VL, et al. Executive summary: heart disease and stroke statistics--2013 update: a report from the American Heart Association. Circulation. Jan 1; 2013 127(1):143–152. [PubMed: 23283859]

6. Aron D, Pogach L. Transparency standards for diabetes performance measures. JAMA : the journal of the American Medical Association. Jan 14; 2009 301(2):210–212. [PubMed: 19141769]

7. American Diabetes Association. Standards of Medical Care in Diabetes-2014. Diabetes Care. Jan 1; 2014 37(Suppl 1):S14–80. [PubMed: 24357209]

8. Lee SJ, Walter LC. Quality indicators for older adults: preventing unintended harms. JAMA : the journal of the American Medical Association. Oct 5; 2011 306(13):1481–1482. [PubMed: 21972311]

9. Pogach L, Aron D. The other side of quality improvement in diabetes for seniors: a proposal for an overtreatment glycemic measure. Archives of internal medicine. Oct 22; 2012 172(19):1510–1512. [PubMed: 22965316]

10. Lee SJ, Eng C. Goals of glycemic control in frail older patients with diabetes. JAMA : the journal of the American Medical Association. Apr 6; 2011 305(13):1350–1351. [PubMed: 21467289]