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Hypoglycemia in the Hospital and in the U.S. Population

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Chapter 1: Introduction to Hypoglycemia

Background

Hypoglycemia is an important adverse health outcome of diabetes management and treatment. Hypoglycemia is defined as low blood glucose and the clinical definition describes it as blood glucose lower than 70mg/dL (ADA, 2020). It is also the most common and serious adverse event of insulin therapy and a main limiting factor of tight glucose control (Shorr et al., 1997; Geller et al., 2013; Freeland, 2017; Lee, 2014). Hypoglycemia is a major barrier to adherence, which often limits care. The impact is also severe among minority and vulnerable populations such as the elderly and African Americans (Flack et al., 2003; Nicolucci et al., 2015). Moreover, while hypoglycemia is common, the incidence and risk factor estimates vary. Therefore, the treatment of hypoglycemia and methods of addressing this complication has greatly developed and emerged in its field over the years providing a more dynamic understanding of its complexity and its risks. For example, the clinical complexity when patients have multiple comorbidities, polypharmacy, the influence of societal factors (low-socioeconomic status, insurance, social norms, etc.) and the effect of intensive treatment to maintain optimal glycemic control present a better understanding of the complexity of hypoglycemia (Tourkmani et al., 2018; Frazier, 2005; Wild et al., 2010; Canedo et al., 2018; McCoy et al., 2016). Therefore, to address the risks and non-adherence that contribute to the complexity of hypoglycemia, the field of preventing hypoglycemia now focuses on individualization and patient centered treatment (Lavernia et al., 2015).

The increased recognition of the root causes or risk factors of hypoglycemia allows one to tailor and address those risks associated to prevent hypoglycemia. Through shared decision-making, patients and clinicians can apply scientific evidence regarding the benefits and risks of glucose-lowering therapy to each patient’s unique circumstance, context, and preferences for care (Silbert et al., 2018). Clinical decision support tools can facilitate this process by integrating a variety of data sources to compute an individualized hypoglycemia risk and alert providers when an intervention may be necessary (Silbert et al., 2018). Therefore, individualized treatment and understanding how social determinants influence behavior and how the relationships between these variables might be modified can help with prevention and management of complications such as hypoglycemia (ADA, 2019).

Individualized treatment should be determined by a close working relationship between a diabetes care team and the patients (Shafiee et al., 2012). The healthcare professionals may improve patient knowledge and produce positive changes in lifestyle and self-care decisions (Shafiee et al., 2012). Therefore, patients experiencing or at risk for hypoglycemia may benefit from diabetes self-management education focused on glucose monitoring, medication management, recognition of precipitating events, and treatment of hypoglycemia (Silbert et al., 2018). Quality diabetes self-management education and support (DSMES) has been shown to improve patient self-management, satisfaction and glucose outcomes (D'Eramo-Melkus et al., 1992). DSMES are educational-related interventions that use an integrated approach that includes clinical content and skills, behavioral strategies (goal setting, problem solving), and engagement with psychosocial concerns (ADA, 2019). When individuals can effectively use the information provided by the DSMES and guidance by healthcare providers their health outcomes and the risk of diabetes related complications such as hypoglycemia can improve (Lamanna et al., 2019; Norris et al., 2002). Thus, the purpose of this dissertation is to determine the gap in DSMES (educational) related interventions in the past 20 years in inpatient settings, implement a pilot randomized control trial that educates patients to reduce hypoglycemia incidence using a decision support provider report in the hospital setting and to estimate the prevalence of overtreatment in the past 10 years, which is also known to increase the risk of hypoglycemia in the U.S. population.

Definition of Hypoglycemia

One of the fundamental issues with understanding the burden of hypoglycemia is the heterogeneity of how hypoglycemia is defined, documented and ascertained. Since 2005, the American Diabetes Association (ADA) has defined *confirmed hypoglycemia* as symptomatic or asymptomatic blood glucose ≤70mg/dL, *probable* as symptoms typical of hypoglycemia in the absence of blood glucose measurements, and *relative hypoglycemia* as typical symptoms accompanied by blood glucose > 70 mg/dL (ADA, 2005; Silbert et al., 2018). The ADA defined *severe hypoglycemia* as requiring assistance of another person for management and symptom recovery after treatment (ADA, 2005; Silbert et al., 2018). In 2013, the ADA focused on patient-reported events when they recommended health care providers to routinely ask at-risk patients about symptomatic and asymptomatic hypoglycemia (ADA, 2013). In 2017, the ADA reclassified blood glucose ≤ 70mg/dL as a *hypoglycemia alert value* warranting treatment with fast-acting carbohydrate and adjustment of glucose lowering therapy; added the category of *clinically significant hypoglycemia* with blood glucose <54mg/dL (ADA, 2017; Silbert et al., 2018). Severe hypoglycemia was redefined as the presence of severe cognitive impairment requiring external assistance for recovery irrespective of glucose level (ADA, 2017; Silbert et al., 2018). These definitions of hypoglycemia suggest the difficulty to operationalize in population based and clinical studies. Most hypoglycemic-related events occur outside of the healthcare system and may go undetected or undocumented. Research studies may use documented hypoglycemia, which are often recorded in the electronic medical record as a lab-result or patient-documented in chart notes. Therefore, this further suggests the complexity and the limitations of identifying and defining hypoglycemic events, which leads to the difficulty of estimating its prevalence.

Disparities in Diabetes-Related Care and Complications

Certain populations are more likely to have poor outcomes and are susceptible to hypoglycemia. Health disparities persist despite improvements in medical care and disease prevention (Thornton et al., 2016). Disease-treatment outcomes strongly effect racial and ethnic minorities but can also exist through a complex network of factors such as genetics, education, adherence to treatment and socioeconomic status that can ultimately impact access to proper medical care (Ferdinand & Nasser, 2015, Walker et al., 2016). African Americans and other economically disadvantaged racial and ethnic minorities and populations of all races with low socioeconomic status, experience large disparities in health (CDC, 2014, AHRQ, 2001). Limited access to healthcare in low socioeconomic populations is often an explanation for racial/ethnic differences in diabetes complications (Ferdinand & Nassar, 2015). However, an observational study from 1995 to 1998 found that ethnic disparities in diabetes complications still exist in patients with uniform healthcare (Karter et al., 2002). Therefore, disparities in hypoglycemia may also exist because of individual level factors or because a population has greater health care needs and demands than other population groups (i.e. elderly with more comorbidities and disabilities).

Preventing hypoglycemia in at-risk populations may be an important step on the road to reduce health disparities. Interventions that target individual level factors include improving health and lifestyle behaviors reducing sociocontextual barriers such as access to adequate food and employment resources (Thornton et al., 2016). In addition, healthcare professionals should be skilled in assessing social determinants of health and taking them into consideration in clinical care to improve and prevent hypoglycemia (Walker et al., 2016). Therefore, it is important to understand the challenges in preventing hypoglycemia in vulnerable populations such as the elderly, minority and low socioeconomic groups.

At-Risk Populations Affected by Hypoglycemia

Older Adults

There were 49 million elderly people (i.e. those aged ≥ 65 years) in the United States in 2016 and the number is projected to increase to almost 95 million by 2060 (Freeman, 2019). Improvements in managing health conditions such as diabetes and glycemic control, that allows individuals to live longer, coincides with an increased prevalence of hypoglycemia, and hypoglycemia is one of the most nonfatal complications in older patients with diabetes (Freeman, 2019).

Hypoglycemia among the elderly is complex due to multiple factors. Elderly people are more prone to hypoglycemia and hospitalization due to a higher rate of comorbidities such as renal failure, malnutrition, malignancies, dementia, and frailty (Kagnasky et al., 2003; Stagnaro-Green et al.,1993). Furthermore, polypharmacy is also common among the elderly due to the greater occurrence of multiple chronic clinical conditions, which may increase the risk of hypoglycemia especially when patients are on diabetes medications such insulin or sulfonylureas (Sircar et al., 2016). Recurrent episodes of hypoglycemia in the elderly is associated with silent and chronic complications which could lead to significant physical and cognitive dysfunction and eventually to frailty, disability, and increased mortality (Abdelhafiz et al., 2015). With a significant decline in clinical status, older adults have increased problems with self-care activities which include errors in calculating insulin dose, skipped meals, skipped insulin doses and difficulty recognizing, preventing, or treating hypoglycemia (ADA, 2020). Lastly, treatment of diabetes is also complex in the elderly due to multiple comorbidities, functional disabilities socioeconomic influences and life expectancy (Freeman et al., 2019). Older adults require assessment of health and personal values prior to determining individualized treatment goals and strategies (LeRoith et al., 2019). Therefore, with the growing population of older adults there is a critical need for research to prevent hypoglycemia in older adults.

Individuals with Low-Socioeconomic Status

Socioeconomic status is based on the measure of several factors, which include education, income and occupation (Pathirana et al., 2018). Research has shown that multimorbidity incidence and prevalence is known to vary by measure of socioeconomic status, with an excess burden in lower socioeconomic groups. (Pathirana et al., 2018). Socioeconomic status may influence access to and quality of care, social support, and availability of community resources (Grintsova et al., 2014). It may also influence diabetes-related knowledge, communication with providers, treatment choices and the ability to adhere to recommended medication, exercise and dietary regimens (Grintsova et al., 2014). Population-based studies have shown that low socioeconomic status is associated with increased risk for hypoglycemia in diabetes patients (Berkowitz et al., 2014). Therefore, low SES may lead to inadequate self-management skills. For example, it can impede patient-clinician communication in patients' understanding of clinician information and instructions, and patients' reporting of symptoms and disease state to clinicians (Sarkar et al., 2010). A better understanding of socioecononomic status and the increase risk of hypoglycemia can help eliminate disparities and reduce the risk of hypoglycemia.

Hypoglycemia in Hospital Setting

Hypoglycemia in the hospital setting is associated with an increase in risk of adverse health outcomes, morbidity and mortality. While hypoglycemia is associated with increased mortality, in many cases it is a marker of underlying disease rather than a cause of fatality. (ADA, 2019). Adverse drug events such as hypoglycemia are the most common cause of complications affecting 1.9 million hospital stays annually with an estimated cost of 4.2 billion per year (Kulasa & Juang, 2017). Over half of all ADEs are from hypoglycemic agents with the majority of these being preventable (Kulasa & Juang, 2017). Individuals without diabetes may develop hypoglycemia in hospitals in association with factors such as altered nutritional state, heart failure, renal or liver disease, malignancy, infection, or sepsis, which also holds true for individuals with diabetes (Shilo et al., 1998; Fisher et al., 1986). Additional triggering of events leading to iatrogenic hypoglycemia include sudden reduction of corticosteroid dose; altered ability of the patient to self-report symptoms; reduction of oral intake; emesis; new NPO status; reduction of rate of administration of intravenous dextrose; and unexpected interruption of enteral feedings or parenteral nutrition (Clement et al., 2004). Under prescribing antihyperglycemic medications are not always protective against the causes of hypoglycemia (Clement et al., 2004). Therefore, in order to shorten hospital stays and readmission as well as improve patient outcomes, hospitals are dedicated to follow well-developed standards and protocols. Hospitals strive for optimal inpatient diabetes management and treatment through established and structured insulin order sets and protocols which include computerized physician order entry (CPOE) that addresses medication related errors and efficiency in medication administration (ADA, 2019). These standardized insulin order sets and protocols are supplemented with diabetes self-management education from a specialized diabetes management team, which include appropriate skills needed after discharge, such as medication dosing and administration, glucose monitoring, and recognition and treatment of hypoglycemia (ADA, 2019). It is through these measures that hypoglycemia can be prevented and hypoglycemic events can be triggered in the hospital setting.

Impact of Hypoglycemia in Hospitalized Patients

The impact of hypoglycemia in hospitalized patients has been a common problem in vulnerable populations such as the elderly. Patients with hypoglycemia can have complications related to consequent cognitive dysfunction such as falls, and can also have neuroglycopenic manifestations such as seizures (Carey et al., 2013). Such complications may be part of the reason hypoglycemia can be associated with longer lengths of stay or the need for higher levels of monitoring (Carey et al., 2013).

Hypoglycemia is also associated with long-term all-cause mortality (Boucai et al., 2011; Garg et al., 2013; Nirantharakumar et al., 2012). Inpatient mortality associated with hypoglycemia can be spontaneous or iatrogenic secondary hypoglycemia (Gomez-Huelgas et al., 2015). However the literature on the latter issue is inconsistent with some studies showing that spontaneous hypoglycemia is associated with increased mortality (Gomez-Huelgas et al., 2015).

Studies have shown that people with diabetes during their hospitalization was associated with an increased likelihood of inpatient mortality. Turchin et al. (2009) found that after retrospectively analyzing 4368 admissions in 2582 patients with diabetes hospitalized in general wards they found the odds of inpatient death rose threefold for every 0.56mmol/l decrease in the lowest blood glucose below 3.9mmol/l during hospitalization (Turchin et al., 2009; Ruan et al., 2019).

Similarly, a study conducted in the U.K, retrospectively looked at routinely available electronic data of 6374 admissions from inpatient with diabetes and showed that, compared to the group without hypoglycemia, the adjusted odds ration of inpatient mortality was 1.62 (95% CI 1.16-2.27) in the group with blood glucose values of 2.3-3.9 mmol/l; the adjusted odds ratio was 2.05 (95% CI 1.24-3.38) in the group with blood glucose values ≤ 2.2mmol/l (Nirantharakumar et al., 2012; Ruan et al., 2019).

Furthermore, patients who present with hypoglycemia may be more likely to have hypoglycemia due to inadequate caloric intake, excess alcohol consumption, or excessive dosages of their antihyperglycemic medications (Curkendall et al., 2009). These causes may be more readily treated in a controlled hospital setting and may explain, in part, why hypoglycemia on presentation is less predictive or a negative outcome (Curkendall et al., 2009). Therefore, when hypoglycemia occurs the cause needs to be elucidated and treatment regimen adjusted appropriately (Carey et al., 2013). Inpatient glycemic protocols and diabetes treatment should be effective, not labor-intensive, patient-centered and individualized to the patient.

Manuscripts

This dissertation will focus on the risk of hypoglycemia in the hospital setting and in the U.S. population. The papers will attempt to better understand the gaps in the literature on multifaceted educational interventions that were implemented to reduce the incidence of hypoglycemia in inpatient settings and to determine whether a randomized control trial that individualized the educational interventions to the patient reduced the incidence of hypoglycemia in the hospital setting. The papers will also attempt to determine overtreatment in the U.S. population, which increases the risk of hypoglycemia.

Manuscript # 1- Role of Diabetes Educational Interventions on Hypoglycemia Reduction and Outcomes in Inpatient Hospitalized Populations.

Manuscript 1 is a literature review with the specific aim of understanding the role of education in multifaceted interventions to reduce the incidence of hypoglycemia among hospitalized inpatient populations in the United States and around the world over the past 20 years. The review spans from simple to sophisticated interventions that have used technology coupled with education to reduce hypoglycemia. To determine the gaps in these types of interventions it is critical to understand the nature of the multi-faceted interventions that have used education to reduce the risk of hypoglycemia. Understanding the implications and limitations of these interventions is critical to tailor and individualize interventions to the needs of the population to reduce the rate of hypoglycemia. The review also helps to understand the evolvement of interventions and the adoption of protocols, which have led to the examination of the risk factors of hypoglycemia according to experts and national guidelines. In addition, strategies to improve adoption of hypoglycemia treatment protocol and proactive management of patients with key hypoglycemia risk factors were shown to reduce rates of both hypoglycemia and recurrent hypoglycemia (Gregory et al., 2018).

Manuscript # 2- Hypoglycemia Investigation, Intervention and Prevention Operation (HIIPO): Screening for Risk Factors for Hypoglycemia Using the HIIPO System: A Randomized Control Trial

Manuscript 2 is a pilot randomized control trial with the specific aim to determine the risk factors of hypoglycemia using the HI-IPO system that uses a decision support provider report from a patient questionnaire and electronic data sources to reduce the incidence of hypoglycemia in primary care clinics at Grady Memorial Hospital. Patient-centered care in which patients and providers work together for disease management is a key component of quality of healthcare. Providers recognition of key risk factors that increase patient's risk of hypoglycemia and patients use of information to reduce the risk of hypoglycemia can address the complex and situational demands of healthcare.

Questions addressed are: What are the risk factors of hypoglycemia? Will a tailored feedback intervention reduce the risk of hypoglycemia?

Identifying the risk factors of hypoglycemia in the hospital setting is complex and depends on the multitude of factors. Tailoring treatment to address these risk factors (especially in minority and vulnerable populations) through the use of education and referring to a specialized diabetes management team are effective means of reducing adverse outcomes such as hypoglycemia in the hospital setting (ADA, 2019).

The provider-patient communication and interaction during a hospital or clinic visit is important. Many patients do not understand medical instructions they receive from physicians and the amount of information provided at one time might be overwhelming (Khurana et al., 2019). It has been reported that patients forget 40-80% of treatment instructions that they are given once they leave the clinic (Khurana et al., 2019). Therefore successful diabetes self-management research relies on patient engagement and strong communication between patients and providers (Kruse et al., 2013). Improving communication between doctors and patients will help patients commit to challenging lifestyle adaptations such as physical activity, diet and medication adherence (Kruse et al., 2013; Brundisini et al., 2015).

Overall, the data from the HI-IPO randomized control study suggest that majority of the patients have low socioeconomic status, have low literacy and are a minority population (African-Americans). Although, most of the population may have a high school diploma, low literacy scores, and the lack of resources due to low-socioeconomic status may affect the way the patients may use health information. However, a specialized diabetes management team with a certified diabetes educator may help with educating patients on the risks of hypoglycemia and ways to prevent it. Furthermore, different stakeholders (pharmaceutical, hospitals, clinics) may specialize and simplify health information to help patients reduce the risk of hypoglycemia.

Manuscript # 3: Potential Overtreatment of Diabetes Mellitus in Older Adults with Tight Glycemic Control

Manuscript 3 through secondary analysis of a nationally available dataset, National Health and Nutrition Examination Survey, NHANES, examines the potential of overtreatment in older adults with tight glycemic control in the U.S. population. Overtreatment occurs when the goal of healthcare providers and patients are to maintain tight glycemic control to better manage their diabetes. However, tight glycemic control can lead to overtreatment with diabetes medications that can increase the risk of hypoglycemia. The specific aim of this paper is to examine the NHANES data from 2009-2018 to determine the trend in glycemic control levels among older adults with diabetes mellitus by health status and to estimate the prevalence of potential overtreatment of diabetes.

Glucose lowering agents have been implicated in one-fourth of emergency hospitalizations for adverse drug events in older U.S adults, nearly all of them for hypoglycemia (Lipska et al., 2015). In 2016, hospital admissions for hypoglycemia surpassed those for hyperglycemia. (CDC, 2020). In addition, hypoglycemia is a dominant complication in older adults and individuals with a longer diabetes duration (Huang et al., 2014).

Higher glycemic targets with an HbA1c <7% may be appropriate for those individuals who are relatively healthy and those with complex poor/ complex intermediate health treated with low risk diabetes medications. However, older adults who try to reach higher glycemic targets with complex poor/complex intermediate health may be at an increased risk of hypoglycemia due to medications that are at high-risk for hypoglycemia. Therefore, it is important to predict overtreatment to recognize the harms and benefits of tight glycemic control to allow professionals in health care to make informed decisions on glucose lowering medications and treatment.

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Chapter 2: Manuscript 1

The Role of Diabetes Education on Hypoglycemia Reduction and Outcomes In Hospitalized Inpatient Populations: A Review of the Literature

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Abstract

Hypoglycemia is a significant barrier to effective diabetes treatment and despite advances in diabetes treatment and self-management, rates of hypoglycemia have led to increased health care costs and hospital admission. It is thus suggesting that in addition to interventions that have used standardized insulin order sets and protocols and technology, human factors such as education and training from a multidisciplinary team are effective in diabetes self-management and hypoglycemia reduction in the hospital setting.

The purpose of the review is to determine the role of diabetes education interventions on hypoglycemia incidence reduction and outcomes among hospitalized inpatient populations in the United States and around the world over the past 20 years. This review helped to determine the gaps in the literature and studies conducted that used diabetes education in inpatient populations to help with diabetes self-management and hypoglycemia reduction.

The searched databases for this study include Medline, Pubmed, CINAHL Plus and Cochrane Library and include English-language titles, abstracts, and full-text articles published primarily in the U.S. and around the world between January 2000 to December 2019 with inpatient hypoglycemia and educational prevention or intervention as the key phrase in the search. Studies with educational interventions or a component of the intervention as educational for the hypoglycemia risk and events were included.

Findings have shown that effective diabetes self-management strategies are important to reduce hypoglycemic events. Most of the evidence of these strategies has found that multifaceted interventions that have had an educational component have been successful in reducing rates of hypoglycemia in the inpatient setting. Although high-quality RCTs have been lacking, the sophisticated interventions that have used technology and an educational component have shown to be successful in reducing rates of hypoglycemia. These studies have shown that education as a sole component does not contribute to the overall success of these interventions and a combination of the multifaceted interventions is important to achieve these results. However, there is an urgent need of research in this area. The use of other technological enabled education tools such as mobile health technologies (i.e.smartphones) and a referral of the patient to a diabetes education program and interdisciplinary educational interventions can further contribute to work in this area.

Introduction

Diabetes is a deadly and costly disease condition that affects millions of people, communities, families, and a nation as a whole. Hypoglycemia, a significant complication of diabetes treatment and self-management, is a common adverse event of inpatient admission for drug reaction and hospitalization (Budnitz et al., 2011).

Common acute complications and chronic diabetes-related problems, such as hypoglycemia, have increased U.S health care costs and hospital admission. National trends in hospital admissions for hypoglycemia have increased during the period when glycemic control improved (Lipska et al., 2014). These trends now exceed those for hyperglycemia (CDC, 2020). Therefore, in response to findings from extensive research trials such as the Diabetes Control and Complications Trial (DCCT) (DCCT Research Group, 1988) and the United Kingdom Prospective Diabetes Study (UKPDS) (United Kingdom Prospective Diabetes Study Group, 1998), which have resulted in stricter clinical guidelines for glycemic control have led to an increased prevalence of emergency department utilization and hospitalization for hypoglycemia, particularly in older adults and minority populations (Lipska et al., 2014, Kattan et al., 2018).

Inpatient Hypoglycemia in Special Populations

Hypoglycemia is common in hospitalized elderly patients and is associated with poor outcomes (Umpierrez & Pasquel, 2017; DeCarlo & Wallia, 2019; Davis et al., 2020). Older adults are more prone to hospitalization because of the higher rate of comorbidities and geriatric syndromes, such as renal failure, malnutrition, malignancies, dementia, and frailty (Kirkman et al., 2012; Sinclair et al, 2018). Polypharmacy, which is more common in the elderly, is due to the higher occurrence of multiple chronic clinic conditions, which may increase the risk of severe hypoglycemia, especially when patients are on sulfonylureas and insulin (Freeman, 2019). Changes in medications are frequent during hospitalization and can lead to hypoglycemia when hypoglycemic agents (i.e., insulin, sulfonylureas, etc.) are used. Additionally, age-related changes in pharmacokinetics and pharmacodynamics have the potential of increasing the adverse effects of polypharmacy in this patient population (Freeman, 2019; Chelliah & Burge, 2004). Furthermore, hypoglycemia symptoms in the elderly are less pronounced than in younger patients (Hope et al., 2018). Elderly patients are susceptible to neuroglycopenic symptoms, which include dizziness, visual disturbances, increased agitation and/ or confusion compared to the usual adrenergic symptoms, which include palpitations, sweating, and tremors, which leads to hypoglycemia unawareness (Hope et al., 2018). Lastly, recent large studies have also shown a lack of benefit and sometimes-higher risk of morbidity and mortality in the elderly treated with tight glycemic control (Skyler et al., 2009; Munshi et al., 2011).

Inpatient hypoglycemia can also affect ethnic and minority populations such as African Americans. For example, in hospitalized African Americans, the rates of hypoglycemic events were 4-fold higher compared to white patients in the 12-year period when glycemic control improved in the United States (Lipska et al., 2014). Hypoglycemia and racial/ethnic inequalities in African Americans and racial minorities are, in part, attributable to differential access to care. Racial and ethnic minorities are also less likely to achieve recommended glycemic targets and more likely to experience long-term diabetic complications compared with whites with diabetes (Karter et al., 2017). In the SUPREME-DM Network, which was a seven-year surveillance study that evaluated race/ethnic differences in the trends in rates of severe hypoglycemia in insured at-risk adults with diabetes, African Americans had consistently higher severe hypoglycemia rates compared with Whites and other racial groups (Karter et al., 2017). There is also some evidence that age and race/ethnicity affect the development of diabetes-related complications and mortality. For example, African Americans have higher rates of diabetes-related complications, which include visual impairment, ESRD, hospital discharges, and mortality compared with non-Hispanic whites (Lopez et al., 2014). Lastly, medication adherence is an important modifiable factor when considering the multidimensional nature of diabetes treatment (Krass et al., 2014). Medical adherence may vary across racial/ethnic groups. Multiple studies have found that African Americans and Hispanics have lower oral antidiabetic medication adherence rates compared to Whites (Lopez et al., 2014). Literature also shows the challenges to proactive diabetes management in minority populations which include limited health literacy, which may decrease ability to comply with lifestyle and medication recommendations, reduced access to preventive healthcare visits and barriers to accessing medications (Shen & Washington, 2008) Minority populations also delay care-seeking and may not have ready access to a primary care physician, which may result in diabetes being out of control, reflecting in acute hyperglycemia and hypoglycemic conditions (Shen & Washington, 2008).

Inpatient Hypoglycemia

In patient care settings, hypoglycemia remains to be a problem. In general medicine and surgical patients with diabetes, hypoglycemia occurs in 12-38% of patients with type 2 diabetes receiving insulin therapy (Umpierrez & Pasquel, 2017; Umpierrez et al., 2011; Newton et al., 2013; Umpierrez et al., 2007; Umpierrez et al., 2013; Wexler et al., 2007; Bueno et al., 2015). Characteristics include an elderly population due to declining renal function and polypharmacy, patients on medications such as insulin and sulfonylureas, duration of the diabetic disease, and, and race with African Americans and Hispanics being more susceptible to hypoglycemia **(**Umpierrez & Pasquel, 2017; Lopez et al. 2015). Moreover, interruptions in usual nutritional intake and changes in medications frequently occur during hospitalization and can precipitate hypoglycemia when hypoglycemic agents are used (Umpierrez & Pasquel, 2017). Events of hypoglycemia can also occur during hospitalization. For example, in a large cohort study by Akirov and colleagues (2018), 15% had at least blood glucose value ≤ 70mg/dL with 7% with at least one glucose value <54mg/dL (serious hypoglycemia). Inpatient hypoglycemia has been associated with prolonged hospital length of stay and with numerous adverse outcomes, including mortality (Seaquist et al., 2013).

As patients transition from one setting to another, or from one provider to another, their risk of adverse events such as hypoglycemia increases. Nearly 2 million elderly patients are in nursing facilities in the U.S with diabetes affecting 25-35% of them (Lubart et al., 2014 & Munshi et al., 2016) and they often have changes in their nutritional intake and organ dysfunction, which increase the risk of hypoglycemic events (Pasquel et al., 2015). In general, therapy is aimed at attaining optimal levels of serum glucose while avoiding the acute complications of hypoglycemia or uncontrolled hyperglycemia and preventing or delaying the progression of the chronic complications of diabetes (Pasquel et al., 2015). Hypoglycemic events in long-term care residents present similar situations as for the elderly population. Most individuals in long-term care facilities are treated with insulin, experience greater emergency department utilization, more frequent hospitalizations, and higher rates of mortality than peers who have never experienced a hypoglycemic event (LaManna et al., 2019).

Delivery of National Recommendations and Guidelines for Inpatient Hypoglycemia Education and Management

Diabetes management is essential in the prevention of diabetes-related complications and physical changes related to changes in glycemic status. Diabetes self-management education and support of a (DSMES) program are considered to be a critical component of effective diabetes care. Several National Initiatives have provided guidelines and recommendations for using structured education to reduce the incidence of hypoglycemia without compromising glycemic control in the inpatient setting. For example, The Joint Commission Advanced Inpatient Diabetes Certification Program is founded on the American Diabetes Association's Clinical Practice Recommendations and is linked to the Joint Commission Standards. They recently revised its certification requirements for inpatient diabetes care. Critical components of this program involve staff education on diabetes management and patient education on self-management of diabetes. The program states that "those identified as having educational deficits in the inpatient setting should receive education, regarding information such as medication management, nutrition exercise, hyperglycemia, hypoglycemia, the importance of blood glucose monitoring, sick day guidelines in addition to contact for in case of emergency and a post discharge plan for continued educational support" (Arnold et al., 2016). Furthermore, the program also emphasizes self-management skills that are conveyed through education so that the patient can transition to home with adequate skills necessary to care for himself/herself (Arnold et al., 2016). In addition, to self-care education, the JC-ADA certification also emphasizes the importance of a multidisciplinary team who will work together to create blood glucose protocols to attain the correct glycemic targets and provide management regarding the optimum outcome for the patient (Arnold et al., 2016). Furthermore, national guidelines state that enrollment in a blood glucose awareness training program will help to recognize subtle cues and early neuroglycopenic indicators of evolving hypoglycemia and respond to them before the occurrence of disabling hypoglycemia (Seaquist et al., 2013).

The American Association of Diabetes Educators', AADE, 2016 position statement also recommends the initiation of diabetes self-management education early during hospitalization to allow time to address potential deficits in patient knowledge. The AADE encourages staff education together with competency testing that can facilitate the ability of nursing personnel to provide both inpatient diabetes management and patient education (Umpierrez et al., 2012). Topics for staff education include recognition of types of diabetes treatment and prevention of hypoglycemia and hyperglycemia symptoms glycemic targets in critical care and non-critical care settings and acute complications such as diabetic ketoacidosis (Umpierrez et al., 2012). The AADE also recommends the inclusion of a diabetes educator in inpatient care teams to improve diabetes patient care (Moghissi et al., 2009). Lastly, implementation of standardized hospital-wide, nurse-initiated hypoglycemia treatment protocols to provide prompt immediate therapy of any recognized hypoglycemia and implementation of a system for tracking frequency of hypoglycemic events with root cause analysis of events are other recommendations for recognition and management of hypoglycemia in the hospital setting in combination of diabetes self-management education (Umpierrez et al., 2012). Therefore, meeting inpatient diabetes educational needs requires a sustained effort of the health care team and patients. The role of national initiatives addressing the need for tailored and individualized treatment and meaningful office interactions with a multidisciplinary approach and national guidelines that empower patients and the healthcare team are essential strategies to reduce the incidence of hypoglycemia. Therefore, the role of this review is to examine educational interventions or multifaceted interventions with an educational component that have been conducted in inpatient settings to reduce the incidence of hypoglycemia. The review will highlight simple interventions that can be easily implemented to more sophisticated technological interventions inherent to the electronic medical record that has used a multifaceted approach with education as a key component.

Methods

For this review, we searched PubMed, Medline, CINAHL Plus, and Cochrane Library from January 2000 to December 2019 using these keywords 'inpatient hypoglycemia' 'inpatient low glucose' 'educational prevention' 'educational intervention'. We filtered the search to include only those individuals that were older than 18 years old and were in inpatient settings and were non-critically ill. We included studies conducted in medical and surgical floors and excluded studies conducted in intensive care settings and studies that initiated insulin use. We also searched for recently published systematic reviews and meta-analysis to reconcile studies on educational interventions for hypoglycemia prevention that were not identified in our original search.

Findings: Article Selection, Characteristics and Findings

Table 1. reports the characteristics of the 15 retained studies. In the early and mid-2000s, the American Diabetes Association and the Task Force to Review and Revise the National Standards for Diabetes Self-Management Education Programs recommended to critically review the current standards and prepare an evidence-based review of the literature and to revise the national standards for Diabetes Self-Management Education Programs. The National Standards for Diabetes Care focused on diabetes self-management, and education programs for patient empowerment and lifestyle modification followed by the introduction of hypoglycemia treatment protocols and development of standardized order sets for use of sliding scale insulin, with the eventual introduction of an Insulin Order Set guiding the use of scheduled and correctional insulin (ADA, 2002; Korytkowski et al., 2006) Since then, studies have focused on these aspects

of diabetes management and care in the inpatient setting. Until the late 2000s, insulin was the only “accepted” agent for effectively controlling glycemia in the hospital. Although there had been studies in the critical care setting through a variety of intravenous infusion protocols which have shown to be effective in achieving glycemic control with a low-rate of hypoglycemic events and improving hospital outcomes during this time (Umpierrez, 2007), there had been no prospective and randomized interventional studies that have focused on the optimal management of hyperglycemia and its effect on clinical outcome among non-critically ill patients admitted to general medicine services (Umpierrez, 2007). The beginning of the 2000s focused on diabetes education and knowledge deficiencies of hospital staff and what to teach newly diagnosed patients (Nettles et al., 2005).

In the U.S., researchers focused on the safety and efficacy of order sets for medications following educational sessions with nurses and doctors for glycemic management and control in the hospital. These studies followed the 2006 ACE/ADA Statement on Inpatient Diabetes and Glycemic Control, which identified key components of an inpatient glycemic control program which included (1) reliable administrative support (2) a multidisciplinary committee (3) assessment of current processes, care and barriers (4) development and implementation of order sets, protocols, policies, and educational efforts (5) metrics for evaluation (ACE/ADA Task Force on Inpatient Diabetes, 2006).

There have been three studies that have focused on the safety and efficacy of order sets for diabetes medications with educational components (Noschese et al., 2008, Hermayer et al., 2009; Thompson et al., 2009).

The safety and efficacy of order sets were well accepted and evidenced by the high prescriber use. Nochese et al. (2008) demonstrated that educational efforts accompanying implementation of the order set have been affected positively accompanying implementation of the order set (Noschese et al., 2008). The inappropriate orders determined by the expert panel review were used to guide prescriber education (Noschese et al., 2008). Furthermore, nurse and doctor internet-based learning modules on diabetes medications have been developed based on identified educational needs. The diabetes order set also served as a tool in the process of educating and encouraging hospital staff to prescribe insulin in a more physiological manner (Noschese et al., 2008). However, the number of doctors ordering insulin was limited due to the investigational period, which were only for two hospital units and the results would have differed on other units represented by other medical specialties (Noschese et al., 2008). Hermayer et al. (2009) also showed the success of the safety and efficacy of hospital-wide insulin order sets. The non-randomized retrospective design with a historical control incorporated the key element of the implementation strategy, which included an educational program for the hospital staff. Although, the rates of hypoglycemia were reduced, the multipronged approach, which began with the treatment protocol followed by changes, may have influenced the rate of hypoglycemia and hyperglycemia (Hermayer et al., 2009). The absence of a control group and the under-power of the study were some of the limitations of this study (Hermayer et al., 2009). Thompson et al. (2009) also showed a significant decrease in hypoglycemia rates that was largely attributed to the education provided by the glycemic control program. The study increased and improved insulin ordering. However, the observational design could not distinguish confounders such as physician preferences and decisions that not easily quantified or controlled for (Thompson et al., 2009). Moreover, the addition of the clinical intervention team came only 6 months before the end of the study period (Thompson et al., 2009).

The American Diabetes Association (ADA) now advocates reasonable metabolic control defined as pre-prandial glucose levels of 90 to 130 mg/dL and peak postprandial glucose levels <180mg/dL in hospitalized non-intensive care units patients (ADA, 2007). To reach these goals, the ADA and American College of Endocrinology suggest that multidisciplinary teams develop and implement hypoglycemia management and protocols (ACE/ADA Task Force on Inpatient Diabetes, 2006). Protocols should promote the use of continuous intravenous insulin infusions or scheduled basal-bolus subcutaneous insulin protocols that should include target glucose levels basal, nutritional and supplemental insulin and daily dose adjustments (Schnipper et al., 2009).

Intervention approaches included structured insulin order sets and protocols for the treatment of hyperglycemia and glycemic control with an educational component to overcome barriers related to hypoglycemia. Three studies used an educational component for these types of interventions (Maynard et al., 2009; Schnipper et al., 2009; Schnipper et al., 2010,).

Intervention approaches that included structured insulin order sets and protocols for hyperglycemia treatment and glycemic control with educational components have shown success in the reduction of hypoglycemia. Maynard et al. (2009)'s observational study design assessed the impact of structured insulin orders on insulin use patterns, hypoglycemia and glycemic control through structured insulin orders and insulin management algorithm. The educational and organizational changes contributed to the overall success of the program and resulted in a 32% decline in the percent of patient days with hypoglycemia (Maynard et al, 2009). However, the limited resources of the multidisciplinary steering committee to create a dedicated team for insulin management, mandated endocrinology co-management or consultations or manual data collection were a hindrance of the program (Maynard et al., 2009). There was only one diabetes educator for 400 adult beds at two sites (Maynard et al., 2009). Moreover, the observational nature of the study design contributes to the difficulty of assessing whether the structured order sets and insulin management algorithm were actually the cause of the improvement seen (Maynard et al., 2009).

Schnipper et al. (2009)'s study was an advancement to the Maynard et al (2009)' study as it determined the effects of a multifaceted quality improvement intervention on the management of medical inpatients with diabetes or hyperglycemia. The study included a detailed subcutaneous insulin protocol, an admission order set built into the hospital's computerized order entry system and case-based education workshops and lectures nurses, physicians and PAs. (Schnipper et al., 2009). The intervention required few resources to continue indefinitely: which include printing costs for the management protocol, 4 hours of education delivered per year and routine upkeep of education delivered each year (Schnipper et al., 2009). However the limited generalizability of the findings and limited statistical power to detect differences in hypoglycemia rates attribute to its limitations (Schnipper et al., 2009).

Schnipper and colleagues (2010) also conducted a cluster-randomized control trial to determine the effects of a computerized order set on the inpatient management of diabetes and hyperglycemia. The addition of the order set built into the hospital's CPOE system in combination with physician and nurse education improved glucose control (Schnipper et al., 2010). The study was also able to rigorously evaluate benefits of particular components of the multifaceted quality improvement intervention in the randomized control trial (Schnipper et al., 2010). Few studies have been able to do this. Moreover, the study required very few resources to continue indefinitely. However, the study had limited generalizability and statistical power.

An advancement within computerized order sets and protocols are alert systems that are highly-reliable methods to improve order set use and daily insulin adjustment to determine when glucose levels are out of control. Glucose alert systems have been shown to improve staff action in response to adverse glycemia (Kilpatrick et al., 2014). In non-critical settings, the efficacy of this approach is to address clinical inertia (Kyi et al., 2018). Furthermore, alert systems are precursors to track hypoglycemic events and encourages root cause analysis for hypoglycemia. Nine studies have used glucose alerts or some sort of alert system in combination of education to reduce the rates of hypoglycemia (Elliot et al., 2012; Kilpatrick et al., 2014; Kyi et al., 2018, Mendez et al., 2015, Maynard et al., 2015; Rajendran et al., 2015; Rushakoff et al., 2017; Donihi et al., 2011, Gregory et al., 2018).

Most of the interventions that used glucose alert systems coupled with education have shown a reduction in rates of hypoglycemia. Although glucose alert systems in non-critical inpatient settings can vary greatly in function and complexity, the role of education in these multifaceted interventions was critical in decreasing the rates of hypoglycemia. A manual alert system may be simple such as a color-coded blood glucose monitoring chart while an electronic alert system uses point of care blood glucose data that generates computerized alerts when a predefined blood glucose criteria has been met (Kyi et al., 2018). The alerts can be generated by the user or in real-time. The integration of the hospital electronic clinical information system is also important in the success of alert systems (Kyi et al., 2018).

Donihi et al (2011) studied a glycemic management team who remotely monitored blood glucose measurements and alerted the health care team of severe hyperglycemia. Prior to the pilot study, educational sessions were provided at resident conferences and faculty meetings to acquaint all physicians with the hospital's existing diabetes guidelines, protocols and order sets (Donihi et al., 2011). The templated note that was put in the medical records, reinforced the educational component of the study (Donihi et al., 2011). However, the multifaceted intervention did not decrease the incidence of hypoglycemia (Donihi et al., 2011). Similar to Kyi et al. (2018), which also alerted the treating team. However, Mendez et al. (2015) who also remotely assisted primary care teams in the management of hyperglycemia and diabetes showed a 41% decrease in hypoglycemia (Mendez et al., 2015) They used a software application linked to the computerized patient electronic medical record, which generated a daily report of hypoglycemia and hyperglycemia (Mendez et al., 2015). The recommendations provided by the health care team, who looked for opportunities for improving glycemic control, was included for educational purposes that improved glycemic control.

Elliot et al. (2012) developed an algorithm for hypoglycemia surveillance coupled with an education program, which produced an increased awareness of the risks of hypoglycemia among hospital staff (Elliot et al., 2012). However, the failure to predict 40% of hypoglycemic events in the original analysis led them to suggest that a predictive equation is only one tool among many that are necessary to protect patients from harm (Elliot et al., 2012). Similarly, Kilpatrick et al. (2014) used the algorithm developed by Elliot et al. (2012) to determine whether a predictive informatics hypoglycemia risk alert supported by trained nurse responders would reduce the incidence of severe hypoglycemia in the hospital setting (Kilpatrick et al., 2014). The extensive training through education and proficiency in patient assessment and the communication process by nurses was paramount in the success of the alert and led to the significant reduction of severe hypoglycemia in the hospitalized patients (Kilpatrick et al., 2014). Moreover, the alert algorithm correctly identified patients who were at high risk of hypoglycemia and allowed caretakers the opportunity to lower that risk (Kilpatrick et al., 2014).

A larger study by Rajendran et al. (2015) showed that a Diabetes Inpatient Care & Education Project and a comprehensive diabetes care pathway significantly decreased the rate of severe hypoglycemia from 15.4% to 9.7% (Rajendran et al., 2015). However, the study was multifaceted with extensive education, included risk assessment for patient self-administration of insulin, blood glucose testing and an increase in medical staff (Rajendran et al., 2015). Similarly, Rushakoff et al. (2017) determined whether a virtual glucose management service improved glycemic control. The remotely located healthcare team was able to review the insulin/glucose charts in the electronic medical records and provide recommendations for insulin changes through a note, which served as an alert (Rushakoff et al., 2017). The study showed that the proportion of hyperglycemic and hypoglycemic patients decreased by 39% and 36% (Rushakoff et al., 2017). Both of these studies showed that an increase in medical staff and extensive educational training may be required to decrease hypoglycemia.

Alert systems and education have also been included in interventions that determine the root cause of hypoglycemia. Maynard et al. (2015) sought to determine the effectiveness of a hypoglycemic reduction bundle, proactive surveillance of glycemic outliers and an interdisciplinary data-driven approach to glycemic management (Maynard et al., 2015). The hypoglycemia reduction bundle coupled with extensive ongoing education, and robust standardized orders and documentation greatly contributed to the significant reduction in inpatient hypoglycemic events (Maynard et al., 2015). However, the multiple interventions made it difficult to specify which interventions had the largest impact in reducing hypoglycemia (Maynard et al., 2015). Similarly, Gregory et al. (2018) identified the root causes of hypoglycemia in medicine inpatient units using an automated tool in the electronic medical records, which served as an alert to implement an educational intervention for safe and effective use of insulin (Gregory et al., 2018). Rates of hypoglycemia decreased from 2.3% to 1.5%

(Gregory et al., 2018). However, the pre-post design without a control group and inability to generalize to other patients were limitations (Gregory et al., 2018).

The studies mentioned have shown that multifaceted interventions with an educational component have been successful in reducing the rates of hypoglycemia. In addition, technology that included alerts and tools inherent to the electronic medical record have made the detection of hypoglycemic events simple and less resource intensive. However, the lack of randomized control trials have made it difficult to determine the cause of improvement and decrease in the rates of hypoglycemia.

Role of Education in Hypoglycemia Risk Prevention: Comparison of Programs in Systematic Reviews

The role of education on hypoglycemia risk reduction in patients with type 1 and type 2 diabetes have been similar. Evidence from trial data suggests that structured education reduces the incidence of severe hypoglycemia and improves awareness of hypoglycemia in those with iatrogenic hypoglycemia in type 1 diabetes (Iqbal & Heller, 2018). Longer-term observational follow-up also indicates a reduction in the rate of severe hypoglycemia of around 50% following educational interventions (Iqbal & Heller, 2018). For patients with insulin-treated type 2 diabetes, high-quality RCTs investigating the role of structured education are generally lacking, and even fewer have reported rates of severe hypoglycemia (Iqbal & Heller, 2018).

Lamanna and colleagues conducted a systematic review of the educational impact on hypoglycemia outcomes and found that DSMES programs can have an impact on hypoglycemia outcomes, which was measured in 14 retained quasi-experimental, RCT and case-control studies. Among 14 studies retained in their review, 8 identified a reduction in hypoglycemia outcomes compared with the control (Lamanna et al., 2019).

Cruz and colleagues (2017) conducted a review to highlight approaches to predict and prevent inpatient hypoglycemia that has been successfully implemented, focusing on developing overlapping policies and procedures that allow safe glycemic management to occur at all levels of the institution. They found that standardizing point-of-care (POC) testing, nursing programs, meal delivery, and formulary restriction are useful tools to prevent hypoglycemia (Cruz et al., 2017). They also found that informatics and real-time alert processes are highly useful tools to reduce hypoglycemia but require a significant investment in time and infrastructure as well as clear policies on how alerts are acted upon (Cruz et al., 2017). Although these studies and findings from the systematic reviews have shown that educational interventions or an educational component of the interventions have shown a reduction in hypoglycemia, there have been few RCTs conducted in this area, and it makes it difficult to establish the benefit of educational interventions.

Summary of Findings and Conclusion

We have described interventions ranging from simple to sophisticated that have used an educational component, which has shown to decrease hypoglycemia in the inpatient setting over 20 years in the U.S and around the world. Evidence from trial data suggests that interventions that have used a multifaceted intervention with a multidisciplinary team and an educational component have reduced the rates of hypoglycemia. The standardization of insulin order sets and the development of hypoglycemia protocols have marked the beginning of sophisticated interventions that use technology and automated tools in electronic medical records. Although standardization of insulin order sets and protocols that used an educational component in non-randomized trials have been successful in reducing the rates of hypoglycemia, they have been labor-intensive and have required rigorous monitoring and required constant staff support.

Furthermore, observational and non-randomized studies for standardizing insulin order sets and protocols could not predict whether the improvements in the pilot study were a result of the increased education provided alone or of increased awareness and general improvement in diabetes management or organizational changes throughout the studies. Furthermore, educational efforts were necessary but not sufficient in and of themselves to effect significant improvement (Maynard et al., 2009). The few randomized controlled trials that have standardized insulin order sets and protocols have shown the benefits of multifaceted interventions. They have found that it is unlikely that an order set by itself without education and other interventions to achieve clinician "buy-in" would have achieved similar results (Schnipper et al., 2010). Also, the use of advanced and sophisticated technology in these randomized control trials required fewer resources to continue indefinitely. The more sophisticated studies that have used computerized order sets and alert systems in the combination of education and multifaceted interventions have increased awareness of risks of hypoglycemia among the hospital staff. They have found that the creation and availability of diabetes protocols and order sets as a guide are not sufficient enough for improving the care of hospitalized patients with diabetes and hyperglycemia (Donihi et al., 2011). The addition of alert systems in a combination of extensive training and education was paramount in the success of the alert and protect patients from medication harm. Furthermore, educational programs have shown an increase in confidence, knowledge, and empowerment of trainee doctors and patients.

The retained studies in this review spanned a variety of recruitment strategies in the hospital setting. Only one study mentioned targeted interventions directed to at-risk minority populations, which include African Americans compared with the general diabetes population (Hermayer et al., 2009). This is particularly significant because hospitalization rates of African

Americans for acute diabetic complications such as hypoglycemia are four times higher than those of the general diabetes population (Lipska et al., 2014). Most of the studies targeted at-risk elderly population compared to younger adults. Therefore, there is a need for research targeting minority populations in order to develop culturally tailored strategies to improve hypoglycemia in these at-risk groups.

High-quality randomized control trials investigating the role of education in a combination of multifaceted interventions for hypoglycemia prevention are lacking, and there is an urgent need for further work in this area, especially in those populations who are at higher risk. Education, as an intervention or a component of multifaceted interventions, has shown success in improving rates of hypoglycemia in the hospital setting. It is crucial to consider the implications and cost-effectiveness of educational interventions in relation to technology. A combination of both types of interventions has shown to be effective in reducing hypoglycemia and have required less intensive resources. Therefore, it is essential to consider these interventions as essential ways to reduce diabetes-related complications such as hypoglycemia. Empowerment of hospital staff and patients on diabetes management through education yields health benefits and can help reduce overall health care costs in the future.

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Source	Sample Characteristics	Study Design	Intervention/Intervention Duration	Change in Rate of Hypoglycemia
Noschese et al. (2008)	N=70 Age=ND Setting Tertiary Care Center University of Pittsburgh Medical Center: 26 non-critical care units and 13 critical care units Duration DiabetesType: ND	Observational: pre-post		There was no significant difference in the number of patients with an an episode of mild hypoglycemia between the two units. There were no episodes of severe hypoglycemia
Hermayer et al. (2009)	N=13.366 BG readings? Age=? Setting: The Medical University of Sourth Carolina Medical Center is a 709 bed hospital and tertiary referral center for partnering hospitals in the Southeastern U.S. Duration Diabetes: Type 1 & Type 2	Retrospective data	Institution of hospital-wide hypoglycemia, hyperglycemia, subcutaneous insulina and intravenous insulin treatment protocols	The percent time in range improved by 10% with no increase in the amount of severe hypoglycemic episodes for the blood glucose resulrs.
Thompson et al. (2009)	N=18,087 Age= 48.4±20.3 Setting: Academic Regional level-one trauma center. Seattles HMC 400 bed level-1 regional trauma center managed by the University of Washington Duration Diabetes Type 1 & Type 2	Observational pre-post	(1) Development of a subcutaneous insulin physician order set (2) Use of a real-time data report to identify patients with out of range glucoses andimplementation of clinical intervention team	Hypoglycemia declined after the intervention 4.3% to 3.6%.
Kyi et al (2018)	N=148 Age=Baseline 70±14 intervention: 68±14 Setting-Non-critical wards of a tertiary hospital Duration: 4 months Diabetes: Type 1 & Type2	Observational pre-post	Intervention consisted of 2 components designed to promote a consistent staff response to blood glucose measurements (1) a clinical escalation pathway the Melbourne Glucose Alert Pathway (2) networked blood glucose meters which provide a visual alert for out of range blood glucose measurement	There was no difference in hypoglycemia incidence
Rajendran et al. (2015)	B=96 Age=ND Setting: Ipswich Hospital: 550 bed secondary care hospital Duration: 1 year Diabetes: Type 1 & 2	Observational pre-post	Evaluation of the impact of the Diabetes inpatient care and education project and a comprehensive diabetes care pathway the diabetes inpatient care and education care pathey on patient outcomes on the knowledge and confidence of trainee doctors	Severe hypoglycemia decreased from 15.4 to 9.7%.

Rushakoff et al. (2017)	N=12,535 Age=61.2 Setting: 3 University of California, Sanfrancisco Hospitals Duration: 3 year period Diabetes: Type 1 & 2	Cross-sectional	Hospitalized adult patients with 2/more glucose values of 12.5mmol/L or greater (Hyperglycemic) and or a glucose level less than 3.9mmol/L (hypoglycemic) in the previous 24 hours were identified using a daily glucose report. Based on review of the insulin/glucose chart in the electronic medical record, recommendations for insulin changes were entered in a VGMS no which could be seen by all clinicians	The hypoglycemic proportion in the VGMS period was 36% lower than in the Pre-vgms period. 40 severe hypoglycemic events occurred during the pre-VGMS period compared with 15 during the VGMS period.
Gregory et al. (2018)	N for 2016: 566 N for 2017: 642 Age for 2016: 62.28±17.88 Age for 2017: 61.86±18.5 Setting: New York Presbyterian Hospital. Two Inpatient General Medicine Units in Academic Medical Center Duration- 2 month period in 2016 and 2017 Diabetes: Type 1 & 2	Observational pre-post	Educational intervention for Safe and Effective use of insulin	Rates of hypoglycemia decreased from 2.3% to 1.5%. The number of patients with recurrent hypoglycemia decreased from 5.7% to 2.2%
Kilpatrick et al. (2014)	N=655 Age=60 years Setting: Barnes-Jewish Hospital. 10 internal medicine and 4 cardiology medicine floors. 6 internal medicine floors were intervention floors amd 8 were control floors Duration: 5-month period Diabetes: Type 2	Prospective-Cohort Intervention	Electronic alert to identify patients at high risk of hypoglycemia. Nurses trained to assess alert. Nurses received 5 hours of hypoglycemia and management training in 3 sessions utilizing a structured curriculum. Session 1 included pretest followed by diabetes management education. Session 2 was devoted to an interactive workshop utilizing case based scenario of diabetes management problems. Final session provided instructions on the electronic alert communication process. Physicians also received training	Decrease of 50% in moderate hypoglycemia and decrease in 68% in severe hypoglycemia
Maynard et al. (2015)	N=22,990 Age=59.7±14.7 Setting: UC Sandiego Health System-Wards Duration-5 Calendar years: 2009-2013 Diabetes: Type 1 & 2	Prospective Observational	Hypoglycemia reduction bundle targeting most common remedial contributors to iatrogenic hypoglycemia. Clnical decision support in standardized and glucose management pages; measure vention (daily measurement of glycemic outliers with concurrent intervention by the inpatient diabetes team; Educational Programs	
Schnipper et al. (2009)	N=169 Age: 63.0±15.7 (pre-int) 64.7±14.3 (Post-int) Setting: Brighams & Women's Hospital. Generally localized. General Medical Service Staffed by Physician Assistants and Hospitalists Duration Diabetes: Type 2	Before-After Trial (Pre-post)	A detailed subcutaneous insulin protocol in admission order set built into the computerized order entry system and case based educational workshops and lectures to nurses, physicians and Pas.	The percent of patient days with any hypoglycemia was 5.5% pre-intervention and 5.1% afterward

Schnipper et al. (2010)	N=177 Age=64.8±15.5 (int) 65.4±12.2 (control) Setting: Brigham & Womens Hospital. General Medical Service of the Academic Medical Center Duration: 2 months Diabetes:	Clustered Randomized Control Trial	Patients randomized on the basis of medical team to usual care (control) or an admission order set built into the hospitals computer provider entry (CPOE) system (Intervention) All received a detail subcutaneous insulin protocol and case-based education	There was no significant difference in the percent of patient-days with any hypoglycemia or severe hypoglycemia
Maynard et al. (2009)	N=9,317 Age=56±17 Setting: University Hospital. 400-bed. University of California. San Diego Duration: November 2002-December 2005 Diabetes: Type 1 & Type 2	Prospective Observational	Structured insulin orders and insulin management algorithm During each intervention, education sessions were given throughout the hospital to staff using departmental grand rounds, nursing rounds and in services to describe the process and goals. Educational template assess patient readiness to learn, home enviornment, current knowledge and other factors.	The percent of patient days with hypoglycemia was 3.8%, 2.9% and 2.6% in 3 time periods, representing a RR for hypoglycemic day in TP3:Tp1 of 0.68
Donihi et al. (2011)	N=654 Age=18≥ years: ND Setting: University of Pittsburgh Medical Center. 800 bed adult tertiary and quarternary academic medical center Duration: 12 week pilot Diabetes: Type 1 & Type 2	Observational pre-post	Patients with blood glucose level ≥300mg/dL. Who were hospitalized on a general medicine unit during three 12-week periods before, during and after the TGM were compared for responsiveness by the primary team, percentage of subsequent severe hyperglycemia and hypoglycemia.	The incidence of hypoglyceia was similar in all 3 periods (3.9%, versus 3.7%, 3.7%)
Elliott et al. (2012)	N=3028 Age=ND Setting: Barnes-Jewish Hospital. 1259-bed tertiary care center in St. Louis, Mo Duration: 5 months Diabetes: Type 1 & 2			
Mendez et al (2015)	N=7,133 Age=69 years Setting: Stratton VA Medical Center in Albany New York Duration: January 2010 to 2013 Diabetes: Type 1 & Type 2	Retrospective study	The use of the DINGS process in which a software application linked to the computerized patient electronic medical record system, a daily report of hypo and hyperglycemia from all hospitals were generated. When opportunites for improving glycemic control were identified a note was entered in the electronic medical records with recommendations for educational purposes.	Rates of hypoglycemia decreased by 40%

Chapter 3: Manuscript Two

Hypoglycemia Investigation, Intervention and Prevention Operation (HIIPO): Screening for Risk Factors for Hypoglycemia Using the HIIPO System: A Randomized Control Trial

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Abstract

Hypoglycemia is an important complication of intensive glucose therapy to achieve optimal glycemic control in patients with diabetes mellitus. Repeated episodes of hypoglycemia can lead to the onset of short and long-term complications that can reduce the quality of life. Early recognition of risk factors followed by an intervention for healthcare professionals to educate their patients are important ways to reduce and prevent the risk of hypoglycemia in order to maintain optimal glycemic control. This study was a pilot randomized control trial that screened for risk factors for hypoglycemia from a provider report using data from a patient questionnaire and electronic data sources, followed by a delivery system of tailored set of interventions for healthcare professionals to educate their patients on risks of hypoglycemia. Phone call follow-ups were conducted 3 months after recruitment. Electronic Medical Reviews were conducted nine months after recruitment and intervention to determine the severity and whether the intervention reduced the incidence of hypoglycemia. Univariate and multivariate logistic regression analysis was used to determine the predisposing risk factors for hypoglycemia. Logistic regression analysis was also used to determine whether the intervention reduced the incidence of hypoglycemia nine months post recruitment. Results indicated that insulin use and age 60+ were significant predictors of hypoglycemia occurrence. Results also indicated that the intervention reduced the incidence of hypoglycemia occurrence nine months post recruitment ($p=0.046$) and that there was a significant reduction in hypoglycemic events after intervention. Therefore, a targeted educational intervention addressing risk factors associated with hypoglycemia was effective in reducing the rates of hypoglycemia and improving overall glycemic control. Ongoing clinician education regarding insulin use and dosing and educational tools and resources targeted for an older population could continue to lower the rate of hypoglycemic occurrence.

Introduction

Hypoglycemia is an important complication of diabetes management and treatment. It is an inevitable consequence of preventing long-term diabetes complications. It is also one of the most common adverse drug events that require emergency department visits and hospitalization. These events are noted in 1.9 million inpatient hospital stays and 838,000 treat-and-release emergency department visits (Lucado et al., 2011) They are also responsible for one-third of hospital acquired conditions and prolong hospital stays by 1.7 to 4.6 days (Gregory et al., 2018). Rates of hypoglycemia in type 1 and type 2 diabetes differ due to the heterogeneity of the disease in how hypoglycemia is defined, measured and reported in type 2 diabetes and the varying incidence in type 1 diabetes depending on the type of treatment (Zammit et al., 2005). In 2014, The Centers for Disease Control, CDC estimated 245,000 visits (11.2 per 1,000 persons) for hypoglycemia to the emergency department, which exceeded the number of emergency department visits for hyperglycemia (CDC, 2017). These estimates show the impact of adverse drug events and the effects of tight glycemic control on diabetic complications.

Research has suggested that tight glycemic control has benefits and success in reducing diabetic complications. Following the publications of the results of the Diabetes Control and Complications Trial (DCCT) with type 1 diabetes and the United Kingdom Prospective Diabetes Study (UKPDS) with type 2 diabetes, strict glycemic control have been heavily emphasized. However, large randomized control trials such as the Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease (ADVANCE) and the Veterans Affairs Diabetes Trial (VADT) have shown no benefit and have shown an increase in risk of hypoglycemia that have counterbalanced the benefits conferred by intensive glycemic control. (ACCORD, 2010; ADVANCE, 2008 & Duckworth, 2009). In response to the results of these studies, clinical practice guidelines, which include the American Diabetes Association (ADA) and the European Association for the Study of Diabetes have focused on individualized and patient centered treatment that focuses on reducing the risk of hypoglycemia (ADA, 2019; Inzucchi et al., 2015). Patient centered treatment involves adequate education, close monitoring and tailored treatment (Brooks, A.D., 2016). While individualized treatment provides a unique management plan for each patient. Both individualized and patient centered treatment is capable of providing support, structure and incentives that lead to appropriate glycemic goals of therapy. Therefore, a risk factor recognition tool coupled with a tailored educational feedback intervention is a type of individualized and patient centered treatment that is key steps for the reduction of hypoglycemia. In this paper, we will discuss and determine the predisposing risk factors for hypoglycemia and determine whether a pilot randomized control trial that used a tailored feedback intervention reduced the risk of hypoglycemia in diabetes patients of an outpatient diabetes clinic that serves predominantly African Americans.

Intensive Glycemic Control

Tight glycemic control recommended by clinical practice guidelines have recommended an HbA1c level less than 7.0% for diabetes and have resulted in the reduction of diabetic microvascular complications, however an increase in the burden of treatment, higher costs, adverse drug reactions and the risk of hypoglycemic episodes have been evident (ADA, 2019).

Several studies have found that the incidence of severe hypoglycemia was significantly higher in the intensive therapy group compared with the standard treatment group. The largest of these trials was The Action to Control Cardiovascular Risk in Diabetes Study Group (ACCORD) trial, which was designed to study the cardiovascular effects of intensive glycemic control, intensive blood pressure control, and fibrate use among people with type 2 diabetes (Punthakee, et al., 2014). The ACCORD trial randomized 10,251 participants to either a standard treatment strategy, which targeted A1c levels between 7.0 and 7.9% or an intensive strategy, which sought to attain A1c <6.0% (Action to Control Cardiovascular Risk in Diabetes Study Group, 2008; Riddle, 2010). The study resulted in a median A1c of 7.5% with the standard strategy and a median A1c of 6.4% for the intensive strategy (Action to Control Cardiovascular Risk in Diabetes Study Group, 2008; Riddle, 2010). The intensive control group also experienced higher mortality, more hypoglycemia and weight gain (Action to Control Cardiovascular Risk in Diabetes Study Group, 2008; Riddle, 2010).

The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial was a study that sought to determine the effect of the lowering of glucose to near-normal levels on cardiovascular risk. The study randomized 11,140 patients in the intensive glucose control arm that received gliclazide MR and any other additional therapy to achieve these glucose targets ;and a standard arm that received therapy according to local guidelines (ADVANCE Collaborative Group, 2008; Heller, 2009). Results indicated that severe hypoglycemia was more frequent in the intensive-control group and that about 2.7% of patients had at least one episode of severe hypoglycemia compared with 1.5% in the standard group (ADVANCE Collaborative Group, 2008; Heller, 2009). By the end of the follow-up the A1c had fallen to a mean of 6.5% in the intensive group compared with 7.3% in the standard group (ADVANCE Collaborative Group, 2008; Heller, 2009). There was sudden death in the trial, however there were no significant differences between the two groups.

The Veterans Affairs Diabetes Trial, VADT, randomly assigned 1,791 military veterans who had type 2 diabetes to receive standard or intensive therapy for glucose control. The goal of the intensive-therapy group was an absolute reduction of 1.5 percentage points in the glycated hemoglobin level as compared to the standard therapy group (Duckworth et al., 2009). Other cardiovascular risk factors were treated uniformly. By the end of the median follow up of 5.6 years, the median glycated hemoglobin were 8.4% in the standard therapy group and 6.9% in the intensive therapy group (Duckworth et al., 2009). The rate of severe hypoglycemia was 24.1% in the intensive therapy group and 17.6% in the standard therapy group (Duckworth et al., 2009). There were no significant differences between the groups in either the primary outcome and no difference was observed in the composite of microvascular complications (Brooks, A.D., 2016). However, hypoglycemia was more common in the intensive control group (Brooks, A.D., 2016).

The results from the ACCORD, ADVANCE and VADT trials have shown that intensive therapy compared to standard therapy increases the risk of severe hypoglycemia and that a one size fits all for strict glycemic control has not been recommended. The studies also show that the failure to deescalate intensive treatment when HbA1c levels are low leads to complications and the risk of severe hypoglycemia.

Defining Hypoglycemia: Causes and Risk Factors

The ADA and the European Medicines Agency (EMA) defines hypoglycemia as ‘any abnormally low plasma glucose concentration that exposes the subject to potential harm with a proposed blood glucose value of ≤70mg/dL (3.9mmol/L) (ADA, 2019; EMA, 2012). Although, there is a lack of consensus regarding the threshold blood glucose levels that classify the different stages of hypoglycemia, the ADA and EMA has defined and confirmed hypoglycemia as symptomatic or asymptomatic and classification of hypoglycemia is based on the level of severity (ADA, 2019; EMA, 2012). Hypoglycemia is classified as mild, moderate and severe. Mild hypoglycemia is defined with a blood glucose value <70 with the presence of autonomic symptoms where individuals are able to self-treat (ADA, 2019). Moderate hypoglycemia is defined with a blood glucose value <54 with the presence of autonomic and neuroglycopenic symptoms where individuals are able to self treat (ADA, 2019). Mild and moderate hypoglycemia, also known as antecedent hypoglycemia, is defined as asymptomatic and can lead to hypoglycemia unawareness. This can trigger a vicious cycle of recurrent hypoglycemia, which can lead to defective glucose counterregulation. Severe hypoglycemia is symptomatic and is defined as hypoglycemia requiring third party assistance for management and symptom recovery irrespective of the glucose level (ADA, 2019; EMA, 2012). The blood glucose level used to define severe hypoglycemia varies widely in the diabetes literature (Oyer, 2013). Levels of <56mg/dL (3.1mmol/L) or <52mg/dL (2.9mmol/L) are often used as cut offs (Oyer, 2013). Severe episodes of hypoglycemia can lead to cognitive impairment, behavioral disturbances, coma and even death (Oyer, 2013).

Iatrogenic hypoglycemia associated with diabetic medications is the most common causes of hypoglycemia in patients with diabetes (Kalra et al., 2013). Insulin, oral antidiabetic agents (OADs) such as sulfonylureas and meglitinides cause majority of hypoglycemic events experienced by patients with diabetes (Freeman, 2019 & ADA , 2019, Kalra et al., 2013). Rates of hypoglycemic events are higher in patients treated with insulin compared to OAD or insulin secretagagoues. For example, in the ORIGIN trial the risk of severe hypoglycemia increased 2-fold with sulfonylureas and 4.5 fold with insulin (Investigators OT, 2015). In observational studies the risk of severe hypoglycemia was increased two-three fold with sulfonylureas and three to four fold with insulin. (Quilliam et al., 2011; Misra-Hebert et al., 2018; Davis et al., 2010). However, the rate of hypoglycemia is increased with prolonged insulin use, which was demonstrated in the UK study that prospectively quantified rates of hypoglycemia in sulfonylurea and insulin-treated adults over a 9-12 month observation period (U.K. Study Group, 2007). Therefore, it can be inferred that episodes of hypoglycemia are related to diabetes medications and insulin therapy.

The risk of hypoglycemia is also influenced by patient and treatment-related factors. One of the strongest predictors of future hypoglycemia is prior hypoglycemia, both severe and nonsevere (Miller et al. 2001; Festa et al., 2017; Karter et al., 2017). Several studies have shown that prior hypoglycemia was predictive of future hypoglycemia. For example, Qulliam et al. (2011) used healthcare claims data to conduct a nested case-control study and found that previous outpatient or emergency department visits for hypoglycemia had increased inpatient hypoglycemia admissions more than 9-fold (Qulliam et al., 2011). Similarly, Misra-Herbert et al. (2018) conducted a retrospective cohort study using the electronic medical record in the Cleveland Clinic Health System and found that more patients with severe hypoglycemia versus those without had a prior diagnosis of nonsevere hypoglycemia and increased the risk of severe hypoglycemia 3-fold (Misra-Herbert et al., 2018).

Other causes of hypoglycemia include older age, longer diabetes duration, frailty, multimorbidity, stress and physical activity (Krinsley & Grover, 2007, Freeman, 2019, Zoungas et al., 2010). Chronic health conditions that increase hypoglycemia risk include chronic kidney disease (CKD), cognitive impairment, cardiovascular disease, depression and heart failure. (Pathak et al., 2016, Zoungas et al., 2010). Poor renal function can delay the clearance of insulin and other glucose-lowering drugs, potentially leading to excess blood levels and increased glucose-lowering effect (Freeland, 2017;). In addition, patients taking beta-blockers for heart failure may not experience early symptoms of hypoglycemia that can significantly delay recognition on treatment (Freeland, 2017; Lilley et al., 2017).

Social determinants of health also contribute to the risk of hypoglycemia, which include food insecurity, alcohol consumption, missed or delayed meals, socioeconomic deprivation and poor health literacy. (Seligman et al., 2010, Cavanaugh, 2011, Berkowitz et al., 2014, Solomon et al., 2000). There is also an increased risk of hypoglycemia in racial/ethnic minorities particularly African Americans. Several studies have found that African Americans have a higher risk of hypoglycemia compared to other ethnic groups. For example, Shen & Washington (2008) used the 2003 National Inpatient Sample to determine patterns of admissions and complications related to diabetes among ethnicities. The study found that African Americans were1.62 times more likely to be admitted to the hospital for acute hypoglycemia compared to Hispanics and Asians (Shen & Washington, 2008). Similarly, Karter and colleagues (2017) conducted a seven-year surveillance study to evaluate race/ethnic differences in the trends in rates of severe hypoglycemia in a population of insured at-risk adults with diabetes. They found that African Americans had consistently higher severe hypoglycemia rates compared with Whites while Latinos and Asians had consistently lower rates compared with Whites in each of the seven years (Karter et al., 2017). The trend increased significantly only among African Americans (Karter et al., 2017).

Achieving glycemic control while avoiding hypoglycemia is one of the challenges of diabetes treatment. Recurrent severe episodes of hypoglycemia can lead to behavioral changes, cognitive impairment and unawareness of hypoglycemia (Stargardt et al., 2009). Because of these negative consequences, patients may develop psychological fear of hypoglycemia (Stargardt et al., 2009). Fear of hypoglycemia is a risk factor most commonly found in patients with severe hypoglycemia and those individuals prone to hypoglycemia unawareness (Weinstock et al., 2016). It is also considered to be a limiting factor in achieving glycemic targets in inpatient settings (Gregory et al., 2018). Variability in blood glucose level and length of time since first insulin treatment also contribute to hypoglycemia unawareness, which increase the risk of fear of hypoglycemia (Anderbro et al., 2010). Furthermore, extreme fear of self-injecting and self-testing are other problems related to fear of hypoglycemia (Anderbro et al., 2010).

The aforementioned risk factors for hypoglycemia provide knowledge and understanding of the risk of hypoglycemia to develop strategies to mitigate its risk. Previous research has focused on the identification of risk factors for hypoglycemia followed by the implementation of an intervention to reduce the incidence of hypoglycemia. Therefore, it is important to examine studies that have focused on the root cause of hypoglycemia and to conduct a study that builds on previous work.

Hypoglycemia Risk Factors and Prevention in Real-World Studies

Identification of key risk factors for hypoglycemia followed by implementation of an intervention or a hypoglycemia reduction program have been confirmed in other studies. For example, the University of California San Diego successfully implemented a hypoglycemia reduction program that identified key risk factors for hypoglycemia in hospitalized patients (Gregory et al., 2018). Gregory et al (2018) identified the root causes of hypoglycemia following the implementation of an automated tool in the Electronic Medical Record. They found that nutrition and insulin were the two most frequent modifiable causes of hypoglycemia and that the targeted educational intervention addressing safe and effective insulin dosing resulted in a significant decrease in both hypoglycemia and recurrent hypoglycemia (Gregory et al., 2018).

Similarly, Kilpatrick and colleagues (2014) conducted a 5-month prospective cohort intervention study to determine whether a predictive informatics hypoglycemia risk-alert supported by trained nurse responders would reduce the incidence of severe hypoglycemia

(Kilpatrick et al., 2014). Results indicated a significant decrease by 68% in the rate of severe hypoglycemia in alerted high-risk patients versus non-alerted high-risk patients (Kilpatrick et al., 2014).

The current study was intended to improve the quality of care and diabetes management in patients at Grady Memorial Hospital by identifying the predisposing risk factors of hypoglycemia using a screening tool followed by an intervention. We used screening data to map patient barriers to determine specific interventions that was recommended in computer-generated reports for providers to educate their patients on the risks of hypoglycemia and interventions to prevent hypoglycemia. We also conducted electronic medical reviews to determine whether the intervention reduced the rates and incidence of hypoglycemia nine months after recruitment. This is a novel approach because this is the first randomized controlled trial that used informatics that predicted the risk factors for hypoglycemia and allowed for tailored provider feedback, provided patient summary flowsheets with individualized decision support, and provided clinical records and program monitoring capabilities. Prior studies have used surveillance systems and chart reviews to determine targeted educational intervention based on what was considered to be the top cause of hypoglycemia (Gregory et al., 2018).

Methods

This study was a pilot randomized control trial. The study population that were recruited included 85 diabetes (type 1 and type 2) patients that were 18 years or older and on medications that effect insulin release (insulin or secretagogues i.e. sulfonylureas and meglitnides) in the Primary Care Centers at Grady Memorial Hospital. Potential participants were identified through review of medical records of diabetes patients with appointments scheduled in the Primary Care Center at Grady Memorial Hospital and were approached in the waiting room. Eligible consented patients went through a preliminary screen to determine assignment to one of the two risk groups. Study participants were assigned to hypoglycemia risk groups, which included very high risk and high risk, which were monitored during the enrollment period. The very high risk group were based on prior history of hypoglycemia documented in prior 12 months. The high risk group were patients on insulin and secretagogues not eligible for very high risk group. Study groups were not assigned to a risk score. After all participants were assigned to their risk group, they were block randomized into the intervention or the usual care group. Diabetes patients were majority African American and female. Primary care providers included physicians, nurse practitioners and Internal Medicine resident-physicians. The risks of hypoglycemia and rates of hypoglycemia were determined through electronic chart reviews nine months after recruitment from September 2016 to 2017.

Development of Screening Tool

In the fall of 2016, we conducted a baseline hypoglycemia survey in the Primary Care Center at Grady. The hypoglycemia survey consisted of hypoglycemia risk questions that included questions on prior hypoglycemia, medications, food insecurity, frequency of meals, demographics, depression, alcohol use, fear of hypoglycemia, vision and health literacy. The questions were selected based on the extensive literature on these risk factors and their association with hypoglycemia. The questions were also developed based on the characteristics of the patient population that attend the Primary Care Center (PCC) at Grady Hospital. Data was collected between September 2016 to December 2016 through the administration of a hypoglycemia survey, exit questions and follow-up questions. The primary purpose of the hypoglycemia questionnaire was to screen for risk factors to prevent the risk of hypoglycemia through the assignment of interventions and provision of recommendations.

The medications on the baseline survey and through the electronic medical reviews determined whether the patient was at risk for hypoglycemia. Patients were screened for insulin and secretagogues such as sulfonlyureas and meglitinides. Patients were asked questions on low blood sugars, symptoms of low blood sugar and the causes of hypoglycemia.

Food insecurity questions allowed researchers to assess for adequacy of food and was from the two item screen from the Household Food Security Survey (Hager et al., 2010). The alcohol questions were from the alcohol AUDIT-C questionnaire, which is a 3-item alcohol screen that can help identify persons who are hazardous drinkers or have active alcohol use disorders (including alcohol abuse or dependence). AUDIT-C is a modified version of the 10-question AUDIT instrument.

Assessment for depression was from the Patient Health Questionnaire-2 (PHQ-2). The PHQ-2 inquires about the frequency of depressed mood and anhedonia over the past 2 weeks. The PHQ-2 includes the first two items of the PHQ-9. The purpose of the PHQ-2 is not to establish final a diagnosis or to monitor depression severity, but rather to screen for depression in a "first step" approach. Fear of hypoglycemia was measured using the Hypoglycemia Fear Survey II (HFS II). HFS II are composed of two subscales, the Behavior (HFS-B) and Worry (HFS-W) (Gonder-Frederick et al., 2011). HFS-B items describe behaviors in which patients may engage to avoid hypoglycemic episodes and/ or their negative consequences (i.e., keeping blood glucose levels above 150 mg/dL, making sure other people are around, and limiting exercise or physical activity) (Gonder-Frederick et al., 2011). HFS-W items describe specific concerns that patients may have about their hypoglycemic episodes (i.e. being alone, episodes occurring during sleep, or having an accident (Gonder-Frederick et al., 2011). Health Literacy was assessed using the Rapid Estimate of Adult Literacy in Medicine-Short Form (REALM-SF).

The REALM-SF is a 7-item word recognition test to provide physicians with a valid quick assessment of patient health literacy.

The stages of chronic kidney disease was determined using the serum creatinine estimates on the day of recruitment in the study. The GFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

The baseline hypoglycemia risk screening tool/survey was used to create a risk report for the intervention group. The assessment portion of the risk report characterized the level of hypoglycemia risk with any identifiable contributing factors. The intervention portion of the risk report provided customized recommendations for management changes or supplemental education.

The risk report was generated using Oracle and was designed to allow input of responses from the baseline hypoglycemia survey screening tool. The risk report summarized data from the hypoglycemia survey screening tool, the Grady Epic Medical Record, Grady EMS hypoglycemia call records and the Grady Diabetes Patient Tracking System database. The research assistant was instructed to input responses from the baseline survey into Oracle to generate a hypoglycemia risk report for the providers, which was specifically tailored for their patient. This study was approved by the institutional review board of Emory University and Georgia State University.

Data Collection

Nine months after recruitment into the randomized control trial, Electronic Medical Reviews were conducted. We conducted a prospective chart review of all patients experiencing a hypoglycemic event. Data from the baseline survey and the Electronic Medical Reviews were compared. The top risk factor for hypoglycemia was insulin use. Of note, all episodes of hypoglycemia were iatrogenic or induced by insulin or oral agents. There were no hypoglycemic events that were attributable to other known causes of hypoglycemia (i.e. food insecurity, renal disease). The EMR reviews determined hypoglycemia severity and occurrence. Hypoglycemia occurrence was determined by documented blood glucose less than 70 (POCTs and lab values), chart review reported hypoglycemia (physician notes), and follow up questionnaire reported hypoglycemia. Hypoglycemia occurrence was characterized as serious or non-serious (mild-to-moderate and unclassified). Severe hypoglycemia was characterized by its clinical definition of requiring third party assistance. Mild-to-moderate hypoglycemia was characterized of no third party assistance required. There was only one severe hypoglycemic event, which was in the intervention group. The severe hypoglycemic event was collapsed with the mild-to moderate events and the final primary outcome was categorized as patients having hypoglycemia and patients not having hypoglycemia.

Educational Intervention-Physician and Physician Assistants

The study population consisted of an intervention and a control group. The patient intervention was an educational information sheet (risk report) that helped the diabetes patients at Grady hospital manage their hypoglycemia. The provider reviewed the hypoglycemia risk report and counseled their patients on appropriate measures to prevent future hypoglycemia. The hypoglycemia risk report was generated with suggested barriers and interventions as well as an educational sheet with general and tailored suggestions. During the medical visit patient’s provider reviewed the hypoglycemia risk report and confirmed the recommendations. The research assistant carried out the necessary logistics for interventions (appointment with CDE, etc.) and confirmed follow-up appointment. A set of tailored interventions were generated for each patient. The system orchestrated implementation of interventions by supplying healthcare providers with risk assessments, prevention suggestions, by referring patients to clinic pharmacists or educators, and supplying provider and patient education personal checklists and personalized recommendations.

Study Visits

Patients were followed up through phone calls. Follow up questions assessed the symptoms and frequency of hypoglycemia, causes of hypoglycemia, things that help prevent hypoglycemia, changes in medications and time of low blood sugars.

Study Outcomes

The primary objective of the study was to determine the risk factors for hypoglycemia and whether the educational intervention reduced the incidence of hypoglycemia nine months post recruitment. A comparison of the intervention and control groups was conducted to determine whether there were significant differences between the groups.

Measures

Measures include patient reported responses to the hypoglycemia survey screening tool and Electronic Medical Reviews incidence of hypoglycemia reported through physician notes and laboratory results (POCTs)

Statistical Analyses

Analyses of the demographics of the baseline data and the EMR chart review data revealed a statistically significant difference between both the intervention and control group. ($p=0.043$). Demographics were described as frequency, percentages, mean and standard deviation and differences between both groups were described through Pearson chi square test with p-values being two-sided with statistical significant evaluated at the 0.05 alpha level. Items identified as risk factors for hypoglycemia were analyzed using univariate and multivariate logistic regression. Logistic regression was also used to determine whether the intervention reduced the incidence of hypoglycemia and to determine linear trends adjusting for other risk factors. Analyses were performed using Statistical Package for Social Sciences (SPSS) version 26.

Results

Baseline Demographics and Clinical Characteristics

This study consisted of 85 patients with diabetes. Eligible participants were randomized with 45 in the control arm and 40 in the intervention arm. The baseline demographics and clinical characteristics of the overall study population are shown in Table 2. There were no differences in baseline characteristics between the two groups. The population consisted of middle-aged adults (mean age 58.7±9.5) mostly African Americans (96.5%) and female gender (64.7%). Majority of the patients were high school graduates (42.4%) and were living alone (41.2%). Most patients had type 2 diabetes (98.8%), a mean duration of diabetes of 13.1±9.8 years and the mean admission HbA1c was 8.6±2.3. The mean eGFR rate in the diabetes patients was 76.8± 32.3 There were no differences in clinical characteristics between the intervention and control groups in comorbidities including hypertension, hyperlipidemia, coronary artery disease, neuropathy, hypertriglyceridemia, retinopathy, cerebrovascular disease and chronic renal disease. Majority of the patients were moderately obese and were in stage 2 of chronic renal disease. Majority of the patients also had cholesterol and triglyceride levels within the normal range.

Frequency of Hypoglycemia

A total of 70 events were reported to be prior hypoglycemia and a total of 33 hypoglycemic events (mild and severe) were reported by the 85 patients nine months after recruitment and intervention. Only one event was reported to be severe and required the assistance of a third party. The severe event was reported to be in the intervention group. The rest of the events were mild. The severe event was collapsed with the mild to moderate events.

Hypoglycemia Risk Factors

In univariate analyses for predictors of hypoglycemia (Table 3) including age, sex, renal function, insulin use, A1c, and the study group we found that insulin use, was an independent predictor of hypoglycemia. We also found that the intervention reduced the incidence of hypoglycemia. In multivariate analyses (Table 4) including insulin, renal function, gender, prior hypoglycemia, age and food insecurity we found trends in insulin use, (p=0.062) and in older patients above the age of 60. (p=0.076). In multivariate analysis adjusted for age, gender, race, insulin use, eGFR, A1c, and study group we found a significant association between insulin use and hypoglycemia occurrence (p=0.037) and a reduction in hypoglycemic events after intervention (p-0.044) and trends in an older population above age 60+ and hypoglycemia occurrence (p=0.067).

Discussion and Conclusion

Results of this pilot randomized control trial indicated that assessment of risk factors followed by a tailored educational intervention reduced the rates of hypoglycemic events. Insulin use and older patients above the age of 60 were the top risk factors identified by the baseline survey and the electronic medical reviews. A tailored educational intervention addressing the risk factors resulted in a significant decrease in hypoglycemia events.

According to the Endocrine Society and the American Diabetes Association guidelines, insulin use is a definite cause of low blood sugar (Donnelly et al., 2005; Heller et al., 2007; Seaquist et al., 2013). Prolonged insulin use and duration of insulin treatment is considered to be a key predictor of hypoglycemia (Donnelly et al., 2005). In our study we observed that there was an increased risk of hypoglycemic events in patients who were on insulin compared to sulfonylureas and glinides. The results support the report of the workgroup of the American Diabetes Association and the Endocrine society, which state that hypoglycemia is more frequent in individuals on insulin compared to sulfonylurea, glinides and other oral agents (Seaquist et al., 2013 & Maynard et al; 2008). Hypoglycemia treatment regimens is often suboptimal and it is important to calculate initial insulin dosages and adjust insulin dosings, mistiming of the antidiabetes regimen with nutritional intake and treatment regimens to reduce and avoid the risk of hypoglycemia (Maynard et al., 2008).

Previous studies have also reported that increasing age and an older population is an independent risk factor for the development of hypoglycemia in insulin-treated type 2 diabetes (Stepka et al.1993; Shorr et al., 1997; Farroki et al., 2012). Our study found that older patients above the age of 60 years were at a higher risk than younger patients and was an independent predictor of hypoglycemia. Elderly patients are at risk of hypoglycemia unawareness and may not recognize symptoms of hypoglycemia. In addition, elderly patients frequently fail to report symptoms to hospital staff and develop symptoms of hypoglycemia at lower glucose concentrations compared to younger patients. Therefore, implementing strategies to reduce hypoglycemia either by avoidance of intensive glycemic control or using agents with lower rates of hypoglycemia can lead to significant reduction in hypoglycemic rates, can improve patient's safety and overall quality of care in the elderly population.

Our study also indicated a severe hypoglycemic event in the intervention group, which suggests that severe hypoglycemia occurs mostly in patients with type 2 diabetes, which is uncommon and that most of the patients were treated with insulin and may have played a minor role in their disease and management.

Another interesting finding is that chronic kidney disease and food insecurity did not predispose patients to hypoglycemia in our population although previous reports have suggested that glomerular filtration rate (chronic kidney disease) and food insecurity increase the risk of hypoglycemia (Waitman et al., 2017; Seligman et al., 2010; Moen et al., 2009; Alsahli & Gerich, 2014). Most of our study population were in stage 2 of chronic kidney disease and were on insulin. A decrease in renal clearance of insulin is evident when the GFR falls below 15 and 20 mL/min per 1.73 m^2. However, this was not evident in our study. Furthermore, a study by Yun et al. reported that the presence of baseline macroalbuminuria (defined as urinary albumin excretion≥ 30mg/dL) was an independent risk factor for the future development of severe hypoglycemia in type 2 diabetic patients with apparently normal/minimally decreased renal function irrespective of whether they were receiving insulin (Yun et al.,2013; Alsahli & Gerich, 2014). Our study population was a low-income population, which makes food insecurity a significant problem for diabetes self-management and managing complications such as hypoglycemia. It is possible that the cost of food may have imposed a competing demand for diabetes medication and supplies and may have encouraged healthcare providers to relax glycemic targets. Furthermore, healthcare providers may have also emphasized alternative medications that lower the risk of hypoglycemia when food access is unpredictable.

Our study also found that the assessment of risk factors followed by an educational intervention reduced the incidence of hypoglycemia. There was a significant reduction in hypoglycemic events after intervention. The reduction in hypoglycemic events may have been due to the tailored risk report and education provided by healthcare providers and referrals to a certified diabetes educator and other members of the healthcare team.

Our study had several limitations. Our study population was from a single academic institution with a large population of African Americans with type 2 diabetes. Therefore, generalizing our results and findings to other patient populations is limited. The sample size of our study population was also small which caused small sample size bias, which affected the reliability of the baseline survey responses. Furthermore sample size calculation and the actual sample size may not have been sufficient to support a robust analysis of multiple factors. Our study also used a paper survey and the use of newer technologies such as an automated tool in the electronic medical records to map the risks of hypoglycemia and to report an hypoglycemic event would simplify the tasks for production of risk reports for the providers to be more sustainable and feasible (Gregory et al., 2018). Furthermore, documentation of hypoglycemia treatment and medication use were based on the baseline survey and electronic medical reviews, so possible causes of the hypoglycemic event as well as the exact treatment and changes made to the regimen were subject to the data collector’s search and interpretation. The baseline survey was also based on responses given by patients, therefore the responses were subject to recall bias.

Still, we think our findings and implications will hold up despite the relative shortcomings because our study design included a control group which involved randomization, we included rigorous data collection techniques, and a logistic regression analysis that adjusts for the effect of multiple cofactors.

Conclusion

Identifying the risk factors of hypoglycemia followed by a tailored educational intervention had shown a significant reduction in hypoglycemia events. Physicians were empowered in understanding and educating their patients on the risks of hypoglycemia. Incorporating a hypoglycemia risk tool in the physician workflow increases the chances of success in reducing the rates of hypoglycemia. Further considerations should include an electronic alert of the risks in the EPIC EMR and an electronic tool to document risks of hypoglycemia to further reduce the rates of hypoglycemia and overall health costs.

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Table 2. Baseline Characteristics of Study Sample

	Baseline, Total (n=85)	Intervention (n=40)	Control (n=45)	Pvalue
Characteristics				
Age, mean (SD)	58.7 (9.5)	57.4(10.1)	59.8 (9.0)	0.240[a]
Age				
<30	1(1.2)	1(2.5)	0(-)	0.799[b]
30-39	3(3.5)	2(5.0)	1(2.2)	
40-49	6(7.1)	3(7.5)	3(6.7)	
50-59	33(38.8)	16(40.0)	17(37.8)	
60-69	33(38.8)	15(37.5)	18(40.0)	
>=69	9(10.6)	3(7.5)	6(13.3)	
Sex				
Male	30(35.3)	13(32.5)	17(37.8)	0.611[b]
Female	55(64.7)	27(67.5)	28(62.2)	
Race				
White	3(3.5)	2(5.0)	1(2.2)	0.488[b]
Black	82(96.5)	38(95.0)	44(97.8)	
Ethnicity				
Non-Hispanic	82(96.5)	39(97.5)	43(95.6)	0.628[b]
Other	3(3.5)	1(2.5)	2(4.4)	
Education				0.947[b]
1-8th Grade	2 (2.4)	1(2.5)	1(2.2)	
Some High School	22 (25.9)	10(25.0)	12(26.7)	
High School Graduate	36 (42.4)	16(40.0)	20(44.4)	
Some College	20 (23.5)	11(27.5)	9(20.0)	
College Graduate	5 (5.9)	2(5.0)	3(6.7)	
Living Arrangements				0.505[b]
Live Alone	35 (41.2)	14(35.0)	21(46.7)	
Live with Significant Other	19 (22.4)	9(22.5)	10(22.2)	
Live with Family	26 (30.6)	14(35.0)	12(26.7)	
Live with Roommates	4 (4.7)	3 (7.5)	1(2.2)	
Shelter/Homeless	1 (1.2)	----	1(2.2)	
Diabetes Medications Use				
Insulin Only				
No	26(30.6)	13(32.5)	13(28.9)	0.718
Yes	59(69.4)	27(67.5)	32(71.1)	
Insulin Type				

Basal Insulin				
No	52(61.2)	26(65.0)	26(57.8)	0.495
Yes	33(38.8)	14(35.0)	19(42.2)	
Basal Bolus				
No	56(65.9)	29(72.5)	27(60.0)	0.225
Yes	29(34.1)	11(27.5)	18(40.0)	
Insulin Combo				
No	62(72.9)	28(70.0)	34(75.6)	0.565
Yes	23(27.1)	12(30.0)	11(24.4)	
Oral Medications Only				
Oral Medications only				
No	31(36.5)	15(37.5)	16(35.6)	0.853
Yes	54(63.5)	25(62.5)	29(64.4)	
Sulfonylureas				
No	60(70.6)	25(62.5)	35(77.8)	0.123
Yes	25(29.4)	15(37.5)	10(22.2)	
Metformin				
No	40(47.1)	20(50.0)	20(44.4)	0.609
Yes	45(52.9)	20(50.0)	25(55.6)	
Glinides				
No	84(98.8)	40(100)	44(97.8)	0.343
Yes	1(1.2)	0(-)	1(2.2)	
Clinical Characteristics: (mean±SD)				
Hemoglobin A1c,	8.6(2.3)	8.8(2.4)	8.3(2.3)	0.355[a]
BMI	35.8(8.7)	37.5(10.2)	34.2(6.8)	0.085[a]
eGFR	76.8(32.3)	75.4(35.5)	78.1(29.6)	0.702[a]
***Cholesterol*:**				
Total Cholesterol	160.3(52.5)	156.0(46.0)	164.3(58.3)	0.534[a]
HDL	46.1(17.2)	45.7(13.7)	46.6(17.2)	0.819[a]
LDL	82.3(37.8)	83.8(41.9)	80.9(34.1)	0.766[a]
Triglycerides	148.1(81.8)	132.7(55.6)	163.0(99.7)	0.148[a]
Comorbidities: (n (%))				
Hypoglycemia				
No	52(61.2)	29(72.5)	23(51.1)	0.043[b]
Yes	33(38.8)	11(27.5)	22(48.9)	
Diabetes Mellitus				
Type 1	1(1.2)	1(2.5)	0(-)	0.286[b]
Type 2	84(98.8)	39(97.5)	45(100)	
Missing n(%):0(0.0%)				
Hypertension				
No HTN	1(1.2)	1(2.5)	0(-)	0.291[b]
HTN	83(98.8)	39(97.5)	44(100)	
Missing n(%) 1(1.2)				

Hyperlipidemia				
No	62(73.8)	32(80.0)	30(68.2)	0.219[b]
Yes	22(26.2)	8(20.0)	14(31.8)	
Missing: n(%) 1(1.2%)				
CAD				
No	69(83.1)	34(87.2)	35(79.5)	0.354[b]
Yes	14(16.9)	5(12.8)	9(20.5)	
Missing: n (%): 2 (2.4)				
Neuropathy				
No	58(70.7)	25(64.1)	33(76.7)	0.209[b]
Yes	24(29.3)	14(35.9)	10(23.3)	
Missing: n(%):3 (3.5)				
Hypertriglyceridemia				
No	80(97.6)	38(97.4)	42(97.7)	0.944[b]
Yes	2(2.4)	1(2.6)	1(2.3)	
Missing: n(%):3(3.5%)				
Retinopathy				
No	62(75.6)	33(84.6)	29(67.4)	0.071[b]
Yes	20(24.4)	6(15.4)	14(32.6)	
Missing: n(%): 3(3.5)				
Cerebrovascular Disease				
No	81(98.8)	39(100)	42(97.7)	0.338[b]
Yes	1(1.2)	0(-)	1(2.3)	
Missing: n(%):3 (3.5)				
Chronic Renal Disease				
No	60(74.1)	28(73.7)	32(74.4)	0.940[b]
Yes	21(25.9)	10(26.3)	11(25.6)	
Missing: n(%):4(4.7%)				

*[a]T-test

*[b]Pearson X^2 test

* Categorical Variables are shown as n(%)

* Continuous Variables shown as mean±SD

*eGFR, Estimated Glomerular Rate Filtration

*Note:Percentages of treatment add up greater than 100 because many patients were treated with more than one medication

Table 3. Univariate Analysis (Logistic Regression) of Predictors of Hypoglycemia

	Odds Ratio	P-Value	95% Confidence Interval
Age <30 years	1 (ref)		
30-39	.000	1.000	.000
40-49	0.250	0.327	(0.016, 3.997)
50-59	0.100	0.077	(0.008, 1.288)
60-69	0.286	0.115	(0.060, 1.355)
69≥	0.325	0.156	(0.069, 1.534)
Sex	0.603	0.275	(0.243, 1.495)
Insulin	0.356	0.053	(0.125, 1.012)
Study Group (Int vs. Control)	2.552	0.046	(1.018, 6.248)
eGFR	0.989	0.131	(0.976, 1.003)
A1c	1.035	0.719	(0.857, 1.250)

Table 4: Multivariate Logistic Regression of Predictors of Hypoglycemia

	Odds Ratio	P-Value	95% Confidence Interval
Age < 30years	1(ref)		
30-39	.000	1.000	.000
40-49	0.089	0.140	(0.004, 2.208)
50-59	0.064	0.076	(0.003, 1.327)
60-69	0.207	0.103	(0.031, 1.375)
69≥	0.202	0.093	(0.031, 1.309)
Sex	0.554	0.292	(0.185, 1.663)
Insulin	0.314	0.062	(0.093, 1.058)
eGFR	0.992	0.329	(0.975, 1.008)
Study Group	2.813	0.051	(0.996, 7.947)
Prior Hypo	0.367	0.198	(0.080, 1.690)
Food Insecurity	0.459	0.158	(0.156, 1.354)

Chapter 4: Manuscript 3

Overtreatment of Older Adults with Complex Intermediate and Complex Poor Health with Tight Glycemic Control
: An Examination of NHANES data from years 2009-2018

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Ike S. Okosun, PhD

Abstract

Objectives: To examine the glycemic control levels among older adults with diabetes mellitus by health status and to estimate the potential of overtreatment with hypoglycemia causing medications (insulin or sulfonylureas).

Design, Setting, and Participants: Cross sectional analysis of the data on 1,642 older adults (≥ 65 years) with diabetes from the National Health and Nutrition Examination Survey (NHANES) from 2009 through 2018 who had a hemoglobin (HbA1c) measurement.

Exposures: Health status categories which include: *very complex/ poor* based on the difficulty with 2 or more daily living or dialysis dependence; *complex/intermediate*, based on the difficulty with 2 or more instrumental activities of daily living or presence of 3 or more chronic conditions; and relative healthy if they did not meet the above criteria.

Main Outcomes and Measures: Tight glycemic control (HbA1c, <7%) and use of diabetes medications likely to result in hypoglycemia (insulin or sulfonylureas).

Results: Of 1,642 older adults with diabetes, 57.8% were relatively healthy, 36.3% had complex intermediate health and 5.9% had very complex/poor health. Participants that had an HbA1c <7% did not differ across health status categories. 54.4% were relatively healthy, 61.1% had complex/intermediate health and 52.1% had very complex/poor health with an HbA1c<7% (P=0.325). Older adults that had an HbA1c level less than 7% and were treated with insulin or sulfonylureas did differ by health status categories. . 48%, 58% and 54% of participants with relatively healthy, complex/intermediate, and very complex/poor health status received insulin or sulfonylurea and had an HbA1c<7%, respectively (P=0.009). During the 10 years there were no significant changes in the proportion with an HbA1c level less than 7% who had complex/intermediate or very complex/poor health (P=0.444). There were significant changes in the proportion with an HbA1c <7% and were treated with insulin or sulfonylureas who had complex/intermediate or very complex/poor health (P=0.005).

Conclusion: Intensive treatment to reach glycemic targets can lead to harm rather than benefit for older adults with complex/intermediate or very complex/poor health. Most of the participants were treated with insulin or sulfonylureas, which can increase the risk of hypoglycemia. Therefore, our findings indicate overtreatment.

Introduction

Diabetes is an important and prevalent health condition in the aging population (ADA, 2020). An estimated 28.9 million U.S. adults have diabetes, which makes it a public health concern and complication due mainly to diabetes-related complications (Casagrande et al., 2017). Approximately 26.8% of the population over the age of 65 years have diabetes (CDC, 2020). This trend will continue to increase over the next decades. Diabetes management in older adults requires regular assessment of medical, psychological, functional, and social domains (ADA, 2020). Assessment through these domains and adequate glycemic control can allow older adults reach and make appropriate treatment goals.

Achievement of adequate glycemic control in this population is an important aspect of diabetes management to reduce diabetes-related complications such as hypoglycemia. The American Diabetes Association recommends a hemoglobin A1c (HbA1c) level of less than 7.5% for healthy older adults with fewer coexisting chronic illnesses, intact cognitive and functional status and the American Geriatrics Society recommends an A1c between 7% to 7.5% in healthy older adults with fewer comorbidities and good functional status (ADA, 2020; AGSEP, 2013). Although the guidelines suggest intensive strategies to lower glucose levels in older adults, the risks and complications are high.

Recent studies have indicated that older adults are at risk of comorbidities, disease duration and adverse events such as hypoglycemia in particular (Gotfredsen et al., 2020). Glucose-lowering medications such as insulin and oral hypoglycemic agents have implicated emergency department visits related to hypoglycemia (Budnitz et al., 2011). For example, among older Medicare beneficiaries with diabetes, hospital admissions for hypoglycemia now outpace those for hyperglycemia (Umpierrez & Pasquel, 2017). In addition, hypoglycemia has emerged and remained a major and common complication related to diabetes management and treatment in older adults. However, guidelines have recommended tight glycemic control in older patients with multiple comorbidities and functional impairments.

The American Diabetes Association and American Geriatrics Society recommend higher glycemic targets for older patients with multiple comorbidities, functional impairments, established diabetic complications or limited life expectancy (Lipska et al., 2015). Higher glycemic targets increase the risk of harm, which implicate diabetes related complications (i.e. hypoglycemia). Research has indicated that some older adults may reach these glycemic targets through lifestyle modification and changes. For example, data from a national sample of overweight and obese subjects with diabetes indicated that majority reported trying to lose weight (75%), increase physical activity (57%), and reduce the number of calories and fat in their diet (71%) (Casagrande et al., 2013). Older adults may also reach these higher glycemic targets with medications that increase the risk of adverse effects, including hypoglycemia. Arnold and colleagues (2018) conducted a cross-sectional analysis of older adults above 75 years with type 2 diabetes from 151 U.S. outpatient sites in the Diabetes Collaborative Registry and found that 25% of older adults with type 2 diabetes were managed with tight control on glucose-lowering medications that have a high risk of hypoglycemia. They also found that insulin and insulin secretagogues continued to be used at high rates in older adults, even when HbA1c levels were low (Arnold et al., 2018). Therefore, treatment that results in harm rather than benefit indicates potential overtreatment.

The purpose of this study is to determine the evidence of potential overtreatment using a nationally available dataset, National Health and Nutrition Examination Survey (NHANES), to assess the health status and treatment patterns among older participants with diabetes who attain tight glycemic control (HbA1c level < 7%).

Methods

This study used exact methods published by Lipska and colleagues (2015). Our study looked at NHANES participants from years 2009-2018.

Study Source

We analyzed data from NHANES years 2009-2010, 2011-2012, 2013-2014, 2015-2016 and 2017-2018. The NHANES uses stratified, multistage, probability-cluster techniques to ensure that sample populations are representative of the nation's non-institutionalized civilians. Data are collected from household interviews and standardized medical examinations and blood sample collections are performed in mobile examination centers.

This study was deemed exempt from IRB review by Georgia State University because it used only de-identified secondary data.

Study Population

We included adults from the NHANES who were 65 years or older, reported a diagnosis of diabetes from a health professional, and had an HbA1c measurement. We used interview responses to classify participants in terms of age, sex, and race or ethnic group.

Health Status

Health Status categories were endorsed by the ADA/AGS framework for considering treatment goals for glycemia. The 3 categories included *relatively healthy*, *complex/intermediate* and *very complex /poor*. The criteria for the three categories are shown in the table below.

Health Status Categories	**Criteria**

Very Complex/Poor	Receiving dialysis or had 2/more activities of daily living impairments
Complex/Intermediate	3/more chronic conditions or 2 or more instrumental ADL impairments
Relatively Healthy	Do not meet above criteria

We could not determine the presence of other indicators of *very complex/poor* health status per the ADA/AGS framework: which include end stage (stage III-IV) congestive heart failure, oxygen-dependent lung disease, uncontrolled metastatic cancer, or severe cognitive impairment. We included chronic illnesses identified by the ADA/AGS framework, including arthritis, congestive heart failure, lung disease, chronic kidney disease, coronary heart disease, stroke, or urinary incontinence, but we did not have information on active cancer, clinical diagnosis of depression or falls (Lipska et al., 2015) Hypertension was not included because it was highly prevalent and is usually not considered a serious chronic illness (Lipska et al., 2015).

We used interview responses to identify chronic conditions (congestive heart disease, lung disease [emphysema, chronic bronchitis, or asthma], coronary heart disease [myocardial infarction or angina pectoris], stroke or arthritis (Lipska et al., 2015). Urinary incontinence status was based on a series of questions about leakage of urine with or without activity. We considered urinary incontinence to be a chronic condition if it occurred at least a few times a week. Chronic Kidney disease was identified based on an estimated glomerular filtration rate of less than 60 $mL/min/1.73cm^2$, calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.

Functional Limitations were assessed based on a series of questions designed to measure participants' functional status (Lipska et al., 2015). These questions were phrased to assess the individual's level of difficulty in performing the task without using any special equipment (Lipska et al., 2015). Patients who reported some or much difficulty or were unable to perform ADL were categorized as having ADL impairment. The table below shows the questions used for ADLs and instrumental ADLs.

Impairments	Questions
ADL	Dressing Feeding Walking from Room to Room Getting in or out of bed
Instrumental ADL	Preparing one's own meals Managing Money Housework Chores

Other ADLs and instrumental ADLs were not assessed in the NHANES.

Glycemic Control

We categorized glycemic control, based on the measured HbA1c level, as tight (HbA1c level, <7%, moderate (7%-8.9%), and poor control (≥9%).

Glucose-Lowering Treatment

Participants were asked to report prescription medications they had taken in the past 30 days and to bring medication bottles to the examination, where the information was documented. Receipt and type of oral glucose-lowering treatment was based on review of medications brought in to the examination; insulin use was based on review of medications brought in or self-reported use of insulin, because participants may not always bring vials or pens to the examination.

Statistical Analyses

We calculated weighted proportions of survey participants with glycemia that was poorly (HbA1c, ≥ 9%), moderately (7%-8.9%), or tightly (<7%) controlled across health status categories. In addition, we calculated the weighted proportions of survey participants whose glycemia was tightly controlled and were treated with either insulin or sulfonylureas across health status categories. We conducted logistic regression analyses to assess linear trends in proportions of participants with tightly controlled glycemia, their health status, and patterns of treatment during the 5 NHANES surveys. To preserve statistical power in the analyses we combined participants with very/complex poor and complex/ intermediate into 1 category. All data, except where otherwise noted show annualized estimates of the number of US adults with the outcome of interest based on the mean of values across the 10 study years. Analyses were performed using SPSS Statistical Subscription. We considered 2 sided P<0.05 to be statistically significant.

Results

During the 10-year period, we identified 6,957 adults 65 years or older of whom 1,810 (26.0%) reported a diagnosis of diabetes. For this analysis we included 1,642 participants who had an HbA1c measurement during the survey period whom had diabetes. The characteristics of the study sample are shown in Table 5. The mean (SD) age 73.0 (5.2) years, and 22.5% were 80 years or older. 13.6% reported at least 1 ADL impairment and 16.6% reported at least 1 instrumental ADL impairment. In the study sample of older adults with diabetes, 57.8% were relatively healthy representing 2.5 million per each 2-year cycle (25,296,488 is the actual number for total 10 years), 36.3% had complex/intermediate health representing 1.6 million for each 2 year cycle (15,856,572 is the actual number for total 10 years) and 5.9% had very complex poor health representing 258,000 for each 2 year cycle. (2577981 is the actual number for total 10 years).

Among older adults with diabetes 56.7% (24801981 actual number for total 10 years) had an HbA1c level of less than 7%, 35% (15317650 actual number for total 10 years) had an HbA1c level of 7% to 8.9% and 8.3% (3611410 actual number for total 10 years) had an HbA1c level of 9% or greater.

There were no significant differences in the proportions of patients who attained tight (HbA1c level, <7%), moderate (HbA1c level, 7%-8.9%), or poor (HbA1c≥9%) glycemic control across health status categories. Specifically, 54.4% were relative healthy with an HbA1c<7%, 61.1% had complex/intermediate health with HbA1c <7% and 52.1% had very complex/poor health with an HbA1c<7% (P= 0.325)

Among older adults with an HbA1c level of less than 7%, 39% were treated with either insulin or sulfonylureas. This proportion differed by health status. 48%, 58% and 54% of participants with relatively healthy, complex/intermediate, and very complex/poor health status received insulin or sulfonylurea and had an HbA1c<7%, respectively (P=0.009).

Table 6 and 7. show the logistic regression for the trend for NHANES 2009-2018. During the 10 years, there were significant trends in the proportion of older adults with HbA1c <7% and who were treated with insulin or sulfonylureas who had complex/intermediate or very complex/poor health (P=0.005). There were no significant changes in proportion of older adults with an HbA1c level of less than 7% who had complex/intermediate or very complex/poor health (P= 0.444).

Discussion

In a nationally representative sample of non-institutionalized adults from 2009 to 2018 a total of 55% of older participants with diabetes had an HbA1c of less than 7%. To achieve tight glycemic targets, older adults with complex/poor and complex intermediate health status were overly treated with insulin or sulfonylureas, which may lead to severe hypoglycemia. We found significant changes in treatment patterns across health status and our findings suggest that substantial proportion of older adults with diabetes in the United States were over treated. This finding may hold true as majority of participants were treated with insulin or sulfonylurea compared to other diabetes medications which increases the risk of hypoglycemia.

Consistent with our findings, studies based on national available data such as from the Department of Veteran Affairs also suggest the overtreatment with hypoglycemic medications such as insulin or sulfonylureas and tight glycemic control (Thorpe et al., 2015). The results from this study suggest that a substantial amount of veterans received intensive treatment despite the risk of hypoglycemia. Overall 52% of veterans had tight glycemic control of whom 75% used sulfonylureas and/ insulin, with a higher risk of hypoglycemia occurring in those aged 75-84 years (Freeman, 2019). Our research further supports this research because we used a nationally representative sample that can be generalizable to the U.S. population.

Another study conducted in Turkey found that 28.7% of patients $\geq$ 65 years and 28.2% of patients $\geq$80 years were over- treated (Akin et al., 2019). They also found that 23.5% of patients were found to have experienced hypoglycemia (Akin et al., 2019). This study indicated that insulin and sulfonylurea treatments should be de-intensified when needed and avoided in in elderly patients with comorbidities (Akin et al., 2019).

In the exact study conducted by Lipska and colleagues (2015) they found that among participants with an HbA1c level of less than 7% who were relatively healthy the proportion treated with insulin or sulfonylureas decreased overtime and the proportion with complex/intermediate health remained stable. In contrast, we found that there were significant changes in older adults with complex/intermediate and complex/poor health over the years of 2009-2018 treated with insulin or sulfonylureas indicating that they were over-treated.

Tight glycemic control such as an HbA1c level than 7% may be common in patients with complex/intermediate or very complex/poor health where physicians and healthcare providers may try to intensify treatment to achieve this target. However, intensive treatment may lead to an increase risk in hypoglycemia. Hypoglycemia has been associated with poor outcomes such as morbidity and mortality and low health-related quality of life (Freeman et al., 2019) Therefore, intensive strategies to lower glucose levels may result in harm than benefit.

Since 2003, it has been generally accepted that the glycemic goals should be more flexible especially in elderly patients according to their life expectancy and co-morbidities (Akin et al., 2019). Therefore, this suggests that only a small percentage of patients older than 65 years should have an HbA1c < 7% and receive hypoglycemic medications (Akin et al., 2019).

To improve quality and reduce the risk of overtreatment for glycemic control, Pogach and colleagues (2017) have proposed an out of range (OOR) measure which would identify patients with diabetes with HbA1c <7% for patients 65 years and older. This measure would focus on quality improvement on individual patient evaluation to reduce the risk of harm (Pogach et al., 2017). The OOR measure would align the concepts of quality (individualizing targets on the basis of the principle of absolute risk reduction, safety (potential reduction in medication harms), and value to health care systems and payers (potential decreased costs of both over treatment and undertreatment) and to patients (improved quality of life, satisfaction) (Pogach et al., 2017). Our finding suggests that this measure will help identify populations that are over-treated with hypoglycemia causing medications.

Our study has some limitations. We did not look at glycemic targets below 7%. This may be due to the unavailability of a lower acceptable limit. We also combined several years of NHANES to increase sample size, but our study may have been underpowered to detect subtle changes in treatment patterns over time. The number of ADL impairments may have also been underestimated due to the limited number of questions used to categorize ADL impairments. Since NHANES is a study of non-institutionalized adults our findings cannot be generalized to other older populations in other facilities.

Conclusions

Using a nationally representative sample of U.S. adults we showed that older adults with diabetes who have complex/intermediate and complex poor health have been over- treated. These individuals are more likely to experience harm and increased risk of hypoglycemia and adverse outcomes rather than benefits of intensive glycemic control. Therefore, recognition of the harms associated with intensive glycemic control is important for patients and healthcare providers to make informed decisions related to diabetes treatment and glycemic control.

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Table 5. Characteristics of Older Adults with Diabetes from 2009 Through 2018 by Health Status.

Characteristic	Overall (N=1642)	Relatively Healthy (N=972)	Complex/Intermediate (N=553)	Very Complex (N=117)
Age, mean (SD), y	73.0(5.2)	72.8(5.2)	73.5(5.2)	72.4(5.4)
Age, %				
65-69y	31.9	33.1	28.2	39.3
70-79y	45.4	45.1	47.1	40.2
≥ 80y	22.5	21.7	24.6	20.5
Male Sex, %	54.6	57.1	50.3	55.6
Race, %				
Non-Hispanic white	41.3	37.3	49.7	35.0
Non-Hispanic black	23.0	23.1	24.6	14.5
Mexican American	13.9	15.3	9.8	21.4
Other Hispanic	10.0	9.9	9.8	12.0
Other/Multiracial	11.8	14.3	6.1	17.1
BMI, mean (SD)	30.8(6.6)	30.2(6.5)	32.1(6.8)	30.5(5.4)
# of Comorbidities (mean, SD)	2.3(1.1)	1.6(0.5)	3.4(0.8)	2.6(1.2)
Comorbidities, %				
Chronic Kidney	95.0	93.7	91.5	100.0
Congestive Heart	14.3	4.2	30.7	80.3
Lung Disease	22.4	9.2	45.6	76.9
Coronary Artery	20.4	7.2	42.5	25.6
Stroke	13.6	5.6	25.3	25.6
Arthritis	56.6	41.8	80.3	67.5
Urinary Incontinence	6.0	2.3	13.2	3.4
≥1 ADL Impairment	13.6	7.0	10.1	84.6
≥1 IADL Impairment	16.6	9.6	19.7	59.8
Diabetes Mellitus Treatment, %				
Insulin	26.6	21.7	32.9	37.6
Sulfonylurea	32.7	32.7	34.5	23.9
Metformin	54.0	59.6	46.1	45.3
Thiazolidenediones	5.8	6.2	5.2	5.1
Other Oral Meds	12.9	13.0	13.6	9.4
No Pharmacotherapy	16.0	15.0	16.6	20.5

Abbreviations: ADL, activities of daily living; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IADL, instrumental activities of daily living.

All percentages were calculated taking into account complex survey design. Raw numbers were omitted because they do not directly correspond to the percentages. Percentages of types of treatment add up to greater than 100 because many participants were treated with more than 1 type of medication. Health Status categories are defined in the Methods section.

Table 6: Logistic Regression of Tight Glycemic control and Insulin/Sulfonylurea by Health status for NHANES years 2009-2018

Ref (Relatively Healthy)	Odds Ratio	P-Value	95%CI
ComplexPoor/Intermediate	0.714	0.005*	(0.563,0.905)

*P<0.05

Table 7: Logistic Regression of Tight Glycemic Control by Health Status for NHANES years 2009-2018

Ref (Relatively Healthy)	Odds Ratio	P-Value	95% CI
Complex/Poor/Intermediate	0.926	0.444	(0.760, 1.128)

*P<0.05

Chapter 5: Summary

The manuscripts presented in this dissertation focus on multifaceted interventions with an educational component that reduce the rate of hypoglycemia and risk factors associated with hypoglycemia in the hospital setting and in vulnerable populations (minority, low SES and older adults). As previously discussed these are vulnerable populations that are at an increased risk of adverse drug events such as hypoglycemia.

The goals of the papers were to (1) understand the gaps in literature and in multifaceted interventions that included an educational component to reduce the rate of hypoglycemia (2) implement a randomized control trial that examined the risk factors of hypoglycemia and provided a tailored feedback intervention to reduce the incidence of hypoglycemia (3) determine the potential overtreatment that increases the risk of hypoglycemia. The first manuscript reviewed the extant literature in the past 20 years and determined the limitations, challenges and implications of the multifaceted interventions with an educational component to reduce the rate of hypoglycemia. Results of the first manuscript indicated that multifaceted interventions with an educational component have been successful in reducing rates of hypoglycemia and that high-quality randomized control trials have been lacking. In addition, sophisticated interventions that have used technology have been successful in reducing the risk of hypoglycemia. The second manuscript was the first randomized control trial that examined the risk factors for hypoglycemia and provided a tailored feedback intervention. Results of the second manuscript indicated that insulin use and adults over the age of 60 were significant risk factors for hypoglycemia. In addition, the tailored feedback intervention reduced the rate of hypoglycemia nine months after recruitment. The third manuscript examined the potential of overtreatment in older adults using NHANES data. Results indicated that individuals with complex/poor and complex/intermediate health were over-treated with insulin and sulfonylureas in the past 10 years (2009-2018). Findings of these three manuscripts shed light on the complexity of hypoglycemia reduction and prevention strategies and further add to the understanding of how health information is used by healthcare providers and patients to reduce the risk of hypoglycemia. The findings also show the impact of education and healthcare services on vulnerable populations to reduce the risk of hypoglycemia and improve diabetes self-management.

Implications for Future Research

Much of the extant of literature on multifaceted interventions with education as a key component to reduce the rate of hypoglycemia focuses on protocols and insulin order sets. The more recent literature focuses on examining the risk factors and individualizing treatment to the patient. This move toward determining the root causes and patient centered treatment suggest that individuals seek information that is tailored to their specific needs and that is culturally competent.

The HIIPO data suggest that individuals with low socioeconomic status and low health literacy need the assistance of a diverse and specialized diabetes management team that can provide cost effective and culturally competent tools and resources. Furthermore, the manuscript suggests that individualized treatment is effective in reducing the risk of hypoglycemia. Therefore, it is critical that health care professionals are trained in health literacy and in methods that meet cultural competency and in management of risk factors supported by DSME.

The findings from manuscript 3 indicate that individuals with diabetes are over-treated with medications that increase the risk of hypoglycemia. Therefore, it is important that healthcare providers make adjustments to glucose lowering therapy and detect overtreatment in patients with diabetes. The manuscript also suggests that glycemic control is best optimized using a patient-centered approach with proactive individually tailored glucose-lowering therapies. Thus, this dissertation affirms a need to further examine ways in which healthcare can effectively manage diabetes without increasing the risk of complications such as hypoglycemia associated with diabetes treatment.

Future Research Directions

Multifaceted Diabetes Management Team and Culturally Competent Tools and Resources

Manuscript 1 and the HIIPO data provide an in-depth understanding of the importance of a multifaceted diabetes management team and the provision of culturally competent tools and resources for vulnerable populations. Diabetes is a complex disease that requires a multifaceted approach to ensure adequate control with minimal complications. An effective team approach requires an efficient clinic appointment booking system that allows the referral to different members of the team (i.e. diabetes educator, dietician, nutritionist etc.) that will allow ample time for health care providers to spend with patients (Pillay & Aldous, 2016). As mentioned previously, patient-provider communication is a critical aspect of health care. Effective communication can ensure compliance to clinical guidelines (Kirkman et al., 2002).

Furthermore, Manuscript 1 also indicated the importance of on-going in-service training of nurses and healthcare providers as an integral component of the multifaceted approach to diabetes care. On-going training and communication among members of the multifaceted diabetes management team ensures structured and standardized management of patients seen for hospital and clinic visits. Members of the multifaceted team may engage in group-based or person-centered diabetes self-management education (Stenov et al., 2019). However person-centered diabetes self-management education has shown to be more successful due to the shift away from one-way transmission of content from medical experts to passive listeners and toward actively incorporating participants' experience, concerns and needs into the curriculum (Stenov et al., 2019). However, many healthcare professionals have not received enough training in how to switch practice from "teach and tell" to collaborate and empower (Kurtz et al., 2005). Thus, there is still a missing link in the process of translating person-centered research approaches into the implementation of skills in clinical practice (Stenov et al., 2019). Further research on how health care professionals facilitate group based patient center treatment on diabetes education can provide a better understanding of this approach. In addition, the incorporation of patient preferences may also be included for types and features of DSME interventions (Fan & Sidani, 2018).

Culturally competent tools and resources are also necessary for effective diabetes self-management and reduction in complications associated with diabetes treatment in vulnerable populations. Cultural competence has emerged as a strategy in healthcare in response to evidence of health disparities, structural inequalities and poorer quality health care among people with minority backgrounds (Horvat et al., 2014). It is built on an awareness of the integration and interaction of health beliefs and behaviors, disease prevalence, and incidence and treatment outcomes for different patient populations (Dauvrin et al., 2015). Culturally competence in general practice and healthcare components may include cultural tailoring (i.e. dietary recipes and cultural appropriate substitutes), communication through leaflets and other educational material provided in the preferred language of the patients (Dauvrin et al., 2015). Furthermore, healthcare professionals may receive education and training to provide culturally appropriate programs and resources to a diverse population regardless of their cultural and language backgrounds (Johnstone & Kanitsaki, 2006). In addition, research should also seek approaches to integrate culturally competent, varying health literacy levels, and linguistically appropriate sources related to the use of the internet and to cost effectively allow access to internet among low-socioeconomic groups that would eliminate disparities caused by digital divide.

Measures for Indicating Overtreatment and Adjustments to Glucose Lowering Therapy

Prevention of adverse drug events such as hypoglycemia should be a national patient safety goal. Manuscript 3 indicated that the vulnerable U.S. population experienced harm (hypoglycemia) from overtreatment in order to reap the benefits of intensive glycemic control. Although the cause of hypoglycemic events is often behavioral and preventable, rates of serious hypoglycemia are markedly higher in individuals receiving intensive glycemic control (Tseng et al., 2014). Therefore it is critical to assess possible overtreatment resulting from intentional or unintentional tight glycemic control in persons with diabetes.

Several studies have developed a performance measure to recognize the risk of hypoglycemia and potential overtreatment. For example, in 2012, Pogach & Aron recognized the unawareness of a performance measure organization or health care system that has addressed the overtreatment of persons with diabetes who are at higher risk for hypoglycemia. They proposed that the risk of hypoglycemia should be abstracted from the electronic medical records and that performance measures should be constructed so that the eligible population (i.e. elderly population) reflected the population (s) that will receive the benefit based on factors such as life expectancy and comorbidity (Pogach & Aron, 2012). They also proposed for an alert in the electronic medical records to raise the issue at a time when action, if needed could be taken (Pogach & Aron, 2012).

Similarly, Tseng et al (2014) assessed potential glycemic overtreatment in persons at hypoglycemic risk. They conducted a cross-sectional study of patients in the Veterans Health Administration receiving insulin and/ or sulfonylureas and they assessed the rates in patients with significant medical, neurologic and or mental comorbid illness (Tseng et al., 2014). Results from their study indicated that patients with risk factors for serious hypoglycemia represent a large subset of individuals receiving hypoglycemic agents; approximately one-half had evidence of intensive treatment (Tseng et al., 2014).

Wilson and colleagues (2017) conducted a serial cross-sectional study that determined how statistical outliers exhibiting low rates of diabetes overtreatment performed on a reciprocal measure, rates of diabetes undertreatment and how high-performing outlier status for diabetes overtreatment is impacted by different criteria (Wilson et al., 2017). The outcome measure was facility rate of HbA1c overtreatment of diabetes in patients at risk for hypoglycemia (Wilson et al., 2017). Results indicated that there was only a modest overlap between facilities identified as top performers based on three thresholds: A1c< 6%, A1c <6.5% and A1c <7% and high performing facilities for overtreatment had higher rates of undertreatment (A1c>9%) than VA average in the population of patients at high risk for hypoglycemia (Wilson et al., 2017). Therefore, statistical identification of positive deviants for diabetes overtreatment was dependent upon specific measures and approaches and that two facilities may arrive at the same results via different pathways (Wilson et al., 2017). In the same year, Pogach and colleagues (2017) proposed for an out-of-range glycemic population health safety measure for older adults with diabetes. The out-of-range measure found that about one-half were significantly under-treatment or over-treatment according to current guideline recommendations (Pogach et al., 2017). The proposed out of range measure aligned the concepts of quality, safety and value to healthcare systems and payers.

The measures to determine overtreatment suggest that individualizing glycemic treatment goals and targets for patients are an important aspect of preventing overtreatment and complications such as hypoglycemia. It is also important to take into account patient-specific factors including age, comorbidities, and risk for hypoglycemia annually. Therefore, the needs, preferences and safety of the patient must always be individualized and should always be paramount. Furthermore the adoption of positive deviance approach in hospitals can further improve health outcomes.

Moreover, it also important for healthcare professionals to adjust glucose-lowering therapy to reduce the risk of hypoglycemia. Physicians and healthcare professionals could adjust medication doses and treat patients on medications that are low-risk medications for hypoglycemia. Adjustments to insulin doses and defining appropriate therapeutic changes for insulin and oral anti diabetic medications can further prevent hypoglycemia.

Technology and Electronic Medical Records Improvements

Advancement in diabetes technology has generated excitement and potential in managing diabetes and its complications. Manuscript 1 and 2 indicated the success associated with the use of informatics and technology to reduce hypoglycemic events. However, due to issues to access, cost, expertise, and complexity its use has been limited (Yeoh & Choudhary, 2015). Adoption of these technologies may be limited due to regulated funding from existing health care systems, medical reimbursements, and insurance but also possibly due to lack of awareness and training of healthcare professionals (doctors, nurse practitioners, dieticians) and people with diabetes (Yeoh & Choudhary, 2015). Moreover, continual advances in diabetes technology span a variety of uses to support optimal diabetes self-management and its complications such as hypoglycemia. Real-time continuous interstitial glucose monitoring, continuous subcutaneous insulin infusion (CSII), electronic tools for the monitoring of therapeutic approaches, automated bolus calculators for insulin and electronic tools for education and information of patients are some of the technologies that have changed and improved hypoglycemia and diabetes practice (Schiel et al., 2018).

Furthermore, insulin pump and sensor technology are other technological devices that are gaining popularity in reducing risks of hypoglycemia. Approximately 30-40% of patients with type 1 diabetes and an increasing number of insulin-requiring patients with type 2 diabetes are using pump and sensor technology (Umpierrez & Klonoff, 2018). The development of sensor-augmented pump therapy allows the user to have continuous, real-time glucose readings and trends that are useful, especially making decisions to adjust insulin infusion rates involving, food, exercise or glucose fluctuations (Lucidi et al., 2018). Sensor-augmented pump therapy can reduce the risk of severe hypoglycemia and improve awareness of hypoglycemia in patients with hypoglycemia unawareness. However usage adherence and the necessity of active involvement of the patient is required.

Mobile Health is the new edge on healthcare innovation. It proposes to deliver healthcare anytime and anywhere surpassing geographical, temporal and even organizational barriers (Silva et al., 2015). Mobile technologies are a means for providing individual level support to healthcare consumers (Free et al., 2013). Moreover, mobile health interventions for health care consumers have been designed to increase healthy behavior (for example, to increase smoking cessation for activity levels) or improve disease management (for example by increasing adherence to prescribed medication, improving management of diabetes/asthma or delivering therapeutic interventions.) (Free et al., 2013). Mobile technologies have a number of key features that give them an advantage over other technologies particularly in health care and public health. First, many MEDS have wireless cellular communication capability, providing the potential for continuous interactive communication from any location i.e. telephone calls, text, and multimedia messaging and also internet access via wireless Application Protocol (WAP) or mobile broadband internet (Free et al., 2010). Second, the devices are portable because of their small size, low weight, and rechargeable, long-life battery power (Free et al., 2010). Furthermore, mobile applications can help with monitoring, prevention and detection of diseases and in more advanced services present basic diagnosis (Silva et al., 2015; Kao & Liebovitz, 2017). However, despite the benefits of mobile health technology, data privacy and security is an issue on information management.

Lastly, the emergence of Electronic Health Records (EHR) offer several advantages which include, lower and more efficient management costs, more efficient management of high-volume patient data, and centralized medical patient records. Advances in electronic health records include alerts that can flag hypoglycemia episodes and EHR incentive programs that improve productivity of healthcare professionals and to make EHR services widely applicable (Evans, 2016). In addition, commonly used functions include accessing, viewing and documenting clinical data such as patient data, laboratory reports and patient visit notes and clinical admissions and discharge (Laerum et al., 2001; Lejbkowicz et al., 2004; Puffer et al., 2007; Simon et al., 2007; Nguyen et al., 2014). The electronic health records also has access to pharmaceutical clinical guidelines and medical references, drug allergy alerts, drug interaction alerts and age-related drug dosing support and electronic reminders (Nguyen et al., 2014). However, a lack of socio-technical connectivity between the clinician, the patient and technology in developing and implementing EHR and future developments in patient-accessible are some of the limitations. (Nguyen et al., 2014; Alkureishi et al., 2016). Therefore, EHR services need to be integrated and provide a SMART platform similar to I-phones with application programming interfaces that allows for easy addition and deletion of third party applications (Evans, 2016). Furthermore, EHRs will need to resolve privacy and security concerns and allow for adequate storage of large and complex data.

Despite all the available technologies for reducing hypoglycemia rates, the provision of training, education and support is required for the best outcome. Furthermore, it is important to match the right person to the right therapy and in healthcare systems with disparities and where resources are limited. It is also important to make and use technologies that are simple, more user-friendly, and are cost-effective.

Conclusion

There has been a shift in healthcare that now focuses on patient-centered treatment and the individualization of education and goals that improves health outcomes and reduces complications associated with treatment. The role of a multifaceted healthcare team has demonstrated success in preventing hypoglycemia. Researchers now understand the importance of examining the risks of hypoglycemia and tailoring interventions that address those risks to prevent hypoglycemia. Education has shown to be a key component in multifaceted interventions to improve health outcomes and prevent hypoglycemia. Furthermore, obtaining optimal glycemic control levels have led to overtreatment, which has now led to overtreatment measures and indicators to prevent overtreatment. Building on this prior work, researchers can now focus on interventions that can improve communication among the multifaceted team and heighten the awareness of risk factors of hypoglycemia for prevention strategies. The incorporation of technology coupled with education can address hypoglycemia in real-time and prevent future hypoglycemic events and reduce overall healthcare costs.

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