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Antipsychotics, delirium and glucose in older patients

Antipsychotica, delier en glucose bij oudere patiënten

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag de rector magnificus, prof.dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op dinsdag 10 april 2018 des middags te 4.15 uur

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Kristy van Keulen

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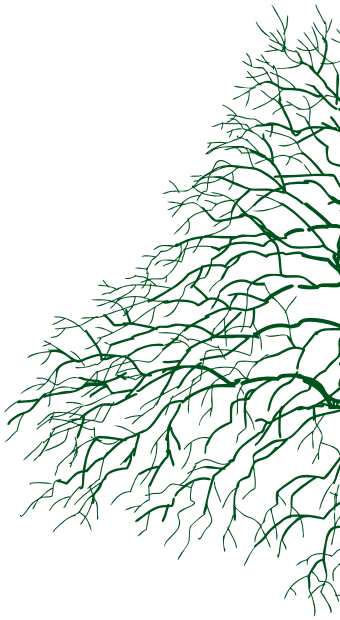

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Introduction

An 83-year-old woman presented at the emergency department with a painful hip. Her home help had found her on the floor of her apartment. The X-ray showed a femoral neck fracture. She had a history of osteoarthritis, diabetes, hypertension, depression, hypothyroidism, mild cognitive impairment, and macular degeneration. Her medication consisted of metformin, gliclazide, perindopril, amitriptyline, levothyroxine, and simvastatin, and she used analgesics to relieve the pain from osteoarthritis. Two months ago, the HbA1c was 56.0 mmol/mol (reference: ≤ 64 mmol/mol), which suggested that her diabetes was under control. Recently, her daughter had told the general practitioner that the family had discussed moving her to a nursing home, because her memory complaints, visual impairment, and immobility had become worse in recent months. The patient was admitted to the geriatric trauma unit and had surgery within three hours. The 'delirium observational scale (DOS)' score was assessed, and the attending nurse noted in the evening that the woman was becoming agitated, hallucinating and pulling out her intravenous line. The geriatrician diagnosed delirium and withdrew amitriptyline and started haloperidol. The patient's fasting blood glucose levels were raised (8.6-10.4 mmol/L), suggesting worsening diabetic control. The dose of metformin was increased and glucose levels normalized. After a few days, the patient was well hydrated and the electrolyte disturbances had been corrected. The delirium faded away and treatment with haloperidol was discontinued. After seven days in hospital, the patient was discharged to a rehabilitation center. Two and a half months after hospital discharge, the patient died.

This case report describes a woman whose delirium responded to haloperidol within days of starting treatment. Even though her diabetes was originally under control, she developed glucose disturbances. Was the delirium or the antipsychotic drug responsible for the worsening diabetic control? Or did the two act in concert, or were there other causes? Were these events related to her death, almost 3 months after hospital discharge?

The world's population is aging and the proportion of the old age (≥ 75 years) will increase during the coming decades. It will almost double in the next 25 years in the Netherlands. It is expected that in 2040, 4.8 million (27%) inhabitants will be 65 years or older, of whom 2.6 million inhabitants (15%) will be 75 years or older (1). Life expectancy is increasing because of improvements in healthcare; several life threatening diseases in the past are chronic diseases nowadays. However, older patients remain more susceptible to illnesses and health states requiring hospitalization and long-term care (2). The occurrence of one adverse event in older patients has often been shown to initiate a series of adverse events, not seldom followed by death (2,3). Hip fracture is a major cause of hospitalization (4-6) and frequently triggers a cascade of other adverse events, as illustrated above.

Antipsychotic drugs

Antipsychotic use has increased steadily over the last decade to approximately 310,000 (1 in 55) antipsychotic users in all age groups, younger and older patients, in 2015 in the Netherlands (7,8). Antipsychotic drugs were approved for psychiatric disorders such as schizophrenia and bipolar depression. First-generation antipsychotic drugs (the conventional antipsychotics) bind to postsynaptic dopamine D2 receptors. To be effective, antipsychotics need to occupy a certain proportion (threshold) of dopamine D2 receptors (6,9). However, dopamine D2 receptor antagonism causes extrapyramidal adverse effects, and recognition of this triggered the development of the second-generation or atypical antipsychotic drugs (10). These drugs are thought to block both serotonin 5-HT2 receptors and dopamine D2 receptors, but in different proportions (6). All atypical antipsychotics have a unique receptor-binding profile that underlies their clinical characteristics. Beside dopamine D2 and serotonin 5-HT2 receptors, antipsychotics interact with numerous other receptors, such as histamine H1, dopamine D3, muscarinic M2 and M3, serotonin 5-HT1 and 5-HT7 and adrenergic alfa-2 receptors (11). These additional receptor interactions are responsible for the broad range of adverse effects associated with antipsychotic drugs. In addition to extrapyramidal adverse effects, other adverse effects of antipsychotic drugs include sedation, raised prolactin levels, cardiovascular effects (QTc interval prolongation and orthostatic hypotension), anticholinergic effects (constipation, dry mouth, and urinary retention), pneumonia, and metabolic syndrome. The latter is the collective name for a group of risk factors (high triglyceride levels, low HDL cholesterol level, high blood pressure, and an impaired fasting glucose level) that increase the risk of cardiometabolic diseases, including coronary heart disease, diabetes, and stroke (12). For this reason, components of the metabolic syndrome are monitored in schizophrenic patients on antipsychotic drugs (13,14). The effectiveness of antipsychotic drugs for especially the positive symptoms of schizophrenia has led to the broad use of antipsychotic drugs for non-approved indications (i.e. off-label use), such as behavioral problems in dementia and delirium. Even though antipsychotic drugs are widely used by older patients in dementia and delirium, there is limited evidence of their efficacy, whereas numerous studies have reported adverse effects and safety concerns in the older population (15-22). It has been suggested that the cardiometabolic adverse effects of antipsychotic drugs contribute to the increased mortality risk seen in older patients using these drugs (23,24). The metabolic effects of antipsychotic drugs in the older population have been poorly studied.

Glucose homeostasis

Diabetes

Approximately 20% of patients aged 65 years and older are diagnosed with diabetes, and the prevalence of diabetes increases with increasing age (25). The incidence and prevalence of diabetes is expected to increase further in the older population in the future

(26). Even more patients have non-diabetic, raised glucose levels without knowing it and without experiencing symptoms (27). Glucose homeostasis regulates the energy supply in the body and maintains blood glucose levels within the normal range (reference fasting glucose level: 3.5-6.0 mmol/L and non-fasting glucose level: 3.5-7.8 mmol/L). High glucose levels in healthy subjects prompt increased insulin production by pancreatic beta cells and inhibited glucagon production by pancreatic alfa cells, leading to increased glucose uptake in peripheral tissues and its conversion glycogen in the liver (glycogenesis). Low glucose levels cause the release of glucagon from pancreatic alpha cells and suppression of insulin production by pancreatic beta cells, leading to the breakdown of glycogen to glucose in the liver, thereby increasing glucose levels (glycogenolysis). Furthermore, glucose is produced by a breakdown of noncarbohydrate molecules such as amino acids and glycerol (gluconeogenesis). In diabetes, high glucose levels are insufficiently corrected by the counter-regulatory system because of a diminished tissue sensitivity to insulin or a decline in beta cell function, or more often a combination of both (28).

Complications of diabetes are retinopathy, nephropathy, neuropathy, dyslipidemia and coronary artery disease. As diabetic patients often have other disorders, such as hypertension, obesity and dyslipidemia, both treated and untreated diabetes increase the risk of stroke and cardiovascular disease (29). In addition, diabetes has adverse effects on brain function and cognition in older patients without dementia. The reported risk of dementia is approximately two times higher in patients with diabetes than in patients without diabetes (30).

Glycemic control in critically ill patients

In 1991, the first prospective study on glycemic control with insulin infusion compared to routine control was conducted to investigate mortality rates and morbidity after cardiac arrests (31). The concept of glycemic control has spread since this attempt. Hyperglycemia, a natural stress response to illness, is caused by the release of hormones and cytokines that stimulate glucose production by the liver and decrease glucose uptake by peripheral tissues (32). Hyperglycemia is commonly seen in critically ill patients and is associated with an increased mortality. A randomized controlled trial published in 2001 (33) involving mechanically ventilated, critically ill patients prompted the worldwide implementation of glucose regulation protocols in the intensive care unit (ICU). The study found that the mortality risk was significantly lower in patients given an insulin infusion to maintain glucose levels between 4.4 and 6.1 mmol/L than in patients treated conventionally to maintain glucose levels between 10.0 and 11.1 mmol/L, with the initiation of insulin infusion if glucose levels exceeded 12.0 mmol/L. The NICE-SUGAR trial reported in 2009, however, a higher mortality risk during intensive insulin treatment (glucose target 4.5–6.0 mmol/L) than during moderate or conventional strategies (34) as a result of hypoglycemia (35). This prompted a wider target level of glucose in glucose regulation protocols, but there is no consensus about the optimal glucose window.

The literature has tended to focus on three aspects of glycemic control in ICU patients: hyperglycemia, hypoglycemia, and glucose variability (35,36). The incidence of hyper-

and hypoglycemia has been studied most extensively with many different thresholds influencing its sensitivity (37). Glucose variability reflects fluctuations in glucose levels between two time points. A gold standard to measure glucose variability lack and definitions in literature are very heterogeneous. The standard deviation (SD) of the mean glucose concentration is one of the most widely used indices to determine glucose variability. Despite the various definitions of glucose variability, high glucose variability is associated with increased mortality. In addition, it seems that patients with diabetes are less sensitive to the potentially harmful effect of high glucose variability than are patients without diabetes (38).

Delirium

Up to 40% of all patients admitted to the emergency department have delirious symptoms and it is a frequently observed complication in older hospitalized patients. The highest incidence (up to 82%) of delirium is reported in patients in postoperative, ICU and palliative care settings (39). In approximately 30-40% of the cases delirium is a preventable complication (39). According to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV criteria), delirium is a syndrome with disturbances in consciousness and cognition that has been developed quickly (usually in hours to days) and fluctuates during the day. There is a reduced ability to focus, sustain or shift attention and delirium is often reversible. An important difference compared to dementia is that dementia is a slowly progressive brain disease and not reversible. The major subtypes are based on clinical symptoms of agitation and/or lethargy: hyperactive, hypoactive and mixed type delirium. Hypoactive and mixed type delirium are frequently seen in older patients, whereas hyperactive delirium is rare (40). Delirium occurs in each patient with different clinical symptoms (39). Delirium is associated with a higher risk of long-term cognitive deterioration, functional decline, institutionalization and mortality (41-47). Delirium at the ICU is associated with a prolonged ICU and hospital stay and a longer duration of mechanical ventilation (46-48). Delirium increases healthcare related costs (46,49). The etiology of delirium is complex and has not been completely understood. It is generally accepted that delirium has a multifactorial cause (50). It has been suggested that an imbalance of neurotransmitters, a relative cholinergic deficiency and a dopamine excess, is a major pathway in the pathophysiology of delirium (51). Other mechanisms postulated to delirium onset are electrolyte and metabolic disturbances, proinflammatory markers, physiological stressors and genetics (39). The occurrence of delirium is dependent on a mixture of predisposing and precipitating factors (52). Predisposing factors, such as advanced age and dementia, increase vulnerability to delirium (50,53,54). The higher the baseline risk of delirium, less precipitating factors are required for delirium onset (52). Precipitating factors in the case described above were the use of psychotropic drugs and analgesia, polypharmacy, acute hospital admission, surgery, and electrolyte disturbances. Each delirious episode has other underlying causes.

The leading risk factor for delirium is pre-existing dementia. Delirium and dementia seems to have overlapping underlying mechanisms (52). It has been hypothesized that delirium is a marker of increased vulnerability in dementia or that delirium is a symptom of unrecognized dementia (53). However, patients with dementia who have had delirium had poorer outcomes compared to patients with dementia alone (53). Research on delirium is hampered by the underrepresented of patients with dementia in clinical research, because they are often excluded from participation in clinical research. Other complicated factors in delirium studies are its fluctuating clinical presentation, the heterogeneity of its underlying causes and its occurrence in different subpopulations (surgical, medical, palliative and ICU patients) (55).

Antipsychotic drugs in delirium

Delirious symptoms can be ameliorated by treating the underlying somatic disease, improving sleep-wake hygiene, correcting hearing and visual impairments, early mobilization, appropriate hydration, and withdrawing anticholinergic drugs (56-59). If these strategies have insufficient clinical effect, antipsychotic drugs in the lowest dose should be titrated according to clinical symptoms for the shortest period of time possible. Haloperidol, olanzapine, or risperidone are the preferred antipsychotics in older vulnerable patients with delirium and behavioral problems of dementia. Even though there is limited evidence that antipsychotic drugs are effective against delirium (60-62), haloperidol is widely prescribed for delirium (63). In recent years, atypical antipsychotic drugs have been prescribed more often because they cause fewer extrapyramidal adverse effects than haloperidol. Although some studies have reported beneficial effects of antipsychotic treatment (63,64), in general there is a relative lack of supporting evidence, possibly because of poorly designed studies, frequent use of rescue medication, high drop-out rates, heterogeneous study populations, prior antipsychotic use, and exclusion of patients with dementia (61-66).

Antipsychotic drugs, delirium, and glucose homeostasis in older patients

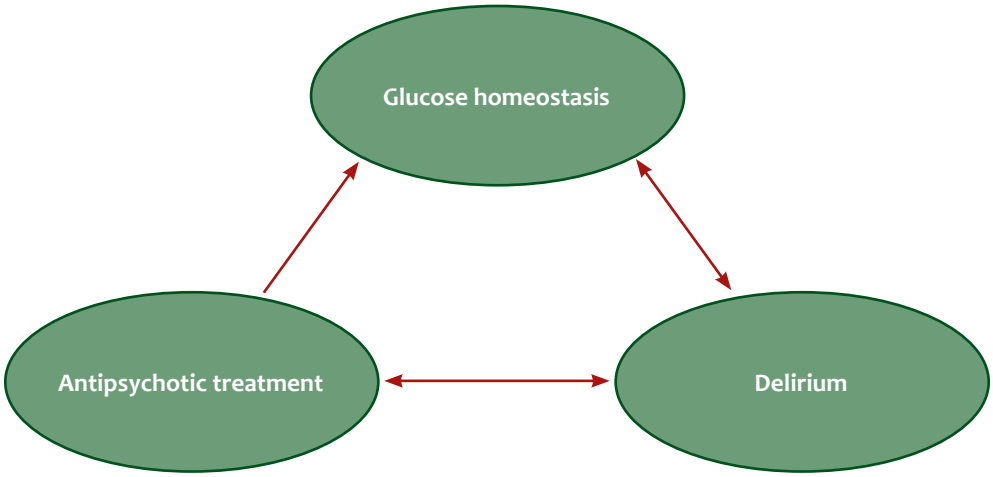
Of the limited studies of antipsychotic use and metabolic adverse effects, the risk of new-onset diabetes during antipsychotic drug use has been studied the most often in the older population, but results are conflicting. Thus it remains unclear whether older antipsychotic users are at risk of diabetes (67-73). One investigation reported that antipsychotic drug use was associated with worsening diabetic control in older patients (74), and some studies have reported that older antipsychotic drug users, diabetics and non-diabetics, have an increased risk of hyperglycemia requiring hospitalization (75-77).

It is not known to what extent the underlying disease influences the relation between antipsychotic drugs and glucose homeostasis in older patients. Even less is known about the mutual relation between delirium and glucose. Limited evidence suggests that hyperglycemia, hypoglycemia, and higher fasting glucose levels are risk

factors for delirium (39,78-81). The role of glucose in delirium has not been studied extensively. Glucose levels were reported to be higher in hyperactive delirium than in non-hyperactive delirium in critically ill patients admitted to the ICU (78). As delirium is an acute illness, it might involve the hypothalamic-pituitary-adrenal axis, resulting in increased cortisol release and subsequent changes to glucose metabolism. It has been suggested that serum cortisol levels correlate with the severity of delirium and the risk of delirium (82).

In summary, the number of elderly patients is increasing worldwide and a substantial proportion of these patients have diabetes. A common complication during hospitalization is delirium, which is often treated with antipsychotic drugs. Both delirium and antipsychotic drug use have been associated with disturbances in glucose levels, but the interplay between antipsychotic treatment, delirium, and glucose homeostasis remains to be clarified (Figure 1).

Figure 1. Schematic outline of the interplay between antipsychotic treatment, delirium, and glucose homeostasis



Objectives of this thesis

The aim of the studies described in this thesis is to gain understanding of the interplay between antipsychotic drugs, delirium, and glucose homeostasis in older patients. The research questions are:

1. Is antipsychotic treatment associated with alterations in glucose levels?
2. Is glucose variability associated with the onset of delirium?
3. Is glucose variability changed in delirium?

Outline of this thesis

The studies of this thesis involved three groups of patients: outpatients (**Chapter 2**), hospitalized patients admitted to non-ICU departments (**Chapter 3**, **Chapter 4**, and **Chapter 5**), and patients admitted to the ICU (**Chapter 6** and **Chapter 7**).

Chapter 2 describes the association between the use of antipsychotic drugs and hypoglycemia requiring hospitalization in older patients with diabetes. **Chapter 3** focuses on the association between antipsychotic drugs and hyperglycemia and hypoglycemia in older hospitalized patients. The effect of prophylactic use of haloperidol on changes in glucose levels in older hospitalized patients is described in **Chapter 4**. **Chapter 5** presents an investigation of glucose variability in older hospitalized patients admitted for hip surgery. The association between diabetes and glucose dysregulation and delirium in ICU patients was investigated in **Chapter 6**. **Chapter 7** describes glucose variability during delirium in diabetic and non-diabetic ICU patients. Lastly, these studies are discussed in a broader perspective in **Chapter 8** and implications for clinical practice and recommendations for future research are presented.

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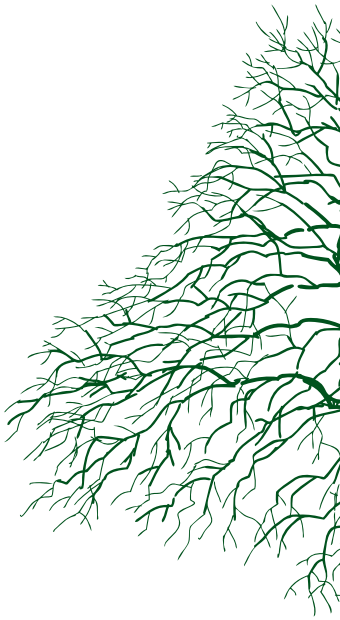

2

Risk of hospitalization for hypoglycemia in older patients with diabetes using antipsychotic drugs

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Abstract

Introduction

Antipsychotics may disrupt metabolic regulation in patients with diabetes mellitus. The risk of hypoglycemia in older users of antipsychotics with diabetes is largely unknown. Therefore, we investigated the association between the use of antipsychotic drugs and hypoglycemia requiring hospital admission in older patients with diabetes.

Methods

In a nested case-control study using community pharmacy records linked to hospital admission data in the Netherlands (1998-2008), a cohort of 68,314 patients of at least 65 years with diabetes was studied. Cases were patients from the study cohort with a first hospital admission for hypoglycemia; up to five comparison subjects were selected for each case. Exposure to antipsychotic drugs was the primary determinant of interest. Logistic regression analysis was performed to estimate the strength of the association between antipsychotic drug use and hypoglycemia, taking into account potential confounders.

Results

Eight hundred fifteen patients were admitted to hospital for hypoglycemia. Current use of antipsychotic drugs was associated with an increased risk of hypoglycemia compared with non-use (adjusted OR: 2.26; 95% CI: 1.45-3.52; Wald $\chi 2 = 13.08$, df = 1, $p \leq 0.001$), especially in the first 30 days of treatment (adjusted OR: 7.65; 95% CI: 2.50-23.41; Wald $\chi 2 = 12.72$, df = 1, $p \leq 0.001$) and with higher doses (adjusted OR: 8.20; 95% CI: 3.09-21.75; Wald $\chi 2 = 17.90$, df = 1, $p \leq 0.001$).

Conclusion

Use of antipsychotic drugs by older patients with diabetes mellitus was associated with an increased risk of hospitalization for hypoglycemia. Our findings suggest that glucose levels should be monitored closely after initiation of antipsychotic drugs.

Introduction

Antipsychotics are increasingly prescribed to older patients to relieve psychotic or behavioral symptoms of dementia, schizophrenia, or delirium (1-3). Their use is hampered by side effects, such as adverse cardiovascular and metabolic effects, and it has been suggested that cardiovascular problems underlie the increased mortality seen in older patients using antipsychotics (4,5). Metabolic adverse effects, especially during atypical antipsychotic use, include insulin resistance and impaired glucose tolerance, which may result in an increased risk of new-onset diabetes mellitus (DM) (6). Antipsychotic treatment among patients with schizophrenia and type 2 DM is associated with the initiation of insulin therapy, which is indicative of worsening of the disease, especially in the first 2 years of antidiabetic therapy (7).

Available studies involving older patients have tended to investigate the risk of new-onset DM during antipsychotic use, but the results are inconsistent (8-14). Although one study reported that atypical antipsychotics do not affect glucose levels (15), another study suggested that fasting glucose levels are abnormal in more than 10% of older users of atypical antipsychotics (16). Lipscombe et al. (17) found an increased risk of hospital admission for the treatment of hyperglycemia during antipsychotic therapy in older patients without DM. The effect of antipsychotic drugs on glycemic regulation in older patients with DM has hardly been investigated. The limited evidence available indicates that the use of antipsychotics by older patients with DM is associated with an increased risk of hospital admission for hyperglycemia (18,19). Some case reports have been published about the incidence of hypoglycemia, the counter effect of hyperglycemia during antipsychotic use (20-27). Only three of these reports concerned older patients, one of which described a younger patient with DM. This potential adverse effect during antipsychotic use is at least as important in clinical practice as hyperglycemia, but large retrospective studies are lacking. In the frail older population hypoglycemia has been associated with an increased risk of falls and fractures (28), cognitive impairment, and acceleration of dementia (29). Furthermore, it has been reported that inhospital hypoglycemia may increase the risk on inpatient mortality and length of hospital stay (30).

Given that DM is a major public health concern, particularly in the older population, and the prevalence of antipsychotic drug use is high among older patients, it is surprising that so little is known about hypoglycemic manifestations during antipsychotic use in older patients with DM. Therefore, the objective of this study was to assess the effect of antipsychotic use on the risk of hypoglycemia requiring hospitalization in older patients with DM.

Methods

Data source

A population-based cohort study was carried out using the Dutch PHARMO Record Linkage System (RLS) (see http://www.pharmo.nl), a population-based, patient-centric data network for the whole country. This network contains high-quality and complete information about, among other things, patient demographics, drug-dispensing records from community pharmacies, and hospital discharge records of more than 4 million individuals (approximately 24% of the Dutch population) (31,32). The drug-dispensing records consist of data on the drug dispensed, the type of prescriber, the dispensing date, the amount dispensed, and the written dose instructions. Hospital records were obtained from the Dutch National Medical Register, which includes data on all hospital admissions in the Netherlands. The hospital records provided information about hospital admission and discharge, together with primary and secondary diagnoses coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Drugs were coded according to the Anatomical Therapeutic Chemical (ATC) codes (see http://www.whocc.no/atc_ddd_index). Information has been collected since 1986 and has been used in many pharmacoepidemiologic and outcome studies (31,32). Hospital diagnoses and drug exposure data retrieved from the prescription records in the PHARMO RLS have been validated in several studies (33-35).

Study design and sample

A nested case-control design was used to study the association between the use of antipsychotics and hypoglycemia requiring hospitalization. The cohort comprised all patients of 65 years and older with at least 1 year of valid medication history and at least three prescriptions for insulin and/or oral antidiabetic drugs (OADs; ATC code A10) filled in 1 year between January 1998 and December 2008 or a discharge diagnosis of DM (ICD-9-CM code 250). This cohort was followed up until the end of the data collection (December 2008), the patient's transfer out of the registry, or the patient's death, whichever occurred first.

Case definition and comparison subjects

Cases were those patients from the cohort with a first hospital admission for hypoglycemia (ICD-9-CM codes 250.3 or 251.0-251.2). The date of hospitalization for hypoglycemia was taken as the index date. Patients were excluded if the index date was before the date of the first prescription for insulin and/or OADs or if there were no prescriptions for antidiabetic drugs in the year before the index date. Up to five comparison subjects from the cohort were sampled to each case (36). Each comparison subject was assigned the index date and sampled by duration of DM treatment from cohort entry ± 30 days of the corresponding case. Comparison subjects had not been admitted to hospital for hypoglycemia before the index date. The date of the first prescription for an OAD or insulin was used to calculate the duration of DM up to the index date.

Exposure assessment and classification

Exposure to antipsychotic drugs (ATC code N05A, except lithium) before the index date was the primary determinant of interest. The duration of antipsychotic use was calculated as the length of the treatment episode, with treatment episodes defined as a series of prescription refills, regardless of changes to another type of drug or to the dosing regimen. A new treatment episode was considered to occur if there was an interval of 14 days or more between the theoretical end date of a prescription and the dispensing date of the next prescription for the same patient. Patients were classified as current users if the index date fell between the start and end dates of a treatment episode. Past users were defined as patients who were not current users at the index date but who had a history of antipsychotic drug use in a 90-day period before the index date. Patients who had no prescriptions for an antipsychotic drug or in whom a treatment episode ended more than 90 days before the index date were classified as non-users. The duration of antipsychotic treatment was defined for current users as the number of days between the start of the prescription period and the index date (up to 30 days, 31-90 days, 91-365 days, ≥ 366 days). The daily antipsychotic exposure was calculated for current users at the index date by expressing the daily dose divided in daily defined doses during the last prescription period. Antipsychotic treatment of current users was divided in individual antipsychotic drugs based on the highest numbers of users.

Potential confounding factors

The following covariates were studied as potential confounding factors: age at index date, sex, type of DM medication, current use of glucose-influencing comedication, use of antibiotic drugs, number of hospital admissions in the year before the index date, discharge diagnoses for cardiovascular diseases, and extent of chronic comorbidity, measured with the chronic disease score (CDS). The type of DM medication was subdivided into three groups: OADs, insulin, or a combination of OADs and insulin. Patients with at least one prescription for an OAD in the 360 days before the index date but without a prescription for insulin were categorized as being treated with OADs. Patients with at least one prescription for insulin in the 360 days before the index date without a prescription for an OAD were categorized as being treated with insulin, and patients with at least one prescription for insulin and also at least one prescription for an OAD in the 360 days before the index date were categorized as being treated with OADs and insulin. Patients were classified as current users of glucose-influencing comedication (37-39) if a drug was dispensed in a 180-day period before the index date. The use of an antibiotic drug (ATC code J01) in the 14 days before the index date was used as a proxy for the occurrence of an infection. The CDS was used to evaluate the chronic disease status of people who used prescribed drugs. This measure can be considered an indicator of an individual's morbidity and overall health status. The CDS is calculated as the number of drugs dispensed in the year before the index date (40).

Data analysis

Patient characteristics are reported as numbers with percentages in the case of nominal data and as means with standard deviations (SDs) in the case of continuous data. Cases and comparison subjects were compared using the $\chi 2$ test in the case of nominal data. Means were compared using Student independent sample t tests when the data satisfied assumptions for parametric analysis; otherwise, the Mann-Whitney U test was used. Differences in baseline characteristics are expressed as p-values. Unconditional logistic regression was performed to estimate the strength of the association between hypoglycemia and antipsychotic drug use in older patients with DM, always including the terms "index date" and "duration of DM treatment". All odds ratios (ORs) are expressed as point estimates with 95% confidence intervals (CIs). The use of glucose-influencing comedication and number of discharge diagnoses for cardiovascular diseases were included in the final logistic regression model to correct for potential confounding and covariates that induced more than 10% change in the regression coefficient of the logistic regression model (41). We studied potential effect modification of sex, age, use of antibiotic drugs, and DM medication by adding the interaction term with antipsychotic use in the regression model. The interaction term was considered as significant when $p < 0.05$. All statistical analyses were carried out with the SPSS statistical package (IBM Corp, Armonk, NY, version 19.0).

Results

The cohort consisted of 68,314 patients with DM with an average follow-up of 4.5 years. From this cohort, 823 patients (1.2%) were hospitalized for hypoglycemia; 4,114 comparison subjects were selected. In the year before the index date, eight cases and 197 comparison subjects had no prescriptions for an antidiabetic drug and were excluded. The final study population therefore consisted of 815 cases and 3,917 comparison subjects.

Table 1 describes the patient characteristics of cases and comparison subjects. The cases were older than the comparison subjects (79.4 versus 76.9 years), and 62% were women. Use of insulin or OADs and insulin was significantly higher among cases (37.5% and 18.7%, respectively) than among comparison subjects (21.3% and 13.2%, respectively). Glucose-influencing comedication, discharge diagnoses for cardiovascular diseases, and treatment with antibiotics were more common among cases (2.9 prescriptions versus 2.2 prescriptions, 1.0 hospital admissions versus 0.5 hospital admissions, and 15.5% versus 2.9% treatment with antibiotics, respectively), as were higher CDS scores (CDS ≥ 7: 69.2% versus 51.5%).

As shown in Table 2, current and past use of antipsychotic drugs was associated with an increased risk of hospitalization for hypoglycemia (adjusted OR: 2.26; 95% CI: 1.45-3.52; Wald $\chi 2 = 13.08$, df = 1, $p \leq 0.001$ and adjusted OR: 2.68; 95% CI: 1.08-6.63; Wald $\chi 2 = 4.53$, df = 1, $p = 0.033$, respectively). The risk of hospitalization for hypoglycemia was highest during the first 30 days after initiation of antipsychotic drug use and decreased with increasing duration of antipsychotic treatment. The risk was significantly higher

Table 1. Characteristic of older patients with DM who were or were not hospitalized for hypoglycemia

Characteristic	Cases (n = 815)	Comparison subjects (n = 3,917)	*p*-value
Mean age, years (SD)	79.4 (6.5)	76.9 (6.4)	≤ 0.001 [e]
Age, n (%)			≤ 0.001 [f]
65-74 years	196 (24.0)	1,563 (39.9)	
75-84 years	438 (53.7)	1,823 (46.5)	
≥ 85 years	181 (22.2)	531 (13.6)	
Sex, n (%)			0.413 [f]
Female	510 (62.6)	2,391 (61.0)	
DM medication [a], n (%)			≤ 0.001 [f]
OAD	357(43.8)	2,565 (65.5)	
Insulin	306 (37.5)	833 (21.3)	
OAD+ insulin	152 (18.7)	519 (13.2)	
Number of glucose-influencing comedication [b], mean (SD)	2.9 (1.7)	2.2 (1.6)	≤ 0.001 [e]
Number of glucose-influencing comedication [b], n (%)			≤ 0.001 [f]
None	59 (7.2)	610 (15.6)	
1-3	468 (57.4)	2,507 (64.0)	
≥ 4	288 (35.3)	800 (20.4)	
Use of antibiotic drugs [c], n (%)	126 (15.5)	112 (2.9)	≤ 0.001 [f]
Number of hospital admissions [d], mean (SD)	1.0 (1.7)	0.5 (1.2)	≤ 0.001 [e]
Number of hospital admissions [d], n (%)			≤ 0.001 [f]
None	402 (49.3)	2,858 (73.0)	
1-2	327 (40.1)	856 (21.9)	
≥ 3	86 (10.6)	203 (5.2)	
Discharge diagnoses for cardiovascular diseases [d], n (%)			≤ 0.001 [f]
None	727 (89.2)	3,735 (95.4)	
1-2	88 (12.1)	182 (4.6)	
Chronic disease score [a], n (%)			≤ 0.001 [f]
≤ 3	58 (7.1)	626 (16.0)	
4-6	193 (23.7)	1,274 (32.5)	
≥ 7	564 (69.2)	2,017 (51.5)	

a. Based on the community pharmacy prescriptions in the 360 days before the index date.
b. Based on the community pharmacy prescriptions in the 180 days before the index date. See appendix for detailed information.
c. Based on the community pharmacy prescriptions for antibiotic drugs in the 14 days before the index date (ATC code: J01) as a proxy for infection.
d. Based on the discharge diagnoses in the 360 days before the index date.
e. Student independent sample t test. t = 9.90, df = 1,167 for mean age; t = 11.4, df = 4,730 for mean number of glucose-influencing comedication; t = 8.43, df = 992.2 for mean number of hospital admissions.
f. $\chi 2$ test. $\chi 2(2) = 86.50$ for age; $\chi 2(1) = 0.670$ for sex; $\chi 2(2) = 139.5$ for DM medication; $\chi 2(2) = 103.0$ for number of glucose-influencing comedication; $\chi 2(1) = 224.3$ for treatment with antibiotic drugs; $\chi 2(2) = 176.6$ for number of hospital admissions; $\chi 2(1) = 47.44$ for discharge diagnoses for cardiovascular diseases hospital admissions; $\chi 2(2) = 92.49$ for chronic disease score.

Table 2. The risk of hospitalization for hypoglycemia related to antipsychotic drugs

	Cases (n = 815) n (%)	Comparison subjects (n = 3,917) n (%)	OR crude [c] (95% CI)	Wald χ2	*p*-value	OR adjusted [cd] (95% CI)	Wald χ2	*p*-value
Use of antipsychotic drugs								
No use	771 (94.6)	3,842 (95.9)	Reference	Reference	Reference	Reference	Reference	Reference
Current use	36 (4.4)	61 (1.6)	2.94 (1.93-4.47)	25.41	≤ 0.001	2.26 (1.45-3.52)	13.08	≤ 0.001
Past use	8 (1.0)	14 (0.4)	2.87 (1.20-6.86)	5.60	0.018	2.68 (1.08-6.63)	4.53	0.033
Duration of use [a]								
No use	771 (95.5)	3,842 (98.4)	Reference	Reference	Reference	Reference	Reference	Reference
Up to 30 days	9 (1.1)	5 (0.1)	9.03 (3.02-27.03)	15.47	≤ 0.001	7.65 (2.50-23.41)	12.72	≤ 0.001
31-90 days	5 (0.6)	6 (0.2)	4.17 (1.27-13.70)	5.52	0.019	3.03 (0.85-10.80)	2.93	0.087
91-365 days	13 (1.6)	24 (0.6)	2.70 (1.37-5.32)	8.19	0.004	2.16 (1.06-4.42)	4.48	0.034
≥ 366 days	9 (1.1)	26 (0.7)	1.72 (0.80-3.68)	1.92	0.166	1.16 (0.51-2.63)	0.13	0.720
Daily dose [a]								
No use	771 (95.5)	3,842 (98.4)	Reference	Reference	Reference	Reference	Reference	Reference
DDD ≤ 0.25	26 (3.2)	53 (1.4)	2.45 (1.52-3.93)	13.56	≤ 0.001	1.67 (1.00-2.74)	3.90	0.048
DDD > 0.25	10 (1.2)	8 (0.2)	6.20 (2.44-15.67)	14.67	≤ 0.001	8.20 (3.09-21.75)	17.90	≤ 0.001
Type [a]								
No use	771 (95.5)	3,842 (98.4)	Reference	Reference	Reference	Reference	Reference	Reference
Haloperidol	12 (1.5)	17 (0.4)	3.52 (1.67-7.39)	11.00	0.001	2.50 (1.15-5.44)	5.31	0.021
Pipamperone	13 (1.6)	15 (0.4)	4.37 (2.07-9.22)	14.93	≤ 0.001	3.05 (1.38-6.72)	7.65	0.006
Risperidone	5 (0.6)	11 (0.3)	2.24 (0.77-6.47)	2.21	0.137	1.57 (0.51-4.89)	0.62	0.433
Other [b]	6 (0.7)	18 (0.5)	1.66 (0.65-4.16)	1.11	0.293	1.67 (0.64-4.35)	1.08	0.300

DDD: daily defined dose. Notes: Each *p*-value was based on a Wald χ2 with df = 1.

a. Among current users (n = 97).

b. Other antipsychotic drugs include bromperidol, fluphenazine, levomepromazine, olanzapine, penfluridol, perphenazine, pimozide, quetiapine, thioridazine, tiapride, and zuclopenthixol.

c. The unconditional logistic regression model includes the index date and the duration of diabetes treatment.

d. Adjusted for age, glucose-influencing comedication, and number of discharge diagnoses for cardiovascular diseases.

with higher drug doses (daily defined dose > 0.25 adjusted OR: 8.20 compared with daily defined dose ≤ 0.25 adjusted OR: 1.67). Treatment with haloperidol and pipamperone was associated with an increased risk of hospitalization for hypoglycemia, whereas treatment with risperidone was not.

Table 3 shows the risk of hospitalization for hypoglycemia among antipsychotic users compared with non-users stratified for sex. Sex was identified as an effect modifier (Wald $\chi 2 = 13.54$, df = 2, $p \leq 0.001$).The adjusted OR of current antipsychotic use for men was 9.74. No effect modification was found for age (Wald $\chi 2 = 7.89$, df = 4, $p = 0.096$), DM medication (Wald $\chi 2 = 0.84$, df = 4, $p = 0.934$), and the use of antibiotic treatment (Wald $\chi 2 = 3.18$, df = 2, $p = 0.204$). However, the risk seems to be slightly increased in current users of antipsychotic drugs in patients with DM without antibiotic treatment in the 14 days before the index date (adjusted OR: 2.32; 95% CI: 1.14-3.77; Wald $\chi 2 = 12.12$, df = 1, $p \leq 0.001$) compared with those with antibiotic treatment.

Discussion

The results of this study show that compared with non-use, the current use of antipsychotic drugs by older patients with DM is associated with an approximately two times higher risk of hypoglycemia and that the risk is highest during the first 30 days of antipsychotic treatment compared with those diabetics not using antipsychotic therapy. Furthermore, the risk of hospitalization for hypoglycemia increased with drug dose, and the use of haloperidol or pipamperone would appear to be more harmful than risperidone. Men (adjusted OR: 9.74) were at highest risk.

To our knowledge, this is the first study to assess the association between antipsychotic drugs and hypoglycemia. The association with dose and time suggests a causal relation between antipsychotic drug use and hypoglycemia, although causality cannot be established in an observational study. Only three case reports were found on hypoglycemia during antipsychotic use in older patients (20,23,27), and one case report was found in a younger patient with DM (24). We found no studies of hypoglycemia and antipsychotic treatment, but an earlier study reported that the risk of hyperglycemia, instead of hypoglycemia, in older patients with DM was highest early during therapy with atypical or conventional antipsychotics (18). Our results and the results of Lipscombe et al. (19) indicate that although few people need to be hospitalized for glucose dysregulation, some individuals, especially those with existing DM, do.

The proposed mechanism by which antipsychotics may increase the risk of hypoglycemia include a direct drug effect, decreased food intake, or anorexia as a consequence of the underlying disease for which the patient is being treated with antipsychotics or the underlying disease itself. Atypical antipsychotics cause insulin resistance by antagonism of serotonin 5-HT2a receptors, increase food intake by antagonism of serotonin 5-HT1a receptors, cause weight gain by antagonism of histamine H1 receptors, and impair insulin secretion by antagonism of muscarinic M3 receptors and serotonin 5HT-2a receptors. However, it has been suggested that antipsychotic drugs may

Table 3. The risk of hospitalization for hypoglycemia related to antipsychotic drugs stratified for sex

		Cases n (%)	Comparison subjects n (%)	OR crude [a] (95% CI)	Wald χ2	*p*-value	OR adjusted [ab] (95% CI)	Wald χ2	*p*-value
Male		**(n = 305)**	**(n = 1,526)**						
Use of antipsychotic drugs	No use	285 (93.4)	1,513 (99.1)	Reference	Reference	Reference	Reference	Reference	Reference
	Current use	17 (5.6)	8 (0.5)	11.26 (4.81-26.36)	31.15	≤ 0.001	9.74 (4.03-23.51)	25.62	≤ 0.001
	Past use	3 (1.0)	5 (0.3)	3.18 (0.75-13.39)	2.48	0.115	2.96 (0.67-13.07)	2.04	0.153
Female		**(n = 510)**	**(n = 2,391)**						
Use of antipsychotic drugs	No use	486 (95.3)	2,329 (97.4)	Reference	Reference	Reference	Reference	Reference	Reference
	Current use	19 (3.7)	53 (2.2)	1.71 (1.00-2.91)	3.86	0.049	1.27 (0.72-2.24)	0.70	0.402
	Past use	5 (1.0)	9 (0.4)	2.69 (0.90-8.06)	3.11	0.078	2.45 (0.78-7.71)	2.34	0.126

a. The unconditional logistic regression model includes index date and the duration of diabetes treatment.

b. Adjusted for age, glucose-influencing comedication, and number of discharge diagnoses for cardiovascular diseases.

have the opposite effect on insulin regulation. Previous studies report that dopamine-2/3 blockade by raclopride, amisulpride, and sulpiride stimulates insulin secretion by pancreatic beta cells (42-44). Furthermore, it has been reported that administration of serotonin in vivo can cause hyperglycemia (45) and hypoglycemia (46). It has been reported that conventional antipsychotics may elevate extracellular glutamate levels during hypoglycemic episodes, resulting in cognitive impairment that delays recovery from hypoglycemia, whereas atypical antipsychotics might be less neurotoxic because they inhibit glutamate release (47). The increased risk of hypoglycemia among past users of antipsychotics was unexpected. It is possible that insulin resistance or hyperglycemia during (long-term) antipsychotic treatment may lead to changes in antidiabetic treatment (48), such that if antipsychotic treatment is discontinued but antidiabetic treatment is not reassessed, the patient may receive too high a dose of antidiabetic treatment and thus be at risk of hypoglycemia. Another explanation for this finding is that patients were misclassified by exposure because we used a strict definition of current antipsychotic use. Male gender has previously been mentioned as a risk factor for hypoglycemia (49-51).

Blood glucose levels tend to be monitored more frequently in diabetics who are using antibiotics, and therefore glucose dysregulation may be detected earlier and prevent severe hypoglycemia. This may explain why older patients with DM treated without antibiotic drugs appeared to be more likely to develop hypoglycemia than patients who did use antibiotics. This study involved a large cohort of older patients with DM with a long follow-up, which made it possible to distinguish between new and long-term antipsychotic use. However, it also had a number of limitations. First, hypoglycemia may have been underestimated because most patients with hypoglycemia are treated as outpatients (52), and only patients with severe hypoglycemia or hypoglycemia complicated by additional conditions (such as falls or loss of consciousness) require hospitalization. Hypoglycemia may also have been underestimated as a result of ascertainment bias if comparison subjects had developed hypoglycemia but were not admitted to hospital. However, because this type of misclassification probably occurred at random among cases and comparison subjects, it was not considered to be relevant. Second, drug exposure was based on drug dispensing data, but there was no information about whether dispensed drugs were actually used. However, this potential misclassification of exposure may have occurred at random among cases and comparison subjects and was not considered relevant. Protopathic bias could also have occurred if an antipsychotic drug was initiated because a patient exhibited delirious symptoms or agitation as a result of hypoglycemia. However, we believe most doctors would measure blood glucose levels, to exclude hypoglycemia, in patients with DM and psychotic symptoms. Therefore, we do not consider this bias as relevant. Unfortunately, we had no information about psychiatric diagnosis and indications for which the antipsychotic drug was initiated. Therefore, confounding by indication may have occurred if the hypoglycemia episode was a result of self-care impairment in dementia or another mental illness instead of a direct antipsychotic effect. Additionally, confounding by

contraindication may have occurred and may be differential because the physician's decision for initiation and type of antipsychotic drug was influenced by the severity of the DM and the extent of the blood glucose control. Finally, residual confounding may have been present, because the PHARMO RLS does not provide information about risk factors, such as body mass index, renal and liver function, blood pressure, or smoking habit (53). We believe the risk of hypoglycemia was probably underestimated. Only community-dwelling older patients were included in our study, and patients living in long-term facilities have a higher estimated risk of hypoglycemia (because they are more vulnerable, with comorbidities) than older patients in the general population.

Despite these limitations, the results of this observational study suggest that older patients with DM on antipsychotics are at risk of hypoglycemia. We suggest this risk is probably additional to the risk of hypoglycemia due to their antidiabetic treatment. Further research is needed to confirm the association between antipsychotic drugs and hypoglycemia and to establish the underlying mechanism. Our findings suggest that in clinical practice glucose levels should be closely monitored in older patients with DM after the prescription or discontinuation of antipsychotic drugs to prevent the serious consequences of hypoglycemia.

Conclusion

The results of this study suggest that the use of antipsychotics increases the risk of hospitalization for hypoglycemia in older patients with DM, compared with diabetics without antipsychotic treatment, especially during the first 30 days of treatment and with higher antipsychotic doses. If confirmed, these findings should prompt the close monitoring of blood glucose levels in older patients with DM prescribed antipsychotics to facilitate the early detection of hypoglycemia.

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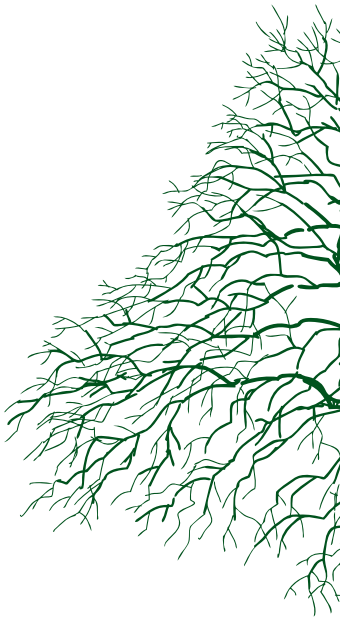
Appendix

Medications influencing the level of blood glucose

Acetaminophen, acetazolamide, angiotensin-converting enzyme inhibitors, beta agonists, beta blockers, calcium channel blockers, central alpha blockers, chlordiazepoxide, corticosteroids, cyclosporine, dapsone, diazoxide, disopyramide, fibric acid derivates, indomethacin, isoniazid, L-dopa, lithium, loop diuretics, mebendazole, monoamine oxidase inhibitors, morphine, nicotinic acid, octreotide, phenytoin, rifampicin, salicylates, selective serotonin reuptake inhibitors, tetracycline, theophylline, thiazide diuretics, thyroid hormones, tricyclic antidepressants, trimethoprim-sulfamethoxazole



3

Hyperglycemia and hypoglycemia in older hospitalized patients using antipsychotic drugs

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Abstract

Introduction

Antipsychotic drugs are associated with an increased risk of hyperglycemia and hypoglycemia in nonhospitalized patients with or without diabetes; however, the risk in older hospitalized patients is largely unknown. The aim of this study was to investigate whether antipsychotic drug use is associated with hyperglycemia and hypoglycemia in older hospitalized patients.

Methods

This nested case-control study involved all patients aged 70 years or older admitted to a general community teaching hospital between 2010 and 2014 with normoglycemia at admission and at least one glucose measurement during hospitalization. Cases were patients who developed hyperglycemia (glucose level ≥ 11.1 mmol/L) or hypoglycemia (glucose level ≤ 3.5 mmol/L) during hospitalization. Up to five controls were selected for each case. Exposure to antipsychotic drugs before the index date was the primary determinant of interest. Logistic regression analysis was used to estimate the strength of the association between antipsychotic drugs and hyperglycemia or hypoglycemia, taking into account potential confounders.

Results

Of 2,054 patients included, 483 (23.5%) developed hyperglycemia and 43 (2.1%) developed hypoglycemia. Haloperidol was the most frequently used antipsychotic drug (hyperglycemia: 47 cases and 64 controls and hypoglycemia: 3 cases and 9 controls). Current use of haloperidol was not associated with an increased risk of hyperglycemia (adjusted OR: 1.34, 95% CI: 0.81-2.21) or hypoglycemia (OR: 0.66, 95% CI: 0.17-2.63). However, hospital initiated haloperidol was associated with hyperglycemia (adjusted OR: 2.02, 95% CI: 1.01-4.03). Diabetes and cognitive deterioration were not identified as effect modifiers.

Conclusion

No evidence was found for an association between antipsychotic use and hypoglycemia in older hospitalized patients. Hospital initiated haloperidol use was associated with hyperglycemia in older hospitalized patients. Our results suggest that closer monitoring of blood glucose levels may be indicated after starting haloperidol in a hospital setting.

Introduction

Antipsychotic drugs are widely used to relieve the psychotic or behavioral symptoms of delirium, and they are the first choice of treatment despite lack of regulatory improvement and with little evidence of effectiveness in delirium. The prevalence of delirium in hospitalized patients on medical wards is about 20% (1). However, antipsychotic drugs are associated with an increased risk of mortality in older patients (2-4), possibly because these patients have underlying cardiovascular and metabolic problems (5-9). The cardiovascular and metabolic problems using antipsychotic drugs in older patients have particularly been studied in outpatients. Although evidence is scarce, it has been suggested that older patients using antipsychotic drugs are at increased risk of diabetes (10-13). In addition, antipsychotic drugs have been associated with an increased risk of hyperglycemia requiring hospitalization in older diabetic and non-diabetic patients (14-16), and with an increased risk of hospitalization for hypoglycemia rather than for hyperglycemia in older diabetic patients (17). In these studies, the risk was highest directly after the initiation of the antipsychotic drug, suggesting an acute effect.

Hyperglycemia has serious consequences, such as diabetes, infections, prolonged hospital stay, cardiac adverse events, and death during hospitalization (18-22). In-hospital hypoglycemia increases the length of stay and risk of mortality during hospitalization (23). Reported long-term effects of hypoglycemia in vulnerable older patients include a higher risk of falls and fractures (24), cognitive impairment and acceleration of dementia (25).

In summary, antipsychotic drugs are associated with both hypoglycemia and hyperglycemia early in the course of therapy in older outpatients. Since both hypoglycemia and hyperglycemia are associated with negative outcomes, it is important to prevent their occurrence. As it is unknown if older hospitalized patients using antipsychotic drugs are at increased risk of hypoglycemia or hyperglycemia, we investigated whether antipsychotic drug use for delirium is associated with hypoglycemia or hyperglycemia in older hospitalized patients.

Methods

Data source, study design and population

This retrospective study was carried out in Tergooi Hospital, a general community teaching hospital with 633 beds at two locations, Hilversum and Blaricum, in the Netherlands. The local Medical Research Ethics Committee considered that this study did not fall under the Medical Research (Human Subjects) Act (declaration CTS 15.26) and informed consent was not necessary. Data for this nested case-control study were retrospectively extracted from the hospital clinical information system between January 2010 and December 2014. The cohort consisted of all patients aged 70 years or older with normoglycemia (3.5-11.1 mmol/L) at admission (measured within the first 12 hours of hospitalization) and with at least one additional glucose measurement during

hospitalization. The cohort was followed up until discharge, transfer to another hospital, or death. Patients admitted to the intensive care unit (ICU) were excluded, because of differences in glucose monitoring protocols (on request on non-intensive care wards versus at fixed time intervals according glucose regulation protocols in the ICU).

Case definition and controls

Cases were those patients who became hypoglycemic or hyperglycemic 12 hours or longer after admission. Hyperglycemia was defined as a fasting blood glucose level ≥ 11.1 mmol/L and hypoglycemia as a fasting blood glucose level < 3.5 mmol/L. The date of hyperglycemia or hypoglycemia was taken as the index date. Controls (1-5 per case) were randomly selected by calendar year of admission (to control for changes in treatment over time) and length of hospital stay in days (to control for disease severity of the corresponding case). Each control was assigned an index date.

Exposure assessment and classification

Exposure to antipsychotic drugs (ATC code: N05A except lithium) before the index date was the primary determinant of interest. Patients were classified as current users if the index date fell between the start and end date of the antipsychotic prescription. Patients who received antipsychotics on the day of admission were considered to use antipsychotic drugs prior to hospitalization and were considered ambulant users. If the antipsychotic drug was initiated the day after hospital admission, antipsychotic drug use was considered hospital initiated. Daily antipsychotic exposure was calculated as the daily-defined dose before the index date. Some antipsychotics were prescribed 'as required'. The dose of these antipsychotics was calculated assuming that 50% of the tablets were administered.

Potential confounding factors

The following covariates were studied as potential confounders: age at index date, sex, cognitive deterioration (mild cognitive impairment, dementia and delirium during hospital stay), diabetes (diagnosis or treatment), the use of glucose-influencing medication (see Appendix) (26-28), antibiotic treatment, admission specialty and comorbidity (assessed with the Charlson Comorbidity Index, CCI) (29). Mild cognitive impairment and dementia were considered present when documented in the electronic medical record before hospital admission. Delirium during hospitalization was considered present when it was documented in the medical record, diagnosed according the Diagnostic Statistical Manual of Mental Disorders (DSM fourth version) and/or clinical experience by the geriatric team or attending physician. Patients were considered to have diabetes when it was documented in the electronic medical record before admission. Antidiabetic drugs were often discontinued at hospital admission and restarted during hospitalization; for example, if patients were admitted for acute renal failure or gastroenteritis. Therefore, exposure to antidiabetic drugs (insulin and/or oral antidiabetic drugs) was based on prescriptions during hospitalization. Antibiotic

treatment (ATC code: J01) up to 48 hours before the index date was used as proxy for infection, except in the case of prophylactic antibiotic use. Use of glucose-influencing medication (see Appendix) was based on its prescription before the index date during hospitalization. The following specialties were considered as surgical: general surgery, orthopedics, urology, gynecology, otorhinolaryngology, plastic surgery, neurosurgery and ophthalmology. The following specialties were considered as medical: internal medicine, gastroenterology, pulmonology and cardiology. Comorbidity was considered present when recorded in the electronic medical record before hospital admission.

Data analysis

Patient characteristics are reported as numbers with percentages in the case of nominal data and as means with standard deviations (SDs) in the case of continuous data. Nominal data for cases and controls were compared using the $\chi 2$ test. Means were compared using Student independent sample t test when the data satisfied assumptions for parametric analysis; otherwise, the Mann-Whitney U test was used. Differences in baseline characteristics with $p < 0.05$ were considered statistically significant. Unconditional logistic regression was performed to estimate the strength of the association between antipsychotic drug use and hyperglycemia or hypoglycemia and included the terms index date, year of admission, and length of stay. All odds ratios (OR) are expressed as point estimates with 95% confidence interval (CI). The final logistic regression model included the covariates that induced more than 10% change in the regression coefficient for current use of antipsychotic drugs. We studied potential effect modification by sex, age, cognitive deterioration, diabetes treatment, antibiotic treatment and admission specialty by adding the interaction term with antipsychotic use in the regression model for hyperglycemia or hypoglycemia. The interaction term was considered significant when $p < 0.05$. All statistical analyses were carried out with the SPSS statistical package (IBM Corp, Armonk, NY, version 22.0).

Sample size calculation

We calculated that 522 cases and 2,610 controls would be needed in order to detect a 1.5-times increased odds of hyperglycemia during antipsychotic treatment in cases compared with controls, based on the assumption that 10% of the population used antipsychotic drugs, five controls per case, α of 0.05 and a power of 80%. For hypoglycemia, we calculated that 127 cases and 785 controls would be needed in order to detect a 2.0-times increased odds in cases compared with controls.

Results

The cohort consisted of 2,054 older hospitalized patients with normoglycemia at hospital admission and with at least one additional glucose measurement taken during admission. Of these patients, 483 (23.5%) developed hyperglycemia and 43 (2.1%) developed hypoglycemia during hospitalization. A total of 1,053 controls were selected.

The mean age in the four groups (hyperglycemia or hypoglycemia, cases and controls) was approximately 80 years, and 58% were women (Table 1). In the hyperglycemic group, 11.8% of the cases and 10.9% of the controls were diagnosed with dementia, and 6.6% of the cases and 5.5% of the controls developed delirium during the hospital stay. Diabetes was diagnosed more often in the patients with hyperglycemia than in the controls (cases 90.9% and controls 58.0%). Overall, 6.6% of the patients with hyperglycemia and 9.9% of the controls with diabetes did not receive antidiabetic medication during hospitalization. The patients with hyperglycemia more often received glucose-influencing medication (mean 2.5 SD 1.4 versus 2.3 SD 1.4, $p \leq 0.001$), had a higher glucose level at admission (mean 7.9 SD 1.7 versus 7.1 mmol/L SD 1.6, $p \leq 0.001$), more often received antibiotic treatment (49.5% versus 34.8%, $p \leq 0.001$), had a higher CCI (mean 3.1 SD 2.0 versus 2.7 SD 1.9, $p \leq 0.001$), and had a prolonged hospital stay (median 7 IQR 4-11 versus 5 IQR 3-9 days, $p \leq 0.001$) compared with the controls. They were more often admitted to surgical (46.0%) or geriatric (15.9%) wards compared with the controls (surgical 31.7% and geriatric 11.7%).

In the hypoglycemic group, 14.0% of the cases and 10.0% of the controls were diagnosed with dementia, and 9.3% of the cases and 7.8% of the controls developed delirium during the hospital stay. Overall, 14.0% of the patients with hypoglycemia and 12.2% of the controls with diabetes did not receive antidiabetic medication during their stay. Controls more often received glucose-influencing medication than did the patients with hypoglycemia (mean 2.4 SD 1.5 versus 1.9 SD 1.3, $p < 0.046$). The patients with hypoglycemia were more frequently admitted to internal (46.5%) and geriatric (20.9%) wards than were the controls (internal 30.0% versus geriatric 8.9%) and had a higher CCI score than controls (mean 4.4 SD 2.2 versus 2.8 SD 1.9, $p \leq 0.001$).

49 (10.1%) of the patients with hyperglycemia and 85 (8.8%) of the controls were treated with antipsychotic drugs. Four (9.3%) patients with hypoglycemia and 11 (12.2%) controls were treated with antipsychotic drugs. Haloperidol was the most frequently prescribed antipsychotic drug (hyperglycemia: 47 cases and 64 controls and hypoglycemia: 3 cases and 9 controls); other antipsychotic drugs used were risperidone (11), quetiapine (4), olanzapine (4), pimozide (2), pipamperone (1), sulpiride (1) and clozapine (1). Thus, limited antipsychotic users were not treated with haloperidol and therefore our analysis was limited to haloperidol users. In the case that patients had been switched between haloperidol and an atypical antipsychotic drug before index date (4 patients), their atypical antipsychotic drug use was studied as potential confounder (glucose influencing medication).

As shown in Table 2, current use of haloperidol was not associated with an increased risk of hyperglycemia (adjusted OR: 1.34, 95% CI: 0.81-2.21) or hypoglycemia (OR: 0.66, 95% CI: 0.17-2.63). However, hospital initiated haloperidol was associated with hyperglycemia (adjusted OR: 2.02, 95% CI: 1.01-4.03) and ambulant use of haloperidol was not (adjusted OR: 2.02, 95% CI: 1.01-4.03). Sex, age, diabetes (diagnosis and treatment), antibiotic treatment and cognitive deterioration did not influence the association between haloperidol and hyperglycemia or hypoglycemia. A sensitivity

Table 1. Characteristic of older hospitalized patients who had, or had not, an event of hyperglycemia or hypoglycemia

	Hyperglycemia			Hypoglycemia		
Characteristic	**Cases (n = 483)**	**Controls (n = 963)**	***p*-value**	**Cases (n = 43)**	**Controls (n = 90)**	***p*-value**
Mean age, years (SD)	80.7 (6.5)	80.9 (6.6)	0.781 [c]	81.5 (6.2)	79.5 (6.2)	0.078 [c]
Age, n (%)			0.781 [d]			0.401 [d]
70-80 years	234 (48.4)	474 (49.2)		22 (51.2)	53 (58.9)	
> 80 years	249 (51.6)	489 (50.8)		21 (48.8)	37 (41.1)	
Sex, n (%)			0.591 [d]			0.768 [d]
Female	284 (58.8)	552 (57.3)		26 (60.5)	52 (57.8)	
Cognitive deterioration						
Mild cognitive dysfunction, n (%)	27 (5.6)	51 (5.3)	0.798 [d]	0 (0.0)	4 (4.4)	0.160 [d]
Dementia, n (%)	57 (11.8)	105 (10.9)	0.610 [d]	6 (14.0)	9 (10.0)	0.500 [d]
Delirium during hospital stay, n (%)	32 (6.6)	53 (5.5)	0.392 [d]	4 (9.3)	7 (7.8)	0.765 [d]
Diagnosis of diabetes, n (%)	439 (90.9)	559 (58.0)	≤ 0.001 [d]	42 (97.7)	50 (55.6)	≤ 0.001 [d]
Diabetes treatment, n (%)			≤ 0.001 [d]			≤ 0.001 [d]
OAD	212 (43.9)	357 (37.1)		15 (34.9)	33 (36.7)	
Insulin	75 (15.5)	51 (5.3)		12 (27.9)	2 (2.2)	
OAD and insulin	120 (24.8)	56 (5.8)		9 (20.9)	4 (4.4)	
No medication [a]	32 (6.6)	95 (9.9)		6 (14.0)	11 (12.2)	
Number of glucose-influencing medication [b], mean (SD)	2.5 (1.4)	2.3 (1.4)	≤ 0.001 [c]	1.9 (1.3)	2.4 (1.5)	0.046 [c]
Number of glucose-influencing medication [b], n (%)			0.025 [d]			0.482 [d]
0-1	111 (23.0)	278 (28.9)		15 (34.9)	23 (25.6)	
2-3	262 (54.2)	508 (52.8)		21 (48.8)	47 (52.2)	
≥ 4	110 (22.8)	177 (18.4)		7 (16.3)	20 (22.2)	
Glucose concentration at admission (mmol/L), mean (SD)	7.9 (1.7)	7.1 (1.6)	≤ 0.001 [c]	6.8 (1.9)	7.1 (1.7)	0.308 [c]
Antibiotic treatment, n (%)	239 (49.5)	335 (34.8)	≤ 0.001 [d]	11 (25.6)	26 (29.9)	0.691 [d]
Admission specialty, n (%)			≤ 0.001 [d]			0.003 [d]
Surgical	222 (46.0)	305 (31.7)		12 (27.9)	28 (31.1)	
Internal	137 (28.4)	294 (30.5)		20 (46.5)	27 (30.0)	
Neurology	47 (9.7)	251 (26.1)		2 (4.7)	27 (30.0)	
Geriatrics	77 (15.9)	113 (11.7)		9 (20.9)	8 (8.9)	
CCI, mean (SD)	3.1 (2.0)	2.7 (1.9)	≤ 0.001 [c]	4.4 (2.2)	2.8 (1.9)	≤ 0.001 [c]
Length of hospital stay in days, median (IQR)	7 (4-11)	5 (3-9)	≤ 0.001 [e]	5 (3-12)	4 (2-11)	0.077 [e]

CCI: Charlson comorbidity index.

a. During hospital stay.
b. See appendix for detailed information.
c. Student independent sample t test.
d. $\chi 2$ test.
e. Mann-Whitney U test.

Table 2. The risk of hyperglycemia and hypoglycemia related to haloperidol use among hospitalized older patients

	Hyperglycemia				Hypoglycemia			
	Cases (n = 483) n (%)	Controls (n = 963) n (%)	OR crude [a] (95% CI)	OR adjusted [ab] (95% CI)	Cases (n = 43) n (%)	Controls (n = 90) n (%)	OR crude [a] (95% CI)	OR adjusted (95% CI)
Current haloperidol use	47 (9.7)	64 (6.6)	1.40 (0.94-2.08)	1.34 (0.81-2.21)	3 (7.0)	9 (10.0)	0.66 (0.17-2.63)	N.A.
Ambulant use	22 (46.8)	43 (67.2)	0.98 (0.57-1.66)	0.79 (0.42-1.52)	1 (33.3)	5 (55.6)	0.39 (0.04-3.52)	N.A.
Hospital initiated	25 (53.2)	27 (42.2)	1.72 (0.98-3.03)	2.02 (1.01-4.03)	2 (66.7)	4 (44.4)	0.99 (0.17-5.97)	N.A.
DDD < 0.25	39 (83.0)	57 (89.1)	1.29 (0.84-1.98)	1.25 (0.74-2.11)	3 (100)	9 (100)	0.66 (0.17-2.61)	N.A.
DDD ≥ 0.25	8 (17.0)	7 (10.9)	2.31 (0.83-6.49)	2.00 (0.57-7.00)	0 (0)	0 (0)	N.A.	N.A.

DDD: daily defined dose; N.A.: not applicable.

a. The unconditional regression model includes index date, length of hospital stay and the year of admission.

b. Adjusted for age, mild cognitive impairment, dementia, delirium during hospital stay, glucose-influencing medication, antibiotic treatment, admission specialty and Charlson Comorbidity Index.

analysis performed without patients using haloperidol as required yielded similar results.

Discussion

In this case-control study, we found that hospital initiated haloperidol use is associated with hyperglycemia and ambulant use of haloperidol is not associated with hyperglycemia in older hospitalized patients. No evidence was found for an association between antipsychotic use and hypoglycemia in older hospitalized patients.To our knowledge, this study is the first to determine the risk of hyperglycemia and hypoglycemia in this patient population. Previous studies have investigated antipsychotic drug use and glucose regulation in outpatients. However, it is difficult to compare our findings with the findings of those studies because in our study antipsychotic drugs were mainly prescribed for delirium, and thus treatment was for relatively a short period of time, whereas outpatients tend to be treated long term with antipsychotic drugs for psychotic or behavioral symptoms of dementia or schizophrenia. The CATIE-AD study reported that atypical antipsychotic drugs (olanzapine, quetiapine, and risperidone) did not have a statistically significant effect on glucose levels compared with placebo over 36 weeks in older patients with Alzheimer's disease (30). In our study, the conventional antipsychotic haloperidol was the most frequently prescribed antipsychotic drug. Earlier studies have reported antipsychotic drugs to be associated with an increased risk of hyperglycemia and hypoglycemia early in the course of antipsychotic therapy in older outpatients (16,17). Another study reported that 10.7% of older patients with dementia developed impaired fasting glucose levels after the initiation of atypical antipsychotic drugs, and that the mean glucose concentration increased by 0.5 mmol/L over 6 weeks to 1 year after initiation (31). However, these studies involved different populations and different types of antipsychotic drugs. Especially antagonism of serotonin 5-HT1a and 5-HT2a, histamine H1, and muscarinic M3 receptors by long-term use of atypical antipsychotic drugs have been linked to disturbances in glucose homeostasis resulting in weight gain, increased food intake, insulin resistance and impaired insulin secretion. The mechanism by which haloperidol could induce hyperglycemia shortly after initiation is unknown; it could be a direct drug effect or an effect of the underlying disease. However, it has been reported that dopamine D2 receptor antagonism is associated with increased glucose levels and diabetes (32).

One of the strengths of our study was that hyperglycemia or hypoglycemia was diagnosed on the basis of glucose measurements and not on clinical symptoms. Secondly, exposure to antipsychotic drugs was based on used medication, because intake was supervised by a nurse, and not on drug-dispensing data. Thirdly, the study population consisted of diabetic and non-diabetic older patients. Lastly, detailed information was available about patients' cognitive status. For this reason, we could study the effect of mild cognitive impairment, dementia, and delirium during the hospital stay.

However, our study had a number of limitations. In our study, fewer patients used antipsychotic drugs than in the earlier studies that reported a positive association

between antipsychotic drugs and hyperglycemia or hypoglycemia. Our study was not powered to confirm an association between antipsychotic use and hypoglycemia in an older hospitalized population. We were unable to adjust for potential confounders in the hypoglycemic group and to differentiate between conventional and atypical antipsychotic drugs because more than 80% of the antipsychotic drug users were treated with haloperidol. Moreover, with our cohort definition, we may have introduced selection bias, because glucose levels were only measured on indication (i.e., in diabetic patients or before surgery). However, blood glucose levels were measured independently of the initiation of antipsychotic therapy, so this potential bias was considered not relevant. In addition, hyperglycemia and hypoglycemia could have been underestimated in both cases and controls, because glucose levels were not continuously monitored during hospitalization. Misclassification of exposure might have occurred if antipsychotic drugs were prescribed for patients who were delirious at admission, because we classified antipsychotic drug use on the day of hospitalization as ambulant use. And vice versa, antipsychotic use was considered hospital initiated if the drug was prescribed the day after admission, and thus patients normally on antipsychotic drugs might not have been given them if their medication history was not available at hospitalization. This misclassification of exposure was not considered relevant as it may have occurred at random among cases and controls. Lastly, residual confounding may have occurred because we did not adjust for potential covariates, such as smoking, nutrition/malnutrition, and body mass index.

It is important to detect glucose dysregulation early because it is easy to correct, and glucose dysregulation has serious consequences in older patients. Moreover, it takes longer for glucose levels to normalize in older patients than in younger patients, potentially exposing older patients to more serious symptoms, such as neurological deficits (33) and an increased risk of falls and fractures (34). Hyperglycemia increases the risk of diabetes and its complications, resulting in an increased cardiovascular risk (35). Because we did detect an association between hospital initiated haloperidol use and hyperglycemia, larger studies may be needed to confirm our findings, to investigate the underlying mechanism and consequences on outcome in the frail older hospitalized population. Our results suggest that closer monitoring of blood glucose levels may be indicated after starting haloperidol in a hospital setting. We excluded patients admitted to the ICU, even though these patients are at highest risk of disturbances in glucose regulation. The risk profile of these patients is different from that of patients on other wards and their glucose levels are monitored more frequently. Stress-induced hyperglycemia is more common in patients on the ICU and they are usually treated with insulin according to ICU glucose regulation protocols, thereby increasing the risk of hypoglycemia relative to that of patients not on the ICU (36).

In summary, the results of our study suggest that hospital initiated haloperidol use is associated with hyperglycemia in older hospitalized patients. We were not able to detect an association between antipsychotic use and hypoglycemia in this vulnerable population, due to a lack of power.

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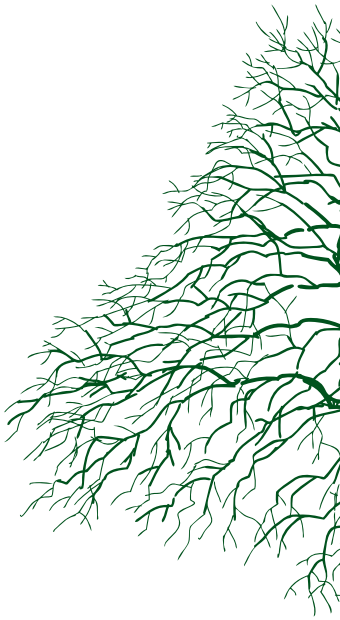
Appendix

Medications influencing the level of blood glucose

Acetaminophen, acetazolamide, angiotensin-converting enzyme inhibitors, beta agonists, beta blockers, calcium channel blockers, central alpha blockers, chlordiazepoxide, corticosteroids, cyclosporine, dapsone, diazoxide, disopyramide, fibric acid derivates, indomethacin, isoniazid, L-dopa, lithium, loop diuretics, mebendazole, monoamine oxidase inhibitors, morphine, nicotinic acid, octreotide, phenytoin, rifampicin, salicylates, selective serotonin reuptake inhibitors, tetracycline, theophylline, thiazide diuretics, thyroid hormones, tricyclic antidepressants, trimethoprim-sulfamethoxazole



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Prophylactic use of haloperidol and changes in glucose levels in hospitalized older patients

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Abstract

Introduction

Treatment with antipsychotic drugs has been associated with glucose dysregulation in older outpatients, especially in the early stage of therapy. The underlying mechanism is, however, unclear. The aim of this study was to investigate changes in glucose levels during haloperidol use compared with the use of placebo among older hospitalized patients.

Methods

This substudy was part of a larger multicenter, randomized, double blind, placebo-controlled clinical trial among hospitalized patients aged 70 years and older who had an increased risk of in-hospital delirium. Patients who were admitted to the Jeroen Bosch Hospital in 's-Hertogenbosch between June 2014 and February 2015 were invited to participate in the study. Participating patients were randomized for treatment and given 1 mg of haloperidol or a placebo twice daily for a maximum of 7 consecutive days (14 doses). Exclusion criteria for this substudy were the use of corticosteroids and changes in diabetes medication. Random blood samples to determine glucose levels were collected before day 1 and on day 6 of the study. Student independent sample *t* test was used to determine differences in glucose changes between both groups.

Results

Twenty-nine patients were included (haloperidol, n = 14; placebo, n = 15). The mean glucose level for placebo users was 7.7 mmol/L SD 2.8 on day 1 and 7.8 mmol/L SD 2.8 on day 6, and the mean glucose level for haloperidol users was 7.8 mmol/L SD 3.9 on day 1 and 8.3 mmol/L SD 2.2 on day 6. The difference was not statistically significant ($p = 0.685$).

Conclusion

Short-term prophylactic use of haloperidol was not associated with changes in glucose levels in older hospitalized patients compared with those given a placebo in this small study.

Introduction

Antipsychotic treatment in older people has been associated with the onset of diabetes mellitus, although evidence is scarce and inconsistent (1-4). In addition, treating older patients with and without diabetes with antipsychotic drugs (APDs) has been associated with hyperglycemia as well as hypoglycemia that may require hospitalization. The highest risk is in the early stage of antipsychotic therapy (5-8).

The number of reports available about older patients using APDs and metabolic adverse effects is limited compared with literature on the metabolic effects of APDs in younger patients with schizophrenia. In younger populations with schizophrenia, the routine measurement of glucose levels during antipsychotic treatment has been implemented as part of metabolic screening and monitoring (9-11). However, it remains unclear to what extent changes in glucose levels are the result of antipsychotic treatment or the underlying disease. Antipsychotic drug use has been associated with higher glucose levels, and schizophrenia has also been linked to a higher prevalence of diabetes compared with that found in the general population (12-14).

Haloperidol is frequently prescribed for a short period of time for older hospitalized patients to relieve psychotic or behavioral symptoms related to delirium (15). It is not clear whether short-term APD use among this vulnerable population influences glucose levels and worsens metabolic abnormalities. Glucose dysregulation in hospitalized patients has been associated with short-term and long-term complications including infections, an increased length of stay, cognitive impairment, falls and fractures, the acceleration of dementia, diabetes mellitus, and mortality (16-23). The objective of this study was therefore to investigate any changes in glucose levels during prophylactic use of haloperidol in comparison with placebo in older hospitalized patients.

Methods

Design, setting and study population

This substudy was part of the larger haloperidol prophylaxis in older emergency department patients (HARPOON) study, which is a multicenter, investigator-initiated, stratified randomized, double blind, placebo controlled clinical trial on the effects of prophylactic haloperidol on delirium incidence among older patients admitted by the emergency department for internal or surgical specialties. Patients admitted to the Jeroen Bosch Hospital in 's-Hertogenbosch between June 2014 and February 2015 were invited to participate in this substudy. The study was approved by the Ethics Committee of the VU University Medical Centre in the Netherlands (2012.177), with local approval of the institution's ethics committee of the Jeroen Bosch Hospital.

All participants provided written informed consent. Patients were eligible if they were aged 70 years or older and were at increased risk of in-hospital delirium according to the Dutch Hospital Patient Safety Program (in Dutch: VMS Veiligheidsprogramma)

for vulnerable older patients (24). The risk of in-hospital delirium was increased if 1 of the following questions was answered positively: if there was any help with activities of daily living in the past 24 hours, a period of confusion during previous illness or hospital stay, or if there were memory complaints. Patients had to speak either Dutch or English, be included within 24 hours of admission, and be able to give informed consent. The treating physician and/or observer determined whether a patient was able to assess and judge the given information about the content of the study independently. If their cognitive competence was in question, the patient was considered as not eligible. The exclusion criteria were a diagnosis of delirium on admission according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria, an inability to take the study medication, Parkinson disease, vascular and Lewy Body dementia, the use of antipsychotic or dopaminergic drugs at admission, hypokinetic movement disorder, neuroleptic malignant syndrome, central anticholinergic syndrome; substance abuse and dependence according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, criteria, epilepsy, and in the case of specific heart conditions (including prolonged QTc interval). A full list of the specific heart conditions is described in the study protocol (25). Patients were randomized for twice daily treatment of 1 mg of haloperidol or identical placebo tablets for a maximum of 7 consecutive days. Early termination of the study medication was possible if a patient was diagnosed with delirium, was transferred to a nonparticipating ward, withdrew their consent, had a QTc interval of more than 500 milliseconds, was discharged from the hospital, or died. Patients were excluded from analysis for this substudy if they received corticosteroids or if patients' medication for diabetes mellitus was altered during hospitalization. Venous (nonfasting) blood samples were obtained before day 1 and on day 6 of the study to measure glucose levels. Glucose levels were determined using the Dimension Vista 1500 Intelligent Lab System (Siemens Healthineers).

Randomization

Randomization was stratified over 4 groups (based on age (< 80 years, and ≥ 80 years and older) and planned surgery (yes / no)) with fixed blocks of 4 (ratio 1:1). All patients and caregivers were blinded to the intervention.

Data collection

Trained research nurses assigned to the study collected data on admission and during the study period from all the enrolled patients. This included demographic data, (chronic) comorbidities, medication use (history and current use), and vital parameters. The extent of chronic comorbidities was measured according to the Charlson comorbidity index (26). A diagnosis of diabetes mellitus was marked as positive when noticed in the medical history or if the patient was taking oral antidiabetic drugs and/or insulin on admission.

Outcome

The primary outcome was a change in glucose levels between day 1 and day 6.

Data analysis

Patient characteristics were reported for each group in percentages in the case of nominal data. Means with SD or a median with an interquartile range (IQR) were reported in the case of continuous data depending on the data distribution. The Mann-Whitney U test was used to compare patients treated with haloperidol and a placebo for not normally distributed continuous variables. Nominal data were compared using the $\chi 2$ test. The effect on the treatment groups of differences in glucose levels was tested using Student independent sample *t* test. Statistical significance was considered at a *p*-value of < 0.05. The statistical analysis was carried out using the SPSS statistical package (version 22.0, IBM Corp, Armonk, NY).

Results

Fifty-two patients at the Jeroen Bosch Hospitalwere included. Of these, 23 patients were excluded from this substudy: 4 developed delirium in the intervention period; 3 patients withdrew their consent; 11 patients were discharged earlier before blood sampling on day 6; 4 patients were prescribed prednisolone; and the diabetes medication of 1 patient was changed during hospitalization. In total, 29 patients were evaluated: 14 received haloperidol and 15 received a placebo.

Table 1 shows that the baseline characteristics were well matched between haloperidol and placebo users, although a higher percentage of females received a placebo and all patients with a history of myocardial infarction received haloperidol. The mean glucose level for placebo users was 7.7 mmol/L SD 2.8 on day 1 and 7.8 mmol/L SD 2.5 on day 6, and the mean glucose level for haloperidol users was 7.8 mmol/L SD 3.9 on day 1 and 8.3 mmol/L SD 2.2 on day 6. The change score for placebo users was 0.1 mmol/L SD 3.2 and for haloperidol users was 0.6 mmol/L SD 3.2. Haloperidol treatment was not associated with a significant increase in glucose levels ($p = 0.685$).

Table 1. Baseline characteristic of the study patients by treatment group

Characteristic	Haloperidol (n = 14)	Placebo (n = 15)	*p*-value
Age, median (IQR)	86.5 (77.5-91.3)	85.0 (81.0-90.0)	0.99 [a]
Sex, female n (%)	6 (42.9)	12 (80.0)	0.04 [b]
Admission specialty			0.84 [b]
Internal, n (%)	6 (42.9)	7 (46.7)	
Surgical, n (%)	8 (57.1)	8 (53.3)	
Drugs at admission, median (IQR)	6.5 (5.0-9.3)	7.0 (6.0-12.0)	0.99 [a]
Diabetes, n (%)	4 (28.6)	4 (26.7)	0.91 [b]
Oral antidiabetic drugs, n (%)	4 (100.0)	2 (50.0)	0.10 [b]
Insulin, n (%)	0 (0.0)	2 (50.0)	0.10 [b]
Dementia, n (%)	1 (7.1)	1 (6.7)	0.96 [b]
Heart failure, n (%)	3 (21.4)	5 (33.3)	0.47 [b]
History of heart attack, n (%)	4 (28.6)	0 (0.0)	0.03 [b]
History of stroke, n (%)	4 (28.6)	6 (40.0)	0.52 [b]

a. Mann-Whitney U test.

b. $\chi 2$ test.

Discussion

This study presents that a low dose of 2 milligrams haloperidol per day for delirium prophylaxis was not associated with a change in glucose levels in older hospitalized patients with an increased risk of in-hospital delirium.

In a previous study, a significant increase of 0.47 mmol/L in fasting glucose levels in patients using haloperidol was reported, although these patients were younger, had schizophrenia, and were treated with haloperidol for 8 weeks (27). This study population is not in line with the vulnerable older population in the current study. Haloperidol has previously been studied in relation to glucose changes in different populations. First, in drug-naive patients with schizophrenia without diabetes, antipsychotic treatment (olanzapine, haloperidol, risperidone, and aripiprazole) was associated with glucose dysregulation with comparable results for all treatment groups after 1 year of treatment (28). Second, in patients with schizophrenia and bipolar disorder, 1 year of olanzapine treatment was associated with changes in glucose levels, but not with haloperidol treatment (29).

Suggested mechanisms for impaired glucose levels during APD use are serotonin 5-HT2a receptor antagonism that cause insulin resistance, serotonin 5-HT1a receptor antagonism that cause an increase in food intake, histamine H1 receptor antagonism that cause weight gain, and antagonism of serotonin 5-HT2 and muscarinic M3 receptors that impairs insulin secretion. In addition, blockage of dopamine D2 receptors has been associated with higher glucose levels and diabetes. Conversely, dopamine D2 receptor antagonism may stimulate insulin secretion by the pancreas (30).

The haloperidol prophylaxis in older emergency department patients study design was a unique setting for our study objective because we were able to investigate the effect of haloperidol on glucose levels in a randomized clinical trial in older patients using a placebo or haloperidol. Because patients in the intervention group received haloperidol as prophylaxis for delirium, we could study the association between haloperidol and glucose homeostasis without any interference of delirium on glucose changes.

This study has some important limitations. First, we had no influence on patients' dietary intake and we were not able to control for its influence on glucose levels. However, this was considered less relevant because blood samples for glucose determination were taken at random during the day among haloperidol and placebo users. The number of participants in this study was small, which means that we might have missed small effects on glucose. Based on our obtained data (change score, 0.5 mmol/L SD 3.2, we would need a sample size of 668 per group (n = 1,336) to detect a statistically significant difference in our investigation with a power of 80% and α of 0.05. This large sample size indicates that the difference in glucose change score during treatment haloperidol compared with placebo is not relevant for clinical practice. In this small study of older patients with a high baseline risk of delirium,we found no significant difference in glucose change score during 5 days of haloperidol prophylaxis.

Our investigation does not provide support for the need of close monitoring of glucose levels in the frail older hospitalized population undergoing surgery using prophylactic haloperidol. Our results should not be generalized to hospitalized populations using haloperidol to reduce delirious symptoms or to nonhospitalized populations.

Conclusion

Short-term prophylactic use of haloperidol was not associated with changes in glucose levels in older hospitalized patients compared with those given a placebo in this small study.

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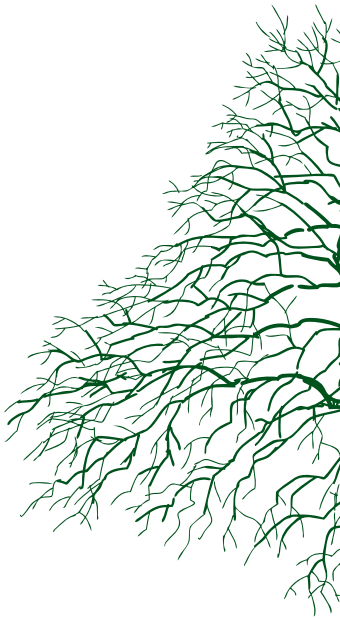

5

Challenges in delirium research: results of a prematurely ended, prospective observational study of glucose variability in older patients with and without delirium after hip surgery

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Submitted

Abstract

Introduction

Hyper- and hypoglycemia has been associated with delirium. The role of glucose variability in delirium has been studied poorly. The aim was to determine glucose variability in older patients with and without delirium.

Methods

Prospective, observational cohort study performed between February 2015 and February 2016 at the geriatric trauma unit and department of orthopedics in a teaching hospital. Patients aged 70 years and older admitted for hip surgery with an increased risk of in-hospital delirium were eligible for participation. Patients were included within 24 hours of hospitalization. Exclusion criteria were diminished cognitive capacity at admission, diabetes and participation in a study of a medical product. Glucose levels were measured four times daily after surgery until hospital discharge, to determine glucose variability, expressed as mean absolute glucose change (MAG change).

Results

In total, 123 of the 331 screened patients met the inclusion criteria. Of these patients, 66 were excluded because they were considered to have diminished cognitive capacity, 27 because they had diabetes, and 18 declined participation. Thus 12 patients (10.2% of the expected inclusion rate) were included. The study was ended prematurely because of recruitment problems. In total, 142 glucose measurements were available. The highest glucose variability occurred in a delirious patient (MAG change 0.44 mmol/L/h).

Conclusion

We were unable to include the intended number of participants and thus could not determine the association between delirium and glucose variability. Broadening the inclusion criteria to allow the inclusion of patients with a diminished cognitive capacity, who are potentially at high risk of developing delirium, is needed in future delirium research. However, the highest glucose variability was measured in a delirious patient.

Introduction

Delirium is a complication of hip surgery in 30% to 50% of older patients (1-3) and has a mean duration of 4 days. It is associated with a prolonged hospital stay and increased healthcare costs (4-8) and may contribute to the high 1-year mortality rate of hip fracture surgery.

The pathophysiology of delirium is complex and heterogeneous and the impact of delirium on the patient and their caregivers is high. Conducting research into the causes and consequences of delirium is of pivotal importance for better understanding of the poor outcome after being delirious. Major risk factors for delirium are advanced age and cognitive impairment (9). Older patients and patients with cognitive impairment represent vulnerable populations in clinical research and therefore require more sensitivity and receive special protection by law. However, this brings about series of difficulties in performing research and has led to the systematic exclusion of patients with the highest delirium risk in delirium research (10).

Reported risk factors for delirium are hypoglycemia and hyperglycemia (9,11-13), although the evidence is scanty. Hyperglycemia is a commonly seen stress response in critically ill patients. Hyperglycemia, a marker of extreme swings in glucose levels is a measure of glucose variability which refers to changes in blood glucose levels over time. Glucose regulation protocols using insulin infusion at the intensive care units are worldwide implemented to maintain glucose levels within a narrow window, because hyperglycemia and a high glucose variability are associated with mortality (14-17).

As delirium arises as a result of an acute illness, it is plausible that this acute illness increases the activity of the hypothalamic-pituitary-adrenal axis, leading to increased cortisol release and disturbed glucose metabolism according to the hyperglycemic stress response in intensive care unit patients. However, this has not been investigated. As it is not known whether glucose has a role in older patients with delirium, the aim of this study was to investigate glucose variability in older patients undergoing hip surgery who did or did not develop delirium

Methods

Design, setting and study population

This observational prospective cohort study was performed in the Department of Orthopedics and the Geriatric Trauma Unit in a teaching hospital (Tergooi Hospital, Hilversum and Blaricum, the Netherlands) in the period February 2015 to February 2016. Patients aged 70 years and older admitted for hip surgery (elective or emergency) with an increased risk of in-hospital delirium were eligible. The risk of delirium was assessed using the criteria of the Dutch National Patient Safety Programme 'Vulnerable older patients' (18) by the attending nurse at admission, namely, the need for help with activities of daily living in the past 24 hours and/or a period of confusion during previous illness or hospital stay, and/or the presence of memory complaints. Patients

had to be enrolled within 24 hours of hospital admission, be able to understand Dutch or English, and give written informed consent. Exclusion criteria were diminished cognitive capacity at admission diabetes (diagnosis in medical history or treatment with insulin or antidiabetic drugs at admission), and participation in a study of a medical product. The investigators checked daily at 8.30 am, except Saturdays and Sundays, to see whether patients had been acutely admitted for hip surgery in the evening before. Between 08:30 am and 06:00 pm on Mondays to Fridays, the investigators checked every 2 hours whether eligible patients had been admitted to the emergency department. The schedule of the preoperative screening clinic was checked daily to determine the eligibility of patients admitted for elective hip surgery. Written informed consent was obtained from each patient by the investigators before surgery. The municipal personal records database was consulted 6 months after hospital discharge to establish whether a patient had died. Enrolled patients received regular care and the study did not interfere with treatment. The study was approved by the Medical Research Ethics Committee (MREC) of the University Medical Centre Utrecht, the Netherlands (14/269D). The MREC did not allow to include patients with diminished cognitive capacity.

Usual care and study procedures

The cognitive competence of each potential participant was carefully assessed. The treating geriatrician judged the cognitive competence of the patient based on clinical experience. If the treating geriatrician decided that the patient was not able to understand the study content, the investigators were not invited to initiate the informed consent procedure. Next, the investigators used the vignette method (19) during the informed consent procedure to check whether patients were able to understand the information about the content and burden of the study. If cognitive competence was in doubt, patients were excluded from participation. Last, a Mini-Mental State Examination (MMSE) score was completed and patients with a score < 23 were excluded. The 'delirium observational scale' (DOS) was completed three times daily by trained nurses for patients at increased risk of in-hospital delirium, as part of usual care. If the DOS score was > 3, the presence of delirium (in the previous 24 hours) was established by the geriatric team, using the Confusion Assessment Method (CAM). According to the hospital protocol, each patient received non-pharmacological treatment to reduce delirious symptoms. The geriatric team decided whether medication was required, based on the seriousness of symptoms and according to protocol. The drug of first choice was haloperidol. If haloperidol was contraindicated, an atypical antipsychotic drug or benzodiazepine was initiated, based on the patient's comorbidity. Demographic data, medical history including cognition, medication use, and admission characteristics were collected at baseline. One blood sample was collected before hip surgery to determine insulin and glucose concentrations at baseline. These measurements were used to calculate HOMA-IR and HOMA-%B as a measure of insulin sensitivity and beta-cell function, using the HOMA2-calculator (20). Blood glucose levels were measured (finger prick testing) by trained nurses four times daily (08:00, 11:00, 16:00, and 22:00) after surgery until hospital discharge or 3 days after

recovery from delirium, whichever occurred first. The ACCU-CHECK Inform II system (Roche®) was used to measure glucose levels. After hospital discharge, information about fracture characteristics, type of surgery and anesthesia, length of hospital stay, and in-hospital death was collected from patients' medical records.

Outcomes

The primary outcome was mean absolute glucose change (MAG change mmol/L/h) (21) in patients with and without delirium, calculated as the sum of the absolute changes in blood glucose concentrations divided by the time between first and last glucose measurement (in hours). Secondary outcomes were other measures of glucose variability, namely, 1) mean glucose concentration (mmol/L), 2) standard deviation (SD, mmol/L) of the mean glucose concentration, 3) coefficient of variation (CV, which is the ratio between the SD and mean glucose concentration), 4) mean glucose daily delta (mean daily Δ, which is the mean of the daily minimum and maximum glucose concentrations, mmol/L) (16), 5) isolated hypoglycemia (glucose concentration ≤ 3.9 mmol/L), and 6) isolated hyperglycemia (non-fasting blood glucose concentration ≥ 11.0 mmol/L).

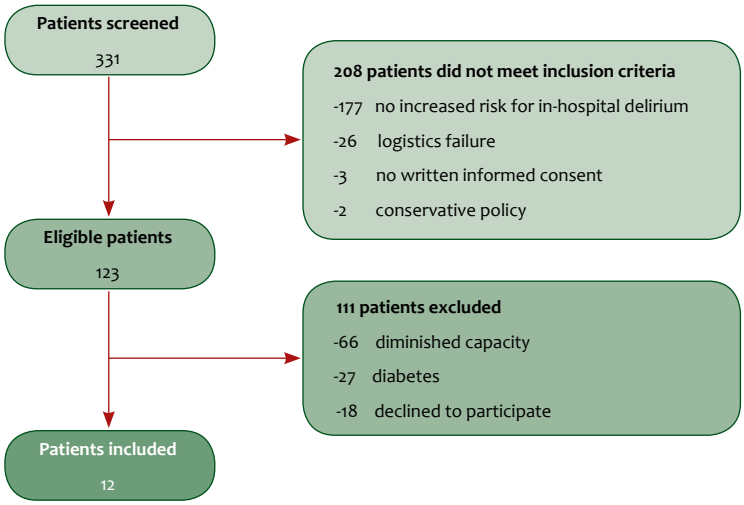
Sample size calculation

A median MAG change of 0.6 mmol/L/h (SD 0.4 mmol/L/h) has been reported in critically ill patients in an ICU (21). This value was used in our population because there are no data in the literature concerning MAG change in non-diabetic older non-critically ill patients. Detection of a MAG change of 0.2 mmol/L/h (power 80%, α of 0.05, 2-sided test) would require the recruitment of 145 patients, based on a delirium incidence of 50% (22) and an estimated loss of 15%. The study was planned to last 15 months, based on the 350 hip surgeries performed in 2011 in the study hospital.

Results

Between February 2015 and February 2016, 331 patients were screened, of whom 123 (37.2%) had an increased risk of in-hospital delirium and were eligible for participation. Of the 208 (62.8%) patients not eligible for participation, 177 (53.5%) were not at increased risk of in-hospital delirium, 26 (7.9%) were excluded for logistic reasons (admitted at Saturdays or Sundays or they underwent surgery before the informed consent procedure could be completed), 3 (0.9%) patients were unable to sign the informed consent form because of functional impairments (Parkinson's disease or rheumatoid arthritis) and 2 (0.6%) did not have surgery. Of the 123 eligible patients, 66 (19.9%) were excluded because they were deemed to have a diminished cognitive capacity, 27 (8.2%) because they had diabetes, 18 (5.4%) because they did not want to participate. In total, 12 (3.6%) patients were included in approximately 12 months (Figure 1), whereas the planned number was 116 patients (10.3% of expected inclusion rate). The MREC was informed about the premature ending of this study because of the poor recruitment of study participants.

Figure 1. Flowchart of study inclusion



The characteristics of the enrolled patients are shown in Table 1. Ten patients were women and the median age was 77.5 (Interquartile range (IQR) 75.3-83.0) years. Five patients had previously had delirium and 7 patients had memory complaints. One patient had temporarily been admitted to a rehabilitation center; the other 11 lived at home, 2 of whom had home assistance. None of the patients used antipsychotic drugs at admission.

Delirium, use of haloperidol and lorazepam, clinical chemistry (glycated hemoglobin, insulin, glucose, HOMA-IR, and HOMA-%B), and different measures of glucose variability are presented for each patient in Figure 2 and Table 2. Two patients were diagnosed with delirium (patients 7 and 9) and 3 patients were treated with haloperidol (patients 6, 7, and 12). All patients had a normal diet, except patient 10, who had a protein-enriched diet. Glucose levels (n =142 measurements) over time for all patients are presented in Figure 2. The highest MAG change (0.44 mmol/L/h), the highest SD (2.8 mmol/L), the highest CV (0.32 mmol/L), and the highest mean daily Δ in glucose levels (5.42 mmol/L) were measured in a patient with delirium (patient 9). There were seven episodes of hyperglycemia, four of which occurred in patient 9 with delirium. There were no episodes of hypoglycemia. The treating physician decided to withdraw patient 8 on study day 3 because the patient had a stroke; the patient later died in hospital. Two patients (patient 5 and patient 9) died within 6 months of hospital discharge.

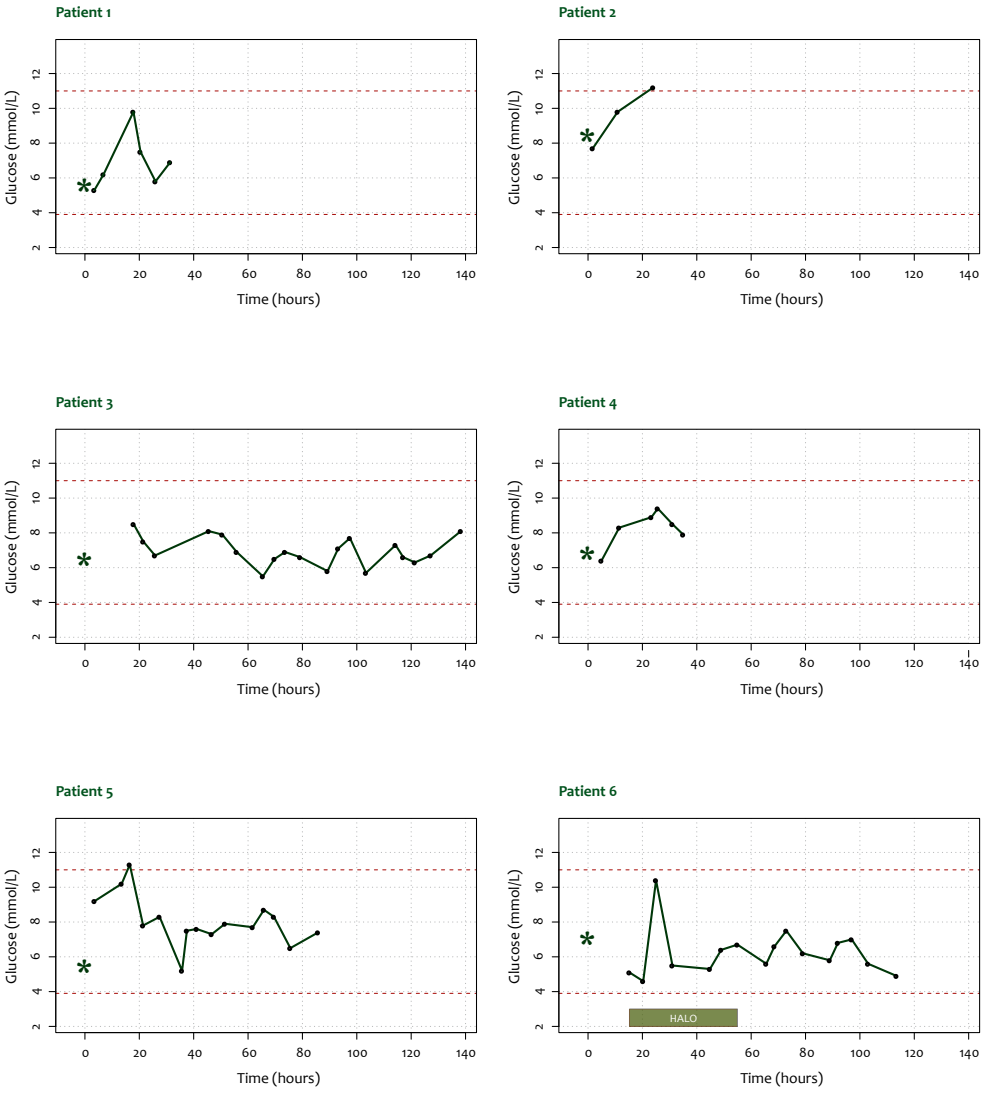
Table 1. Characteristic of the enrolled patients

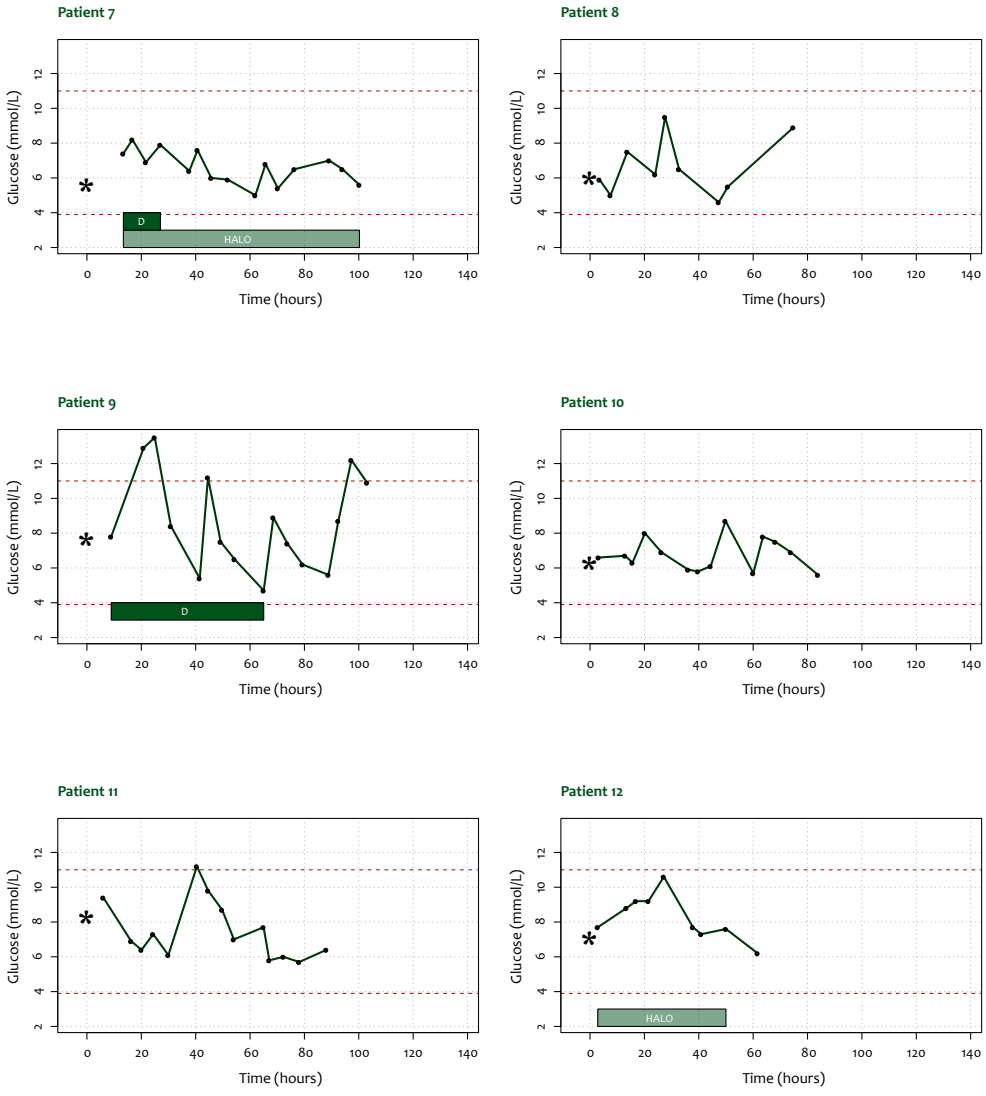
	Patients (n = 12)
Age in years, median (IQR)	77.5 (75.3-83.0)
Sex female, n (%)	10 (83.3)
MMSE, median (IQR)	25.0 (23.3-27.8)
Prior delirium, n (%)	5 (41.7)
Memory complaints, n (%)	7 (58.3)
KATZ-ADL at admission, median (IQR)	1.5 (0.0-3.5)
CCI, median (IQR)	1.0 (0.0-2.0)
Medication at admission, n (%)	
Benzodiazepines	2 (16.7)
Antidepressants	2 (16.7)
Living at home, n (%)	11 (91.7)
Planned admission, n (%)	4 (33.3)
Hip fracture, n (%)	8 (66.7)
Fracture on day of admission	7 (87.5) [a]
Femoral neck fracture	5 (62.5) [a]
Surgery on day of admission	7 (87.5) [a]
Type of surgery, n (%)	
Hip replacement	4 (33.3)
Internal fixation	4 (33.3)
Other	4 (33.3)
Spinal anesthesia, n (%)	5 (41.7)
MDRD < 30 mL/min/1.73 m^2, n (%)	1 (8.3)
Sodium mmol/L, median (IQR)	139 (137-142)
Potassium mmol/L, median (IQR)	4.1 (4.0-4.6)
Hemoglobin mmol/L, median (IQR)	8.0 (6.9-8.6)

MMSE: Mini-Mental State Examination (23); KATZ-ADL: Katz Index of Independence in Activities of Daily Living (24, 25); CCI: Charlson comorbidity index (26); MDRD: Modification of Diet in Renal Disease.

a. Percentage of patients with hip fracture is shown.

Figure 2. Glucose levels during hospitalization for each patient after hip surgery





When appropriate, the use of haloperidol (HALO) and the incidence of delirium (D) are indicated with bars. Glucose levels of 3.9 mmol/L and 11.1 mmol/L are given as dotted lines.

Table 2. Delirium, haloperidol and measures of glucose variability in 12 patients

Pat.	BMI	Deli	HALO (total mg)	HALO [c] (ug/L)	LORA (total mg)	Hb1ac [d]	Insulin [d] (µU/mL)	Glucose [d] (mmol/L)	HOMA-IR	HOMA-%β	No. of glucose levels	Time (h)	MAG (mmol/L/h)	Mean glucose (SD)	CV	Mean daily Δ (mmol/L)	Hyper (n)	Death after 6 months
1 [a]	27.9	No	N.A.	N.A.	N.A.	36	12.3	5.7	1.64	101.1	6	27.9	0.34	6.9 (1.6)	0.23	2.45	0	No
2 [a]	39.9	No	N.A.	N.A.	N.A.	49	36.6	8.6	5.10	104.7	3	22.3	0.16	9.6 (1.8)	0.18	2.10	1	No
3 [a]	19.9	No	N.A.	N.A.	N.A.	33	4.2	5.6	0.57	50.3	19	155.6	0.11	7.0 (0.9)	0.12	1.48	0	No
4 [a]	29.0	No	N.A.	N.A.	N.A.	45	18.9	6.6	2.57	103.0	6	30.1	0.15	8.2 (1.0)	0.13	1.70	0	No
5	27.4	No	N.A.	N.A.	N.A.	39	14.9	7.2	2.08	73.9	15	82.2	0.20	8.1 (1.5)	0.18	2.80	1	Yes
6	22.2	No	3	0.2	N.A.	36	3.8	5.7	0.51	45.4	16	106.5	0.20	6.3 (1.4)	0.22	2.63	0	No
7	23.5	Yes	5	0.2	16.5	29	5.6	7.0	0.79	39.2	15	96.4	0.15	6.6 (0.9)	0.14	1.55	0	No
8	18.7	No	N.A.	N.A.	1.5	Missing	Missing	6.1	Missing	Missing	9	71.3	0.24	6.6 (1.7)	0.26	2.23	0	Yes,IH
9	21.9	Yes	N.A.	N.A.	0.5	43	0.8	7.8	N.A.	N.A.	16	94.1	0.44	8.6 (2.8)	0.32	5.42	4	Yes
10 [b]	21.2	No	N.A.	N.A.	N.A.	40	6.6	6.4	0.91	52.5	14	80.7	0.18	6.8 (1.0)	0.14	2.23	0	No
11	27.5	No	N.A.	N.A.	N.A.	41	20.7	8.4	2.95	70.8	14	82.0	0.22	7.5 (1.7)	0.23	2.47	1	No
12	19.8	No	3	0.3	1.5	32	5.2	7.2	0.74	35.3	9	58.8	0.13	8.3 (1.3)	0.16	1.10	0	No

BMI: body mass index; Deli: delirium; HALO: haloperidol; LORA: lorazepam; N.A.: not applicable; unable to calculate (20); MAG: Mean absolute glucose change; IH: in hospital.

a. Hip replacement surgery, other patients had surgery for hip fracture.
b. Protein-enriched diet, other patients had normal diet.
c. Determined from fasting blood sample 72-96 hours after initiation of haloperidol.
d. At baseline.

Discussion

To our knowledge, this is the first study to investigate glucose variability in non-diabetic older patients with and without delirium. Unfortunately, for a number of reasons there were too few participants to determine the potential association between delirium and glucose variability in non-diabetic older patients undergoing hip surgery. Most potentially eligible patients were excluded because they were considered to have diminished cognitive capacity. Although patients with diminished cognitive capacity are considered indispensable in delirium research, the medical research ethics committee denied permission to include patients with diminished capacity. Cognitive impairment is a major risk factor for delirium, and so the exclusion of people with cognitive impairment would reduce the external validity of findings, because the study population would differ from the general, clinical population. On the other hand, for reasons of protection of vulnerable people in non-therapeutic investigations even with negligible risks and minimum burden to participants, patients with diminished capacity could be included only if the research question could not be answered without the inclusion of these individuals. Our investigation illustrates the difficult balance between the interpretation of the ethical principles to protect vulnerable patients by the Medical Research Ethics Committee and practical issues in performing research for the clinicians and investigators. Some patients (7.9%) were excluded because they underwent surgery before the informed consent procedure could be completed. Some patients had functional impairments that physically prevented them from signing the informed consent form. Most patients considered to have diminished cognitive capacity were diagnosed with dementia. However, low MMSE scores do not mean that a patient is incapable of making decisions (23,24). It is possible that some of the patients considered to have a diminished cognitive capacity were not demented but only temporarily confused as a result of their fall/fracture.

Among many patients with an increased delirium risk, we did not expect to find such a small number of patients after careful consideration of mental capacity to provide informed consent using judgement of the geriatrician, the vignette method and the MMSE. The study procedures (repeated glucose level monitoring in patients with no known diabetes) may have confused some patients, especially those with a lower educational level or minor cognitive impairment. Complex study designs may increase the number of patients excluded because it is more difficult to establish whether patients are able to judge the consequences of their participation. In general, research is needed to increase our knowledge of delirium, so as to improve its management, especially in those individuals at highest delirium risk. However, before therapeutic studies can be carried out, it is first necessary to perform observational studies. The question is how to learn more about precipitating factors in delirium, given current regulations regarding study participation. Our study participants were typical of those seen in daily practice, with the exception that those with a diminished cognitive capacity and potentially at the highest risk of delirium were excluded. However, these patients must be included

in order to determine whether delirium is associated with glucose variability in older patients. Involvement of older patients without an increased risk of delirium in delirium research increases the heterogeneity of the study population contributing to a limited generalizability of results to those patients with the highest delirium risk. We underpin the difficult consideration to expose the most vulnerable patients to invasive measurements in exploratory research.

For future research, it would be advisable to reconsider the initiation of recruitment if inclusion of those with the highest risk is denied, but their participation is of importance to answer the research question of those with the highest delirium risk. While medical research ethics committees have an essential role in protecting vulnerable people against the risks of research, this should not lead to these individuals being denied the benefits of research. Different medical research ethics committees have different interpretations of guidelines (25) which may have consequences for non-therapeutic research in delirium. It would be helpful if these rules could be clarified and made more uniform. Furthermore, it would be advisable to include a geriatrician in medical research ethics committees, so that they can evaluate the risk and benefit ratio of study participation for vulnerable older participants. This recommendation was proposed in the guidelines of medical research for and with older people in Europe (26).

In this study, 12 eligible patients (median age 77.5 years, IQR 75.3-83.0) were enrolled in approximately 12 months. The incidence of delirium was 16.7% (2 of 12 patients), which was in line with the recently reported rate of delirium in older patients undergoing hip surgery (27), although other studies have reported higher delirium rates in this population (28-31). Of the 66 patients excluded because they had a diminished cognitive capacity at admission, 15 (22.7%) had delirium. The main finding of this study was that the median MAG change in non-diabetic patients after surgery was 0.18 mmol/L/h (IQR 0.15-0.24), which was lower than that reported earlier during delirious (0.39 mmol/L/h, SD 0.27) and non-delirious days (0.36 mmol/L/h, SD 0.27) in non-diabetic patients on an intensive care unit (unpublished data). However, one of the two non-diabetic patients with delirium in our study had the highest measured glucose variability (MAG change, SD, CV, mean daily Δ) and the most episodes of hyperglycemia, which supports our hypothesis that a high glucose variability may be associated with delirium.

Conclusions

In this study, patients with a diminished cognitive capacity were excluded from participation, which meant that we were unable to include the intended number of participants. Therefore, we could not determine the association between delirium and glucose variability. Broadening the inclusion criteria to allow the inclusion of patients with a diminished cognitive capacity, who are potentially at high risk of developing delirium, is needed in future delirium research. In this study, the highest glucose variability after hip surgery was measured in a delirious patient; however, no formal statistical testing was performed due to low numbers of participants.

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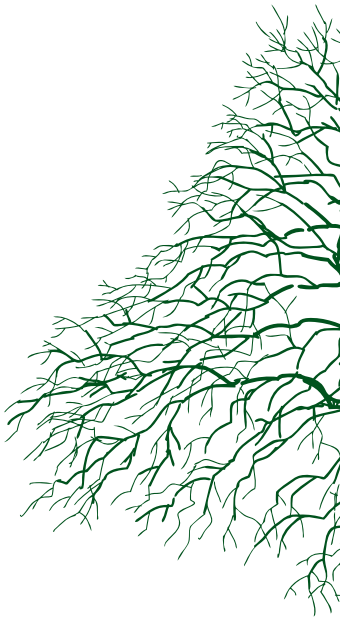

6

Diabetes and glucose dysregulation and transition to delirium in intensive care unit patients

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Abstract

Introduction

To investigate whether diabetes and glucose dysregulation (hyperglycemia and/or hypoglycemia) are risk factors for intensive care unit (ICU) delirium.

Methods

Critically ill patients admitted to the ICU with transitions of mental status from awake and non-delirious to delirious or remaining awake and non-delirious on the next day were selected for this investigation. Patients admitted because of a neurological illness were excluded. Generalized mixed-effects models with logit link function were performed to study the association between diabetes mellitus, glucose dysregulation and delirium, adjusting for potential confounders.

Results

The study population consisted of 2,745 patients with 1,720 transitions from awake and non-delirious to delirious and 11,421 non-transitions remaining awake and non-delirious. Generalized mixed-effects models with logit link function were performed to study the association between diabetes mellitus, glucose dysregulation and delirium, adjusting for potential confounders. Diabetes was not associated with delirium (adjusted OR: 0.93; 95% CI: 0.73-1.18, $p = 0.52$). Hypoglycemia did not significantly increase the risk of transition to delirium (adjusted OR: 1.86; 95% CI: 0.73-3.71, $p = 0.19$). In patients without diabetes the occurrence of hyperglycemia (adjusted OR: 1.41; 95% CI: 1.16-1.68, $p \leq 0.001$) and the occurrence of both hyperglycemia and hypoglycemia on the same day (adjusted OR: 1.87; 95% CI: 1.07-2.89, $p = 0.02$) were associated with transition to delirium.

Conclusion

Diabetes mellitus was not associated with the development of ICU delirium. Hyperglycemia increased the risk of ICU delirium, but only in patients without diabetes. Hypoglycemia increased the risk of delirium non-significantly. This investigation contributes to the understanding of the etiology of delirium and supports the use of measures to prevent hyperglycemia.

Introduction

Delirium is very common in Intensive Care Unit (ICU) patients with an occurrence rate of more than 50% (1-3). Delirium is associated with serious negative outcomes such as prolonged ICU stay (4), increased health care costs (4,5) and long-term cognitive impairment (6,7).

Several predisposing and precipitating risk factors contributing to ICU delirium have been reported in previous research with very heterogeneous study designs and strategies to account for potential confounders (8). Gaining more knowledge of risk factors in ICU delirium is of importance to increase our knowledge of the pathophysiology and to identify patients at risk in order to prevent the condition and ultimately improve outcomes.

Diabetes has been linked to cognitive dysfunction, including dementia and Alzheimer disease (9) which may be driven by insulin resistance, altered glucose metabolism, vascular changes, and metabolism of β-amyloid and tau (10). Past studies concerning the association between diabetes and delirium were small or retrospective and yielded conflicting results. Hyperglycemia and hypoglycemia have been suggested as precipitating risk factors for ICU delirium, but this was found in studies that were subject to various methodological limitations (8,11-14).

The interplay between diabetes mellitus and glucose dysregulation has never been investigated in relation to ICU delirium. Based on previously conducted research on diabetes, glucose variability and mortality in ICU patients (15), our hypothesis is that diabetes may modify the risk of ICU delirium after glucose dysregulation. We expected patients without diabetes who experience glucose dysregulation to be at higher risk of ICU delirium than patients with diabetes. Therefore, this study aims to determine whether diabetes mellitus, hyperglycemia and hypoglycemia are associated with development of delirium in ICU patients.

Methods

Design, study population and procedures

The design of this prospective cohort study conducted in the 32-bed mixed ICU of the University Medical Centre Utrecht (UMCU), the Netherlands has been described elsewhere (16). Briefly, patients were included when they stayed for more than 24 hours at the ICU in the period between January 2011 and July 2016. Patients were excluded in case of admission to the ICU because of a neurological illness, if delirium assessment was hampered due to deafness or if patients were unable to understand Dutch or English. The local Institutional Review Board waived the need for informed consent in this non-interventional investigation (IRB 010/056/c and 12/421/c) and approved further research with anonymized data.

During the study period, the applicable glucose regulation protocol (see Appendix) was used to maintain target glucose levels between 5.0 and 8.0 mmol/L,

except in those ICU patients with a low risk of prolonged hyperglycemia such as patients who underwent uncomplicated surgery. During insulin infusion glucose levels were measured repeatedly on fixed time points between 0.5-4 hours after the last glucose measurement according to the protocol (Appendix). Glucose levels were measured in blood samples obtained from an arterial catheter using BeckmanCoulter AU5800 (Beckman Coulter Inc., Brea CA, USA) or if an arterial catheter was absent by finger stick using Precision Xceed Pro (Abbott, Abbott Park, USA). Glucose levels were automatically stored in the electronic patient data management system (EPDMS).

Trained research-physicians collected the following data at admission and daily thereafter: demographic data, (chronic) co-morbidities, medication use, ICU admission characteristics, daily physiological measurements and vital signs as well as therapeutic interventions. The Acute Physiology and Chronic Health Evaluation (APACHE) IV score was used to classify admission diagnosis, severity of disease and infection at ICU admission (17). The extent of chronic comorbidities was assessed with the Charlson comorbidity index (CCI) (18). The Sequential Organ Failure Assessment (SOFA) score without the central nervous system component was used to classify the daily severity of disease (19). The presence of severe sepsis or septic shock was classified using international sepsis definitions at the time of patient inclusion (20).

For this investigation, we selected from the above described cohort all patients who had at least one transition from 'awake and non-delirious' at a certain day during ICU admission (day *t*) to either 'awake or non-delirious' (reference) or 'delirious' at day *t+1* (index transition), as described in more detail below. Patients were excluded for this investigation when the status of diabetes at hospital admission was missing.

Determinants

The determinants of interest were diabetes and glucose dysregulation (hyperglycemia and/or hypoglycemia). The presence of diabetes mellitus at ICU admission was defined as present in the medical record (diagnosis or treatment) or use of insulin and/or oral antidiabetic drugs before hospital admission. Glucose dysregulation was explored in four categories. Hyperglycemia was defined to be present at day *t* if at least one blood glucose level was measured > 8.0 mmol/L on that day (day *t*), and hypoglycemia was defined as at least one measured glucose level < 3.5 mmol/L on day *t*. When both were present on day *t*, the exposure was categorized as both hyperglycemia and hypoglycemia. Day *t* was marked with 'normoglycemia' when none of the determined blood glucose levels met the criteria for hyperglycemia or hypoglycemia.

Outcome

The mental status on each ICU day was classified into the following five categories awake and non-delirious, delirious, comatose, dead, or discharged alive. Mental status was evaluated by the research team using a previously validated algorithm (interobserver agreement, 0.94-0.97; sensitivity, 0.75; and specificity, 0.85) (16). This multistep algorithm incorporates a review of all Confusion Assessment Method for the ICU (CAM-ICU) (21)

assessments conducted by bedside nurses, whether treatment with haloperidol was initiated for delirium, and meticulous chart review for the presence of documented terms clinically associated with delirium, as well as CAM-ICU assessments by researchers. Patients' wakefulness was evaluated every four hours with the Richmond Agitation and Sedation Scale (RASS). A RASS of ≤ -4 was denoted as coma.

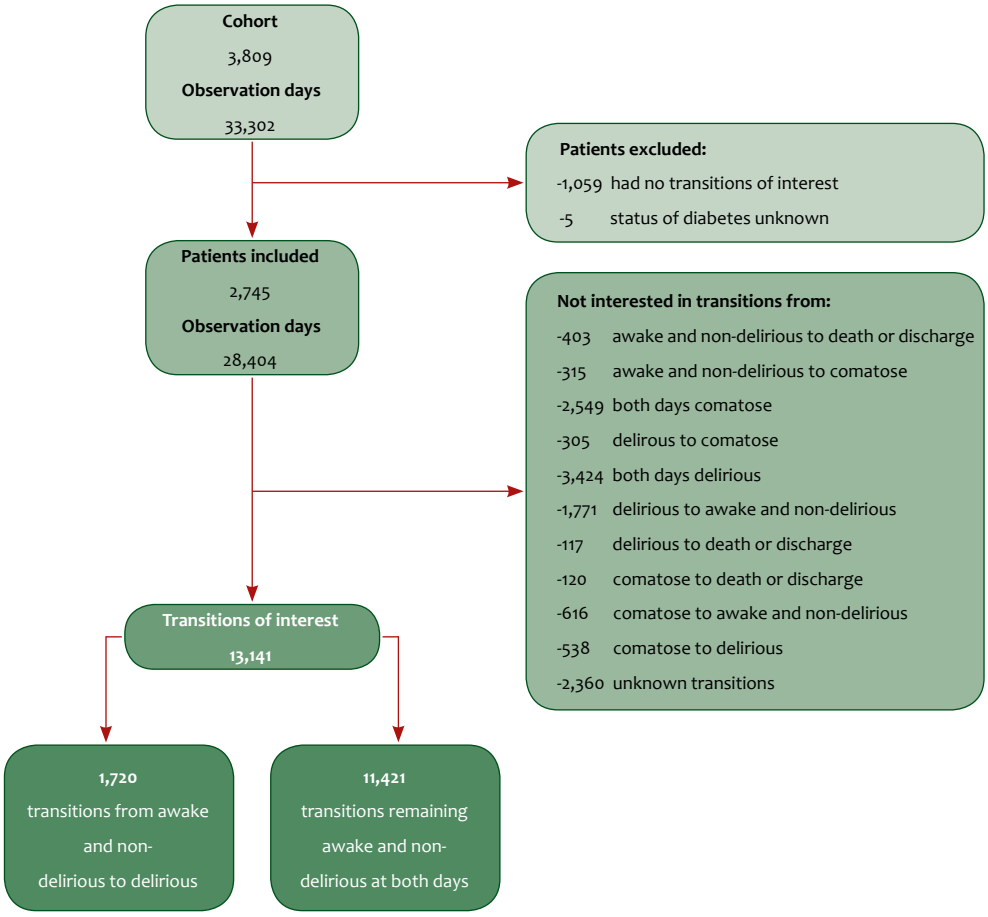
Data analysis

Patient characteristics were reported as frequencies with percentages, and as means with standard deviation (SD) in case of normally distributed continuous data. In case of a skewed distribution of continuous variables, medians with interquartile ranges (IQR) were presented. Characteristics of patients with and without delirium were compared with the Student independent sample *t* test or the Mann-Whitney U test as appropriate in case of continuous data, or with the chi-square test in the case of nominal data. The proportion of transition to delirium was graphically plotted against age. Generalized mixed-effects models with logit link function were performed to investigate the association between diabetes or glucose dysregulation with delirium. Patients were able to have more than one transition to delirium. Non-transitions remaining awake and non-delirious were collected from patients without delirium, and from patients with delirium before delirium and after delirium resolved. Effect modification of diabetes was studied by adding diabetes and either hypoglycemia or hyperglycemia and the product interaction term in the regression model. The following potential confounders were tested based on a systematic review (8): age, gender, admission type, planned admission, confirmed infection, APACHE IV score, CCI, SOFA score, support of mechanical ventilation, presence of severe sepsis or septic shock. The effects of the following variables were not investigated as potential confounder, because they were presumed to be on the causal pathway of exposure and outcome, and did therefore not meet the criteria for a potential confounder(22): insulin use, corticosteroid use and the frequency of blood glucose measurement. Confounders were selected based on *p*-values (< 0.05) and effect sizes in de regression model. Covariates were included in the final regression model as fixed effects, when possible as time dependent covariate and patient (participant number) as random effect. Statistical significance was considered when *p*-value < 0.05, when appropriate 95% bootstrap percentile confidence intervals (CIs) or confidence bands (CBs) were expressed. Two-stage bootstrap resampling procedure with 'patient' as cluster variable was used for obtaining CIs, plot CBs and/or *p*-values from 1,000 replications. The effects were expressed as odds ratio (OR) with 95% CIs. All statistical analyses were carried out with R version 3.2.3 with package 'lme4' (R Foundation for Statistical Computing, Vienna, Austria).

Results

During the study period, 3,809 patients were admitted to the ICU, with a total of 33,302 observation days. After exclusion (Figure 1), a total of 2,745 patients were included in the

Figure 1. Flowchart of study inclusion



present investigation with 1,720 transitions from awake and non-delirious to delirious and 11,421 non-transitions remaining awake and non-delirious.

Patient characteristics of the included 2,745 patients are presented in Table 1. Of those, 1,127 patients (41.1%) had a delirium at any time during ICU stay. Patients with a delirium during ICU stay were on average older, were more often male than female, and had a longer ICU stay. Furthermore, delirious patients were compared to non-delirious patients, more frequently acutely admitted to the ICU and admitted by medical rather than surgical disciplines, had higher APACHE IV and CCI scores and had more often an infection in the first 24 hours of ICU stay. Of the cohort, 543 (19.8%) patients had a diagnosis of diabetes at hospital admission of whom 225 (41.4%) had a delirium during ICU stay. Of the 2,202 patients without diabetes 902 (41.0%) patients experienced delirium during ICU stay.

Table 1. Characteristic of the study population

Characteristic	All patients (n = 2,745)	Patients with delirium (n = 1,127)	Patients without delirium (n = 1,618)	*p*-value
Age in years, mean (SD)	60.3 (15.8)	62.5 (14.8)	58.8 (16.3)	≤ 0.001 [c]
Age ≥ 65 years, n (%)	1,198 (43.6)	537 (47.6)	661 (40.9)	≤ 0.001 [d]
Male gender, n (%)	1,732 (63.1)	740 (65.7)	992 (61.3)	0.020 [d]
Diagnose [a], n (%)				≤ 0.001 [d]
Medical	1,120 (40.8)	530 (47.0)	590 (36.5)	
Surgery elective	1,007 (36.7)	300 (26.6)	707 (43.7)	
Surgery emergency	606 (22.1)	295 (26.2)	311 (19.2)	
Planned admission [a], n (%)	977 (35.6)	274 (24.3)	703 (43.4)	≤ 0.001 [d]
Confirmed infection [a], n (%)	819 (29.8)	553 (40.2)	366 (22.6)	≤ 0.001 [d]
APACHE IV score [a], mean (SD)	59.9 (25.5)	72.2 (26.6)	51.4 (20.7)	≤ 0.001 [c]
CCI [b], mean (SD)	7.2 (6.7)	7.9 (6.8)	6.5 (4.9)	≤ 0.001 [c]
LOS on ICU in days, median (IQR)	4 (2-10)	10 (5-20)	3 (2-5)	≤ 0.001 [e]

APACHE: Acute Physiology and Chronic Health Evaluation; CCI: Charlson comorbidity index; LOS: length of stay.

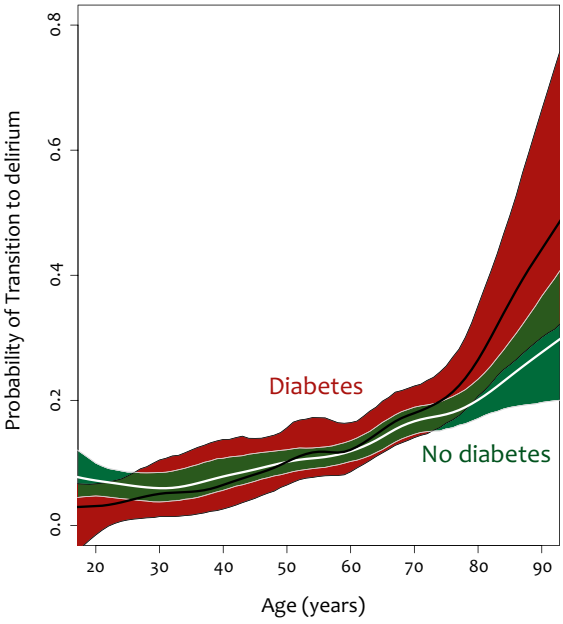
a. At ICU admission. Missing values for diagnose: 12 for all patients, 2 for patients with ever delirium and 10 for patients without delirium.
b. At hospital admission.
c. Student independent sample *t* test.
d. $\chi 2$ test.
e. Mann-Whitney U test.

Figure 2 shows the risk of delirium with age for patients with and without diabetes. Visually plotted, diabetes seems to be associated with a higher delirium transition rate in older patients. Patients who had a transition from awake and non-delirious on day *t* to delirious on day *t+1* had a similar mean glucose level on day *t* as patients who remained awake and non-delirious (7.46 mmol/L SD 1.27 respectively 7.41 mmol/L SD 1.48, OR: 1.04; 95% CI: 0.99-1.09, $p = 0.11$, not presented).

In total, 65,727 glucose values were determined on day *t*. As presented in Table 2 on the whole study population, hyperglycemia increased the risk of transition to delirium (adjusted OR: 1.35; 95 CI: 1.15-1.59, $p \leq 0.001$), whereas a non-significantly increased risk was observed for hypoglycemia (adjusted OR: 1.86; 95% CI: 0.73-3.71, $p = 0.19$). In addition, patients with both hyperglycemia and hypoglycemia on day *t* had an increased risk of delirium on day *t+1* (adjusted OR: 1.65; 95% CI: 1.12-2.28, $p = 0.003$).

Diabetes was identified as effect modifier in the association between hyperglycemia and transition to delirium ($p = 0.03$), but not in the association between hypoglycemia ($p = 0.76$) or both hyperglycemia and hypoglycemia on the same day and transition to delirium ($p = 0.06$). Table 3 presents the association between glucose dysregulation and transition to delirium stratified for diabetes. In patients without diabetes, hyperglycemia (adjusted OR: 1.41; 95% CI: 1.16-1.68, $p \leq 0.001$) and both hyperglycemia and hypoglycemia on the same day (adjusted OR: 1.87; 95% CI: 1.07-2.89, $p = 0.02$) were associated with transition to delirium. In patients with diabetes, glucose dysregulation was not associated with transition to delirium.

Figure 2. The proportion of transition to delirium the next day is plotted against increasing age for transitions in patients with and without diabetes



Black line is plotted for patients with diabetes and the white line for patients without diabetes. The 95% confidence bands are plotted in red for patients with diabetes and in green for patients without diabetes.

Discussion

In summary, we found that diabetes mellitus was not associated with the development of ICU delirium. For hypoglycemia, only a non-significantly increased risk of ICU delirium could be noted. In contrast, hyperglycemia during ICU stay increased the risk of delirium, but only in patients without diabetes.

To our knowledge, our study is the first exploring the association between diabetes, glucose dysregulation and their interplay in relation with delirium. Literature concerning the association between diabetes and delirium in ICU patients shows conflicting results. Our results are in concordance with three investigations (n = 112-196 patients) on ICU patients that did not report an association between diabetes and delirium (11,23,24). An investigation with mixed ICU patients (n = 67,333) reported that diabetes was not associated with acute brain failure (25). This study may have subject to residual confounding, did not provide a definition for diabetes, and did not report on delirium. However, further comparison is difficult, since the authors did not report the definitions of diabetes and diabetes with complications. In contrast, in cardiac surgery patients, diabetes was associated with an OR of 1.38-1.96 on delirium (26,27), and a positive association was reported in ICU patients from India (14), though extrapolation

Table 2. Crude and multivariate model for diabetes and glucose dysregulation and the risk of transition to delirium the next day for all transitions

Exposure [a]	Transitions to delirium, n (%) (n = 1,720)	Transitions to AND, n (%) (n = 11,421)	OR crude [b]	95%CI	*p*-value	OR adj. [c]	95%CI	*p*-value
Diabetes mellitus	372 (21.6)	2,170 (19.0)	1.05	0.83-1.32	0.74	0.93	0.73-1.18	0.52
Normoglycemia	484 (28.1)	3,861 (33.8)	Reference	Reference	Reference	Reference	Reference	Reference
Hyperglycemia	1,129 (65.6)	6,450 (56.5)	1.49	1.29-1.75	≤ 0.001	1.35	1.15-1.59	≤ 0.001
Hypoglycemia	16 (0.9)	55 (0.5)	2.43	1.01-4.81	0.05	1.86	0.73-3.71	0.19
Both hyperglycemia and hypoglycemia on the same day	76 (4.4)	327 (2.9)	1.92	1.29-2.78	≤ 0.001	1.65	1.12-2.28	0.003

AND: awake and non-delirious.

a. Missing values for glucose levels: 15 transition to delirium and 728 transitions to awake and non-delirious.

b. Crude model include diabetes and glucose dysregulation (diabetes, glucose level within window, hyperglycemia, hypoglycemia and both hyperglycemia and hypoglycemia).

c. The adjusted model include diabetes, glucose dysregulation, age per 10 years and age > 65 years, gender, APACHE IV score, SOFA score without the central nervous system component and presence of severe sepsis or septic shock.

Table 3. Crude and multivariate model for glucose dysregulation and the risk of transition to delirium the next day stratified for diabetes

Exposure [a]	Transitions to delirium, n (%) (n = 1,720)	Transitions to AND, n (%) (n = 11,421)	OR crude [b]	95%CI	*p*-value	OR adj. [c]	95%CI	*p*-value
No diabetes	1,348 (100.0)	9,251 (100.0)						
Normoglycemia	446 (33.1)	3,619 (39.1)	Reference	Reference	Reference	Reference	Reference	Reference
Hyperglycemia	838 (62.2)	4,749 (51.3)	1.57	1.35-1.86	≤ 0.001	1.41	1.16-1.68	≤ 0.001
Hypoglycemia	13 (1.0)	48 (0.5)	2.24	0.82-4.95	0.11	1.85	0.59-4.17	0.25
Both hyperglycemia and hypoglycemia on the same day	38 (2.8)	163 (1.8)	2.27	1.43-3.42	≤ 0.001	1.87	1.07-2.89	0.02
Diabetes	372 (100.0)	2,170 (100.0)						
Normoglycemia	38 (10.2)	242 (11.2)	1.69	0.96-2.75	0.07	1.35	0.82-2.20	0.22
Hyperglycemia	291 (78.2)	1,701 (78.4)	1.54	1.18-2.03	0.003	1.25	0.93-1.65	0.11
Hypoglycemia	3 (0.8)	7 (0.3)	5.15	1.09-22.89	0.04	2.15	0.71-7.39	0.23
Both hyperglycemia and hypoglycemia on the same day	38 (10.2)	164 (7.6)	1.82	1.00-3.15	0.05	1.42	0.76-2.42	0.20

AND: awake and non-delirious.

a. Missing values for glucose levels for patients without diabetes: 13 transition to delirium and 672 transitions to awake and non-delirious. Missing values for glucose levels for patients with diabetes: 2 transition to delirium and 56 transitions to awake and non-delirious.

b. Crude model include diabetes and glucose dysregulation (diabetes, glucose level within window, hyperglycemia, hypoglycemia and both hyperglycemia and hypoglycemia).

c. The adjusted model include glucose dysregulation, age per 10 years and age > 65 years, gender, APACHE IV score, SOFA score without the central nervous system component and presence of severe sepsis or septic shock.

of these findings to the western population may be difficult. The differences in study population and methodology may explain these different results.

Few studies have investigated the association between glucose dysregulation and delirium, though with methodological limitations. In patients undergoing non-cardiac thoracic surgery, abnormal glucose levels (glucose levels below 3.4 mmol/L or above 16.5 mmol/L) have been linked to postoperative psychiatric disorders including delirium (12). Comparison with our study is difficult because their study was conducted in non-ICU patients, their outcome had a broader definition than delirium and their threshold for hyperglycemia was higher. Our results are in concordance with a previous study with 196 ICU patients of whom 91.8% was non-diabetic (11). This study reported an association between higher glucose levels and the occurrence of hyperactive delirium, however the timing of both glucose and delirium was unclear. Our finding of the positive association between hyperglycemia and delirium and the lack of an association between glucose concentration and delirium suggests that patients with diabetes tolerate a higher range of glucose levels better compared to patients without diabetes with regard to delirium. This finding has been previously reported with regard to the risk of mortality at the ICU (15).

This investigation presents new insights on the etiology of delirium, especially patients without diabetes having glucose dysregulation were found at higher risk for delirium. Our study was conducted in by far the largest investigation on the etiology of delirium in the world. We carefully investigated potential risk factors for delirium that influence the association between diabetes and glucose dysregulation and their interplay in relation with delirium, including time-dependent covariables. As we used models on daily transitions, we also accounted for fluctuations of delirium status over time. Our analysis was less prone to fluctuating numbers of glucose measurements, because hyper- and hypoglycemia were marked on a daily base per protocol (Y/N). Another strength was the high completeness of the data: 91.7% of the daily transitions were adequately recorded in the database.

Our study has some limitations. It was performed as mono-center study in a tertiary care centre which may limit the generalizability of our results. Another limitation is the possibility that peaks and nadirs in blood glucose levels could have been missed because glucose levels were not measured continuously. In addition, confounding may have occurred as there could have been unmeasured confounding covariates.

It has been suggested that metabolic disorders, including impaired glucose oxidation, causes disturbances in neuronal networks in the brain that may lead to delirium (28,29). Glucose dysregulation may be more harmful compared to chronic high glucose level with regard to development of delirium, because we did not find an association between mean glucose level and delirium. Our results show that ICU clinicians should prevent glucose dysregulation, in particular hyperglycemia in ICU patients. Of these, especially patients without diabetes, are at risk of delirium.

Conclusion

In this large ICU study, diabetes mellitus was not associated with the development of ICU delirium. Hyperglycemia during ICU stay increased the risk of delirium, but only in patients without diabetes. For hypoglycemia, only a non-significantly increased risk of ICU delirium could be noted. These results contribute to the understanding of the etiology of delirium and support the use of measures to prevent hyperglycemia.

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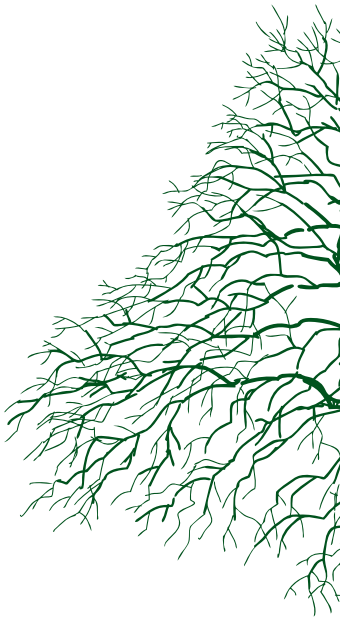
Appendix

Table 1. Glucose regulation protocol

Glucose concentration (mmol/L)	Action	Check glucose concentration
> 20	Bolus of 8 IU insulin and start or increase dose insulin infusion with 4 IU/hr	1 hr
16-20	Bolus of 4 IU insulin and start or increase dose insulin infusion with 2 IU/hr	1 hr
12-16	Bolus of 2 IU insulin and start or increase dose insulin infusion with 2 IU/hr	1 hr
10-12	Start or increase insulin infusion with 1 IU/hr	1 hr
8-10	Decrease of glucose concentration ≥ 50%: decrease dose insulin infusion with 50%	2 hrs
	Decrease of glucose concentration < 50%: start or increase dose insulin infusion with 1 IU/hr	3 hrs
5-8	Decrease of glucose concentration ≥ 50%: stop insulin infusion	1 hr
	Decrease of glucose concentration 25-50%: do not change dose insulin infusion	1 hr
	Decrease of glucose concentration < 25%: do not change dose insulin infusion	4 hrs
3.5-5	Decrease of glucose concentration ≥ 50%: stop insulin infusion	1 hr
	Decrease of glucose concentration < 50%: decrease dose insulin infusion with 50%	1 hr
< 3.5	Stop insulin infusion and bolus of 25 ml dextrose 50% (If blood glucose after 0.5 hr > 5.0 mmol/L: start dose insulin infusion after consultation of an intensivist, but increase the insulin infusion in steps of 50%)	0.5 hr
Total Parenteral Nutrition stop	Stop insulin infusion (If blood glucose after 1 hr > 5.0 mmol/L: start dose insulin infusion with 50% of last dose)	1 hr

IU: international units.



7

Glucose variability during delirium in diabetic and non-diabetic intensive care unit patients: a prospective cohort study

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Submitted

Abstract

Introduction

To determine whether measures of glucose variability are altered during delirium days compared to non-delirious days in critically ill patients with and without diabetes at the intensive care unit (ICU).

Methods

Critically ill patients with delirious and non-delirious days during ICU stay were included from a prospective cohort study which was conducted from January 2011-June 2013. Glucose variability was measured each observation day. Mixed-effects models and generalized mixed-effects models with logit link function were performed to study the association between delirium and glucose variability, adjusting for potential confounders.

Results

Delirium was not associated with a higher glucose variability assessed with mean glucose, standard deviation, mean absolute glucose change, daily delta and hyperglycemia. Delirium was associated with an increased risk of hypoglycemia in diabetic patients (adjusted OR: 2.78; 95% CI: 1.71-6.32, $p = 0.005$), but not in non-diabetic patients (adjusted OR: 1.16; 95% CI: 0.58-2.28, $p = 0.689$).

Conclusion

Despite the positive association between delirium and hypoglycemia in critically ill patients with diabetes, delirium was not associated with glucose variability. Our findings suggest that glucose levels should be monitored more closely in diabetic patients during delirium at the ICU to prevent hypoglycemia.

Introduction

Delirium is a frequently observed complication in patients in an intensive care unit (ICU) (1-3), that has been associated with long-term cognitive impairment (4,5), prolonged length of ICU stay (6) and with increased health care costs (6,7). The pathophysiology of delirium is complex and heterogeneous. Metabolic disorders such as hypo- and hyperglycemia have been identified as risk factors for delirium onset, but extensive research is lacking (8-11). To improve patient related outcomes, identification of modifiable factors in delirium need to be further explored.

Tight glucose control has been implemented as regular care in critically ill patients to reduce extreme glucose deviations as glucose variability and hypo- and hyperglycemia, and to decrease the mean glucose concentration with decreased mortality risk as result (12,13). However, the optimal blood glucose range in tight glucose control is controversial. Intensive glucose control (glucose target between 4.5-6.0 mmol/L) has been shown to increase mortality compared to conventional glucose control (glucose target ≤ 10.0 mmol/L) (14). The occurrence of hypoglycemia during intensive glucose control may be responsible for this increased risk of death (15). Furthermore, it has been reported that the mortality risk after hyperglycemia is higher in non-diabetic patients compared to diabetic patients (16,17). It has been suggested that diabetes is a protective factor for death after hyperglycemia due to adaptive mechanisms to chronic hyperglycemia (18).

Glucose variability has been associated with higher mortality risk in critically ill patients (19,20). A gold standard for measurement of blood glucose fluctuations is lacking (21-23). Glucose fluctuations were frequently reported as glucose variability and refer for example to mean glucose concentration, mean absolute glucose (MAG) change, standard deviation (SD) or hypo- and hyperglycemia.

Delirium and glucose variability have both been associated with negative outcomes, but their mutual relation has been poorly studied. Higher glucose values have been reported in critically ill patients with hyperactive delirium compared to critically ill patients with non-hyperactive delirium (10). Given that delirium results from acute illness, it is plausible that this acute illness may increase activity of hypothalamic-pituitary-adrenal axis leading to increased cortisol release and subsequent interference with glucose metabolism. It is unclear whether glucose variability is higher during delirium within the window of glucose control during ICU admission. The aim of this study was to determine whether measures of glucose variability are altered during delirium in critically ill patients with and without diabetes at the ICU.

Methods

Setting, study design and population

Data was used from a prospective cohort study conducted in the 32-bed mixed ICU of the University Medical Centre Utrecht (UMCU), the Netherlands. All patients hospitalized for longer than 24 hours on the ICU in the period from January 2011 to June 2013 were

included in this study, except in the case of neurological illness, if delirium assessment was impossible or patients were unable to speak Dutch or English. The local Institutional Review Board waived the need for informed consent in this non-interventional investigation (IRB 010/056/c and 12/421/c).

The mental status of all ICU patients was daily classified by the research team as 'delirious', 'awake and non-delirious' or 'comatose' using a 5-step validated algorithm (interobserver agreement, 0.94-0.97; sensitivity, 0.75; and specificity, 0.85) (24). This multistep algorithm incorporates a review by a research nurse of all Confusion Assessment Method for the ICU (CAM-ICU) (25) assessments conducted by the bedside nurses, whether delirium treatment was initiated and a meticulous chart review for the presence of documented terms clinically associated with delirium. When delirium could not be ruled in or out using this procedure, the research nurse conducted an additional CAM-ICU assessment. Delirium episodes were recorded and delirium subtype was classified using the 3 hourly registered RASS scores (10 point scale ranging -5 (comatose) to +4 (heavily agitated)) (26). A delirium episode ended if a patient had a classification of 'awake and non-delirious' or a classification of 'comatose' for at least two days.

For this study, patients with delirious and non-delirious observation days were selected from the study cohort. In the case of one delirious episode during ICU stay all observation days were included until ICU discharge. In the case of more than one delirious episode, observation days until the start day of the second delirious episode were included for that patient. Patients were excluded if there was no glucose value available during a delirious episode or during a non-delirious episode. Observation days were excluded from the study if there were no glucose values available or if the observation day was classified as 'comatose'.

Data collection

Trained, assigned physicians collected data (baseline and per day) from all ICU patients including demographic data, (chronic) co-morbidities and medication use, ICU admission characteristics, daily physiological measurements and vital signs, and therapeutic interventions. Diabetes was marked present if noted in the medical record or if patients used insulin and/ or oral antidiabetic drugs at ICU admission. Current alcohol intake was marked as positive if patients used more than three units of alcohol per day, as documented in the medical records or history. Current smoking was marked as positive if smoking was written in the medical records or history. Planned admissions were those admissions which could be postponed for at least 12 hours without adverse consequences. The Acute Physiology and Chronic Health Evaluation (APACHE) IV classification was used to determine the admission diagnosis, severity of disease, and infection at ICU admission (27). The extent of chronic comorbidities were measured with Charlson comorbidity index (CCI) (28). The Sequential Organ Failure Assessment (SOFA) score without central nervous system component was used daily to classify severity of disease (29). The presence of severe sepsis or septic shock was classified using international sepsis definitions at the time of study (30-33).

During the study period, a glucose regulation protocol was used to maintain the target glucose concentration during ICU admission between 5.0 and 8.0 mmol/L (see Appendix), except in ICU patients with a low risk on prolonged hyperglycemia such as per- and postoperative patients with one bolus injection of dexamethasone. Continuous insulin infusion was initiated in patients with diabetes and in ICU patients with a (drug-induced) glucose concentration > 8.0 mmol/L. Glucose levels were measured on fixed time points between 0.5-4 hours after the last glucose measurement (details are described in the glucose regulation protocol) from blood samples obtained from an arterial catheter using BeckmanCoulter AU5800 (Beckman Coulter Inc., Brea CA, USA) or if arterial catheter was absent by finger stick using Precision Xceed Pro (Abbott, Abbott Park, USA). Glucose levels were automatically stored in the electronic patient data management system (EPDMS).

Medication use (drug, dose, route and time of administration including total parenteral nutrition) and glucose measurements (concentration and time of measurement) were retrieved from the EPDMS and added to the prospectively collected data. Continuous infusions, such as insulin, were recorded in the EPDMS, including end date and time of administration. A change in infusion rate resulted in a new medication record. If a continuous infusion covered more than one day, the dose per day was calculated using the ratio between infusion times of both days. Energy intake was defined as the sum of daily caloric intake from continuous infusion of glucose, total parenteral or enteral nutrition, and high caloric medication, such as propofol.

Outcome

The primary outcome was the within-patient difference in glucose variability during delirious and non-delirious observation days. Glucose variability was measured each observation day, expressed by the following five measures: 1) mean glucose concentration (mmol/L). 2) SD of all glucose levels (mmol/L). 3) MAG change was defined as the mean absolute glucose change per hour (mmol/L/hour). To calculate the MAG, all absolute changes in blood glucose levels were added up and were divided by the time between first and last glucose levels (in hours) (19). 4) Daily delta defined as the difference of daily maximum and daily minimum glucose concentration (mmol/L). 5) The occurrence of hypo- and hyperglycemia. Hypoglycemia was defined as a glucose concentration < 3.5 mmol/L and severe hypoglycemia was defined as a glucose concentration < 2.2 mmol/L. Hyperglycemia was defined as glucose concentration > 8.0 mmol/L and severe hyperglycemia as glucose concentration > 11.0 mmol/L.

Data analyses

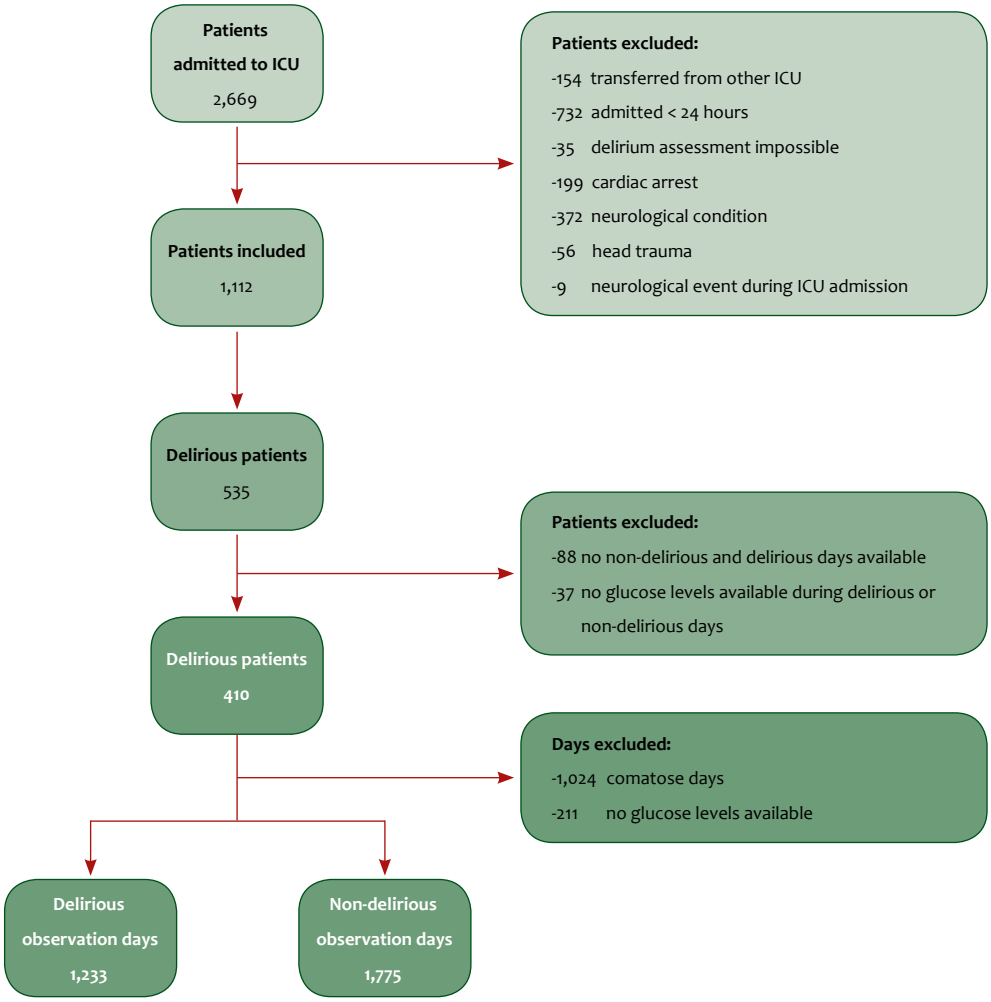
Patient and observation day characteristics were reported as numbers with percentages in the case of nominal data and means with SD or median with interquartile range (IQR) in the case of continuous data. Continuous data were compared using Student independent sample *t* tests when the data was normally distributed; otherwise the Mann-Whitney U test was used. $\chi 2$ tests were used to compare nominal data. Characteristics of

delirious and non-delirious days in non-diabetic and diabetic patients were compared in a multilevel technique using linear mixed-effects models for continuous characteristics and generalized mixed-effects models with logit link function for dichotomous characteristics. Statistical significance was considered at p-value < 0.05, when appropriate 95% bootstrap percentile confidence intervals (CIs) were expressed. Two-stage bootstrap resampling procedure with 'patient' as cluster variable was used for obtaining CI's and p-values from 1,000 replications. In the case of one glucose concentration per day the mean glucose concentration, SD and the difference of daily maximum and minimum could not be calculated. The MAG change was calculated if there were more than two glucose levels per day available. Hyperglycemia and hypoglycemia were described as dichotomous outcome per observation day, but glucose values were analysed individually. Linear mixed-effects models and generalized mixed-effects models with logit link function were used as multilevel techniques to test whether delirium was associated with increased glucose variability. The effects were expressed as regression coefficients or odds ratios, both with bootstrap 95% CIs. Covariates were included in the model as fixed effects, when possible as time dependent covariate. The use of medication was classified dichotomous per day. All models included random effects for 'patient'. The degree of glucose variability depends on diabetic status (18), therefore separate models were developed for patients without and with diabetes. The adjusted models always included the following covariates; age, gender, total dose of insulin (bolus injection and continuous infusion) in the 30 minutes before glucose measurement or total dose of insulin per day and energy infusion in the 30 minutes before glucose measurement or energy infusion per day. Confounders were selected based on p-values (< 0.05) and effect sizes. The following variables were tested as potential confounders: age, gender, body mass index (BMI), current alcohol intake, current smoking, admission type, planned admission, confirmed infection, APACHE IV score, CCI, SOFA-scores, support of mechanical ventilation, presence of severe sepsis or septic shock, number of observation days, length of stay (LOS) at ICU, the use of antipsychotic drugs, norepinephrine, corticosteroids, clonidine, ACE-inhibitors, cyclosporine or tacrolimus, beta blockers and beta-agonists. All statistical analyses were carried out with R version 3.2.3 with package 'lme4' (R Foundation for Statistical Computing, Vienna, Austria).

Results

During the study period, 2,669 patients were admitted to the ICU of whom 1,557 patients were excluded. Delirium was diagnosed in 535 patients. Of those patients 125 patients were excluded, 88 (16.4%) patients because they had only delirious or comatose observation days during their ICU admission and 37 (6.9%) patients because of the absence of glucose values during delirious or non-delirious observation days. Therefore, the final population consisted of 410 patients with 1,233 delirious and 1,775 non-delirious observation days (Figure 1).

Figure 1. Flowchart of the study population



Patient characteristics are shown in Table 1. Diabetic patients were on average older, had a higher BMI and had a higher APACHE IV score compared to non-diabetic patients. The number of delirious days was higher in diabetic patients compared to non-diabetic patients. Diabetic patients had a higher maximum glucose concentration in the first twenty-four hours of ICU stay than patients without diabetes.

Table 1. Patient characteristic of the study population

Characteristic	ICU patients (n = 410)		
	Non-diabetic patients [b] (n = 323)	Diabetic patients [b] (n = 87)	*p*-value
Age, mean (SD)	61.7 (14.6)	66.7 (12.0)	0.001 [c]
Male gender, n (%)	203 (62.8)	54 (62.1)	0.894 [d]
BMI in kg/m², mean (SD)	25.3 (5.3)	29.0 (8.7)	≤ 0.001 [c]
Current alcohol intake [a], n (%)	19 (5.9)	4 (4.6)	0.644 [d]
Current smoking [a], n (%)	31 (9.6)	4 (4.6)	0.139 [d]
Diagnosis [b], n (%)			0.494 [d]
Medical	133 (41.2)	42 (48.3)	
Surgery elective	97 (30.0)	23 (26.4)	
Surgery emergency	93 (28.8)	22 (25.3)	
Planned admission [b], n (%)	91 (28.2)	22 (25.3)	0.593 [d]
Confirmed infection [b], n (%)	115 (35.6)	38 (43.7)	0.167 [d]
Diabetes mellitus and organ damage [b], n (%)	N.A.	7 (8.0)	N.A.
APACHE IV-score [b], mean (SD)	77.5 (24.9)	88.1 (28.1)	0.001 [c]
CCI [a], mean (SD)	7.4 (6.5)	8.7 (6.2)	0.099 [c]
Delirium days first episode, mean (SD)	3.1 (3.7)	4.2 (5.4)	0.085 [c]
Subtype delirium, n (%)			0.384 [d]
Hypoactive	101 (31.3)	23 (26.4)	
Hyperactive	0 (0.0)	0 (0.0)	
Mixed type	222 (68.7)	64 (73.6)	
One day episode, n (%)	142 (44.0)	29 (33.3)	0.074 [d]
> 1 delirium episode, n (%)	92 (28.5)	33 (37.9)	0.089 [d]
Number of delirious days, median (IQR)	2 (1-3)	2 (1-5)	0.019 [e]
Number of non-delirious days, median (IQR)	3 (2-5)	3 (2-5)	0.686 [e]
Max. glucose concentration in first 24h in mmol/L, mean (SD)	10.0 (2.7)	12.6 (4.0)	≤ 0.001 [c]
ICU LOS in days, median (IQR)	9 (5-20)	10 (5-21)	0.425 [e]
ICU mortality, n (%)	39 (12.1)	12 (13.8)	0.666 [d]

BMI: Body mass index; APACHE: Acute Physiology and Chronic Health Evaluation; CCI: Charlson comorbidity index; LOS: length of stay, N.A.: not applicable.

a. At hospital admission.
b. At ICU admission.
c. Student independent sample t test.
d. $\chi 2$ test.
e. Mann-Whitney U test.

Table 2 shows the characteristics of delirious and non-delirious days in non-diabetic and diabetic patients. During delirious days, diabetic and non-diabetic patients had more often insulin infusions, had more insulin rate adjustments, and had a higher average of numbers of glucose measurements in comparison with non-delirious days.

Table 2. Variables per observation day in critically ill patients during their stay at the intensive care unit

Variables	Non-diabetic patients (n = 323)			Diabetic patients (n = 87)		
	Delirious days (n = 908)	Non-delirious days (n = 1,395)	*p*-value	Delirious days (n = 325)	Non-delirious days (n = 380)	*p*-value
Illness						
Mean SOFA score, mean (SD)	6.0 (3.1)	4.7 (3.0)	≤ 0.001 [a]	6.2 (3.1)	4.8 (2.8)	0.072 [a]
Mechanical ventilation, n (%)	769 (84.7)	1,045 (74.9)	≤ 0.001 [b]	253 (77.8)	285 (75.0)	0.029 [b]
Severe sepsis or septic shock, n (%)	280 (30.8)	223 (16.0)	≤ 0.001 [b]	119 (36.6)	93 (24.5)	0.272 [b]
Max. Richmond Agitation Sedation Score, n (%)			≤ 0.001 [a]			≤ 0.001 [a]
Deep coma (-5 or -4)	1 (0.1)	4 (0.2)		0 (0.0)	0 (0.0)	
Light sedated (-3, -2, -1)	180 (19.8)	178 (12.8)		50 (15.4)	46 (12.1)	
Alert, Calm (0)	166 (18.3)	844 (60.5)		55 (16.9)	247 (65.0)	
Agitated (+1,+2,+3,+4)	561 (61.8)	369 (26.5)		220 (67.7)	87 (22.9)	
Medication						
Antipsychotics, n (%)	514 (56.6)	201 (14.4)	≤ 0.001 [b]	205 (63.1)	67 (17.6)	≤ 0.001 [b]
Oxazepam, n (%)	137 (15.1)	312 (22.4)	0.373 [b]	53 (16.3)	45 (11.8)	0.100 [b]
Clonidine, n (%)	191 (21.0)	137 (9.8)	0.039 [b]	82 (25.2)	32 (8.4)	0.001 [b]
Norepinephrine, n (%)	342 (37.7)	347 (24.9)	≤ 0.001 [b]	144 (44.3)	109 (28.7)	0.039 [b]
Glucocorticosteroids, n (%)	311 (34.3)	482 (34.6)	0.012 [b]	142 (43.7)	161(42.4)	0.988 [b]
Insulin						
Insulin infusion, n (%)	738 (81)	1,042 (75)	0.001 [a]	314 (96.6)	332 (87)	0.011 [a]
Insulin infusion total dose IU, mean (SD)	45 (39)	45 (44)	0.018 [a]	88 (53)	60 (47)	0.013 [a]
Insulin rate adjustments, mean (SD)	4.1 (3.4)	3.6 (3.1)	≤ 0.001 [a]	6.8 (4.4)	5.8 (3.8)	≤ 0.001 [a]
Insulin bolus, n (%)	83 (9.1)	92 (6.6)	0.018 [a]	77 (23.7)	90 (23.7)	0.314 [a]
Insulin bolus total dose IU, mean (SD)	2.6 (2.7)	2.8 (3.5)	0.620 [a]	4.3 (3.7)	5.9 (10.0)	0.517 [a]
Blood glucose						
Number of glucose measurements, mean (SD)	6.7 (2.5)	5.9 (2.4)	≤ 0.001 [a]	8.7 (2.7)	7.6 (2.8)	≤ 0.001 [a]

IU: international units.

a. Linear mixed-effect models.

b. Generalized mixed-effect models with logit link function.

In total 19,962 glucose levels were collected. As shown in Table 3 and Table 4, measures of glucose variability were presented per observation day. Delirium was associated with an higher MAG change (β: 0.038; 95% CI: 0.017-0.061; $p = 0.001$) and increased daily delta (β: 0.325; 95% CI: 0.134-0.494; $p = 0.001$) in patients without diabetes, In the adjusted model for non-diabetic patients both associations lost its significance (MAG change; adjusted β: 0.021; 95% CI: -0.004-0.043; $p = 0.076$ and daily delta; adjusted β: 0.100; 95% CI: -0.096-0.282 $p = 0.287$). Delirium was positively associated with hypoglycemia in diabetic patients (adjusted OR: 2.78; 95% CI: 1.71-6.32, $p = 0.005$), but not in non-diabetic patients (adjusted OR: 1.16; 95% CI: 0.58-2.28, $p = 0.689$). Generalized mixed-effects models with logit link function were not performed for the association between delirium and severe hypoglycemia as the number of glucose levels below 2.2 mmol/L was insufficient.

We found similar results for glucose variability if all delirious and non-delirious days during ICU stay were analysed compared to the observation days of the first episode, or when consecutive episodes (delirious and non-delirious episodes) were analysed (data not shown).

Discussion

In this cohort of ICU patients, mean glucose concentrations, its SD, MAG change, daily delta and the risk of hyperglycemia were unaltered during delirious days compared to non-delirious days in non-diabetic and diabetic patients. Furthermore, we demonstrate that in diabetic patients delirium was associated with hypoglycemia. The association was even stronger after adjustment for several confounding factors. This association was not found for non-diabetic patients.

Little is published about the mutual relation between glucose levels and delirium. It has been reported that mean glucose levels were not significantly different in non-critically ill older patients with delirium compared to those patients without delirium (34). Although we conducted our study in an ICU cohort with critically ill patients our results are in concordance with their study. In the ICU setting, one study has been conducted reporting higher mean glucose levels in patients with hyperactive delirium compared to patients with non-hyperactive delirium (10). In our study, we were not able to identify any hyperactive delirium. This may be related to the use of sedatives (24). Additionally, our study was designed to compare mean glucose concentrations during delirious and non-delirious days per individual.

One of the strengths of our study is that we were able to conduct our study in one of the largest high quality cohorts with ICU patients with different delirium episodes (24). Glucose variability was determined within patients during delirious and non-delirious ICU days. Therefore, patients were their own controls. In our opinion, our design is preferable to determine glucose variability on the level of delirious and non-delirious patients, because the largest number of patients were delirious on a few days and not during the whole ICU stay. Secondly, glucose variability during delirium was determined in non-diabetic and diabetic patients. Thirdly, we designed this study to explore all kinds of intraday fluctuations in blood glucose levels as literature

Table 3. The association between delirium and continuous measures of glucose variability presented per day in non-diabetic and diabetic patients

Measures of glucose variability	Delirious days, n	Non-delirious days, n	Regression coefficient crude	95% CI	*p*-value	Regression coefficient adj.	95% CI adj.	*p*-value
Non-diabetic patients [a]	**908**	**1,395**						
Mean glucose concentration (mmol/L), mean (SD)	7.25 (0.99)	7.25 (1.09)	0.037	-0.067-0.126	0.466	-0.005 [c]	-0.116-0.089	0.940
SD glucose concentration (mmol/L), mean (SD)	1.28 (0.77)	1.26 (0.86)	0.049	-0.013-0.105	0.100	0.027 [c]	-0.034-0.088	0.374
MAG change (mmol/L/hr), mean (SD)	0.39 (0.27)	0.36 (0.27)	0.038	0.017-0.061	0.001	0.021 [c]	-0.004-0.043	0.076
Daily delta (mmol/L), mean (SD)	3.49 (2.32)	3.28 (2.43)	0.325	0.134-0.494	0.001	0.100 [c]	-0.096-0.282	0.287
Diabetic patients [b]	**325**	**380**						
Mean glucose concentration (mmol/L), mean (SD)	7.86 (1.43)	8.02 (1.63)	-0.177	-0.443-0.052	0.157	0.066 [d]	-0.121-0.288	0.525
SD glucose concentration (mmol/L), mean (SD)	1.94 (1.07)	1.98 (1.18)	0.021	-0.153-0.202	0.794	0.084 [d]	-0.075-0.251	0.291
MAG change (mmol/L/hr), mean (SD)	0.61 (0.39)	0.61 (0.41)	0.030	-0.029-0.088	0.305	0.036 [d]	-0.026-0.096	0.235
Daily delta (mmol/L), mean (SD)	5.64 (3.15)	5.56 (3.55)	0.280	-0.246-0.763	0.289	0.339 [d]	-0.115-0.777	0.146

MAG: Mean absolute glucose change.

a. Missing values for mean glucose concentration, SD and daily delta; 0 delirious days and 2 non-delirious days. Missing values for MAG change; 39 delirious days and 136 non-delirious days.
b. Missing values for mean glucose concentration, SD and daily delta; 0 delirious days and 1 non-delirious days. Missing values for MAG change; 1 delirious days and 15 non- delirious days.
c. Adjusted for age, gender, BMI, confirmed infection, APACHE IV score, SOFA-score, presence of severe sepsis or septic shock, total dose of insulin by continuous infusion per day, total dose of insulin by bolus injections if > 0, energy infusion per day, ICU observation day > 2, use of corticosteroids, ACE-inhibitors, antipsychotic drugs, cyclosporine or tacrolimus, beta-agonists and norepinephrine.
d. Adjusted for age, gender, admission type, APACHE IV score, SOFA-score, presence of severe sepsis or septic shock, total dose of insulin by continuous infusion per day, total dose of insulin by bolus injections if > 0, energy infusion per day, ICU observation day > 2, use of ACE-inhibitors, beta-agonists and beta blockers.

Table 4. The risk of hyper- and hypoglycemia during delirious days in non-diabetic and diabetic patients

Measures of glucose variability	Delirious days, n (%) Patients, n (%)	Non-delirious days, n (%) Patients, n (%)	OR crude	95% CI	*p*-value	OR adj.	95% CI adj.	*p*-value
Patients without diabetes	**908 (100.0)** **323 (100.0)**	**1,395 (100.0)** **323 (100.0)**						
Hyperglycemia > 8 mmol/L, n (%)	619 (68.2) 251 (77.7)	885 (63.4) 271 (83.9)	1.10	0.96-1.25	0.177	1.04 [a]	0.90-1.19	0.594
Severe hyperglycemia > 11 mmol/L, n (%)	146 (16.1) 79 (24.5)	217 (15.6) 79 (24.5)	1.09	0.80-1.45	0.59	0.93 [a]	0.66-1.29	0.648
Hypoglycemia < 3.5 mmol/L, n (%)	41 (4.5) 27 (8.4)	39 (2.8) 25 (7.7)	1.45	0.75-2.79	0.243	1.16 [b]	0.58-2.28	0.689
Severe hypoglycemia < 2.2 mmol/L, n (%)	6 (0.7) 4 (1.2)	4 (0.3) 4 (1.2)	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
Patients with diabetes	**325 (100.0)** **87 (100.0)**	**380 (100.0)** **87 (100.0)**						
Hyperglycemia > 8 mmol/L, n (%)	278 (85.5) 85 (97.7)	313 (82.4) 84 (96.6)	0.90	0.76-1.07	0.269	0.96 [c]	0.81-1.16	0.648
Severe hyperglycemia > 11 mmol/L, n (%)	143 (44.0) 52 (59.8)	173 (45.5) 68 (78.2)	0.88	0.63-1.21	0.451	1.00 [c]	0.69-1.33	0.986
Hypoglycemia < 3.5 mmol/L, n (%)	38 (11.7) 29 (33.3)	26 (6.8) 14 (16.1)	2.33	1.24-5.43	0.038	2.78 [d]	1.71-6.32	0.005
Severe hypoglycemia < 2.2 mmol/L, n (%)	4 (1.2) 3 (3.4)	4 (1.1) 2 (2.3)	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.

a. Adjusted for age, gender, BMI, confirmed infection, APACHE IV score, SOFA-score, presence of severe sepsis or septic shock, total dose of insulin by continuous infusion + bolus injections in 30-minutes before glucose measurement, energy infusion in 30-minutes before glucose measurement, ICU observation day, use of corticosteroids, ACE-inhibitors, antipsychotic drugs, cyclosporine or tacrolimus, beta-agonists and norepinephrine.

b. Adjusted for age, gender, BMI, confirmed infection, SOFA-score, presence of severe sepsis or septic shock, total dose of insulin by continuous infusion + bolus injections in 30-minutes before glucose measurement, energy infusion in 30-minutes before glucose measurement, ICU observation day, use of corticosteroids and antipsychotic drugs.

c. Adjusted for age, gender, admission type, SOFA-score, APACHE IV score, presence of severe sepsis or septic shock, total dose of insulin by continuous infusion + bolus injections in 30-minutes before glucose measurement, energy infusion in 30-minutes before glucose measurement, ICU observation day, use of ACE-inhibitors, beta-agonists and beta blockers.

d. Adjusted for age, gender, admission type, SOFA-score, APACHE IV score, total dose of insulin by continuous infusion + bolus injections in 30-minutes before glucose measurement, energy infusion in 30-minutes before glucose measurement, use of beta-agonists and beta blockers.

describes a set of heterogeneous indicators for glucose variability (20). In our study, glucose variability was determined as dispersion around a central tendency (mean glucose concentration), as deviation from blood glucose target (SD and daily delta), as extreme excursions (hyper- and hypoglycemia), and over time (MAG change). Fourthly, the final classification of mental status in the past 24-hours distinguish between 'non-delirious', 'delirious' and 'comatose' days based on a previously described algorithm (24). Therefore, we were able to exclude 'comatose' days in our analyses because patients were more vulnerable to unrecognized hyper- and hypoglycemia and delirium assessment was impossible. Finally, we were able to control for confounding by entering glucose-influencing drugs including insulin, norepinephrine, corticosteroids and energy infusion as time-dependent covariates in our analyses.

However, this study has some limitations. The generalizability is possibly limited as this study was performed as monocenter study at a university hospital. Another limitation is the possibility that peaks and nadirs in blood glucose levels have been missed as glucose levels were not measured continuously. We considered this misclassification as non-differential as this misclassification occurred at random during delirious and non-delirious days. Due to the multiple testing, it remains a possibility that the association between delirium and hypoglycemia was based on a type I error, despite the stronger positive association after adjustment for confounders. Residual confounding may have occurred as there could have been unmeasured confounding covariates. The measures of glucose variability could depend on the number of glucose determinations. Especially, the MAG-change is sensitive for higher frequency of measurement. We consider this as less important because observation days were compared, but not whole ICU stays. Furthermore, we adjusted for disease severity and insulin infusion which indirectly correct for the frequency of measurement. The number of glucose measurements has not been adjusted because this indices can been seen as glucose variability measure. Our study suggests that there is no involvement of delirium in glucose metabolism, but that hypoglycemia is less recognized in diabetic patients in delirium. Hypoglycemia at the ICU has been associated with increased mortality independent of diabetic status (35). For this reason, our findings suggest that in clinical practice blood glucose levels should be monitored more often during delirium in critically ill patients with diabetes to avoid hypoglycemia. More research is needed to explore the impact of our findings concerning diabetic patients on ICU outcome and determine whether any causality consists between delirium and glucose variability.

Conclusion

Mean glucose concentration, its SD, MAG change, daily delta and the risk of hyperglycemia were not significantly altered during delirium in non-diabetic and diabetic ICU patients. Delirium in critically ill patients with diabetes was associated with hypoglycemia. This association was not found for non-diabetic ICU patients. Our findings suggest that glucose levels should be monitored more closely in diabetic patients during delirium at the ICU to prevent hypoglycemia.

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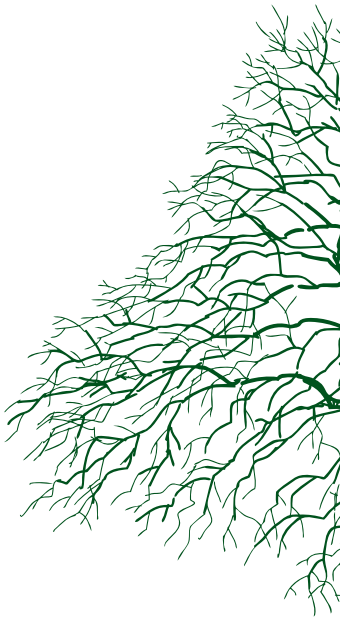
Appendix

Table 1. Glucose regulation protocol

Glucose concentration (mmol/L)	Action	Check glucose concentration
> 20	Bolus of 8 IU insulin and start or increase dose insulin infusion with 4 IU/hr	1 hr
16-20	Bolus of 4 IU insulin and start or increase dose insulin infusion with 2 IU/hr	1 hr
12-16	Bolus of 2 IU insulin and start or increase dose insulin infusion with 2 IU/hr	1 hr
10-12	Start or increase insulin infusion with 1 IU/hr	1 hr
8-10	Decrease of glucose concentration ≥ 50%: decrease dose insulin infusion with 50% Decrease of glucose concentration < 50%: start or increase dose insulin infusion with 1 IU/hr	2 hrs 3 hrs
5-8	Decrease of glucose concentration ≥ 50%: stop insulin infusion Decrease of glucose concentration 25-50%: do not change dose insulin infusion Decrease of glucose concentration < 25%: do not change dose insulin infusion	1 hr 1 hr 4 hrs
3.5-5	Decrease of glucose concentration ≥ 50%: stop insulin infusion Decrease of glucose concentration < 50%: decrease dose insulin infusion with 50%	1 hr 1 hr
< 3.5	Stop insulin infusion and bolus of 25 ml dextrose 50% (If blood glucose after 0.5 hr > 5.0 mmol/L: start dose insulin infusion after consultation of an intensivist, but increase the insulin infusion in steps of 50%)	0.5 hr
Total Parenteral Nutrition stop	Stop insulin infusion (If blood glucose after 1 hr > 5.0 mmol/L: start dose insulin infusion with 50% of last dose)	1 hr

IU: international units.

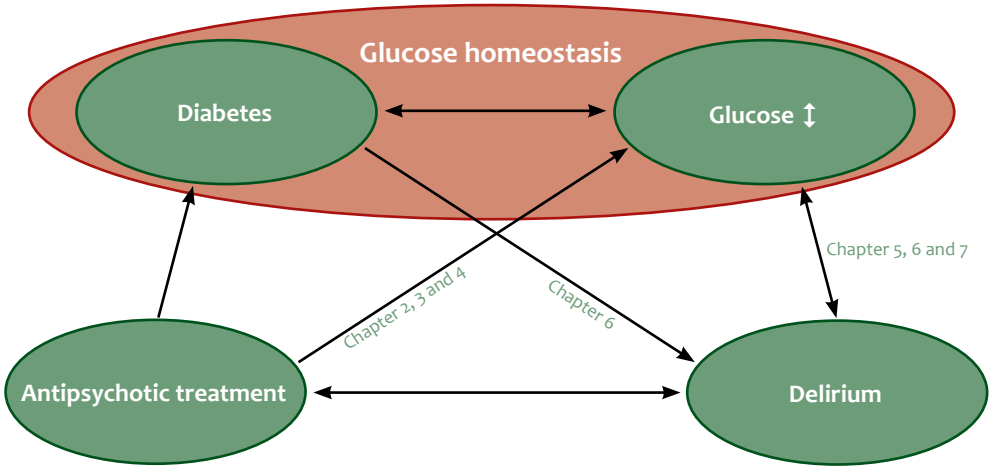


8

General discussion

Since the first studies in the early 1990s (1-3), increasing attention has focused on adverse events occurring during hospitalization. A large proportion of these events occur in older patients (2) and are related to medical procedures or medication use (i.e. adverse drug events) (4). Because of polypharmacy, comorbidity, medication procedures, and longer hospital stays, care for older patients is often more complex than for younger patients. These factors, plus the often-diminished physical strength and condition of older individuals, are thought to increase the risk of adverse events during hospitalization in older patients (4,5). However, many adverse events are preventable (6) and should be identified in order to improve healthcare. In the introduction of this thesis, the clinical story of an older woman undergoing hip surgery was described. Her hospital stay was complicated by the development of delirium, followed by a cascade of adverse events. This illustrates the vulnerability of older hospitalized patients. Delirium is the most frequently observed neuropsychiatric syndrome in hospitalized patients. It has become increasingly clear that older hospitalized patients who develop delirium have a substantially increased risk of negative health outcomes, including cognitive deterioration and even death. The underlying pathology of delirium is not completely understood, which complicates its prevention and treatment. Antipsychotics are the drugs of first choice for the treatment of severe symptoms, despite the lack of evidence of their effectiveness in delirium. In contrast, numerous reports have described the adverse effects of antipsychotics, especially in older patients. Previous research has suggested that antipsychotic drugs acutely act on glucose metabolism in older patients. Hypoglycemia and hyperglycemia have both been suggested as risk factors for delirium, although the contribution of glucose to the etiology of delirium has not been studied thoroughly. The studies included in this thesis investigated the interplay between delirium, antipsychotic drugs, and glucose homeostasis in older patients (Figure 1).

Figure 1. The interplay between delirium, antipsychotic drugs, and glucose homeostasis in older patients



The studies were designed to investigate 1) the association between antipsychotic treatment and alterations in glucose levels; 2) the association between glucose dysregulation and the onset of delirium; and 3) changes in glucose variability in delirium. The studies involved three older populations, namely, a) outpatients, b) patients admitted to non-intensive care wards, and c) patients admitted to the intensive care unit (ICU).

The first study described the association between antipsychotic drugs and hypoglycemia requiring hospitalization. The study (**Chapter 2**) was conducted with a cohort of 68,314 older diabetic outpatients included in the PHARMO Database Network. Antipsychotic drug use was associated with an increased risk of hospitalization for hypoglycemia, especially early in treatment, and with higher antipsychotic drug doses. In addition, haloperidol and pipamperone appeared to be more harmful than risperidone. Although not described in **Chapter 2**, we identified cases of hospitalization for hyperglycemia, diabetic ketoacidosis, and coma in the PHARMO Database Network in users of antipsychotics, but the incidence was too low to further investigate the association between antipsychotic drugs and hyperglycemia.

The next chapters described the association between antipsychotic drugs or delirium and glucose homeostasis in patients admitted to non-intensive care wards. We were unable to confirm the association between antipsychotic drugs and hypoglycemia in patients admitted to a hospital (**Chapter 3**). We identified hypoglycemia in only 43 of 2,054 older hospitalized patients (2.1%); in contrast, 423 hyperglycemic events were detected (23.5%). Hospital-initiated haloperidol use was associated with hyperglycemia, while ambulant haloperidol use was not. In the study reported in **Chapter 4**, involving a small sample (n=29) of older hospitalized patients with a high risk of in-hospital delirium, 5 days of prophylactic haloperidol was not associated with a difference in glucose change score compared with placebo. In **Chapter 5**, we investigated glucose variability in older hospitalized patients who developed, or who did not develop, delirium after hip surgery. This prospective cohort study carried out in Tergooi Hospital was ended prematurely after the inclusion of twelve patients owing to recruitment problems. Of the twelve patients included, two had delirium, one of whom had the highest glucose variability score of the study, which supports the hypothesis that glucose variability is increased in delirium.

The last studies of this thesis focused on glucose homeostasis and delirium in ICU patients (**Chapter 6** and **Chapter 7**). The study described in **Chapter 6** investigated whether diabetes and glucose dysregulation are risk factors for delirium in a cohort of 2,745 ICU patients. The mental status of all patients on each ICU day was classified as awake and non-delirious, delirious, comatose, dead, or discharged alive. We made a selection of patients with a mental status changing from awake and non-delirious to delirious and/or a status of remaining awake and non-delirious on the next day. Diabetes was not associated with delirium. Hyperglycemia increased the risk of ICU delirium, but only in patients without diabetes, and hypoglycemia increased the risk of delirium, but non-significantly because of its low incidence. The study presented in **Chapter 7** investigated glucose variability during delirium in a cohort of 464 ICU patients with and

without diabetes with at least two ICU observation days, of which one non-delirious day and one delirious day. Despite the association between delirium and hypoglycemia in ICU patients with diabetes, delirium was not associated with glucose variability. The findings of the studies included in this thesis are summarized in Table 1.

In this general discussion the findings of the studies described in this thesis are put in a broader perspective, focusing on three themes: analysis and interpretation of glucose measurements, the barriers to research involving the geriatric population, and the interplay between delirium, antipsychotic drugs, and glucose homeostasis. For each theme, implications and/or recommendations are provided, and overall conclusions are presented.

Table 1. Associations evaluated in this thesis between antipsychotic drugs, delirium, and glucose homeostasis in older patients per research question

Population	Chapter	Determinant	Outcome	Adjusted OR
1. Antipsychotic drugs and alterations in glucose levels				
Outpatients with diabetes	2	Antipsychotic drugs	Hypoglycemia requiring hospitalization	2.26
Hospitalized patients (non-ICU)	3	Haloperidol	Hypoglycemia	NS
Hospitalized patients (non-ICU)	3	Hospital-initiated haloperidol	Hyperglycemia	2.02
Hospitalized patients (non-ICU)	3	Ambulant use of haloperidol	Hyperglycemia	NS
Hospitalized patients (non-ICU)	4	Prophylactic haloperidol	Change in glucose levels	NS
2. Glucose dysregulation and onset of delirium				
ICU patients	6	Diabetes	Delirium	NS
ICU patients without diabetes [a]	6	Hyperglycemia	Delirium	1.41
ICU patients without diabetes [a]	6	Hypoglycemia	Delirium	NS
ICU patients without diabetes [a]	6	Both hyperglycemia and hypoglycemia	Delirium	1.87
ICU patients with diabetes [a]	6	Hyperglycemia	Delirium	NS
ICU patients with diabetes [a]	6	Hypoglycemia	Delirium	NS
ICU patients with diabetes [a]	6	Both hyperglycemia and hypoglycemia	Delirium	NS
3. Changes in glucose variability in delirium				
Hospitalized patients (non-ICU)	5	Delirium	Glucose variability	Insufficient data
ICU patients without diabetes	7	Delirium	Hypoglycemia	NS
ICU patients without diabetes	7	Delirium	Hyperglycemia + glucose variability	NS
ICU patients with diabetes	7	Delirium	Hypoglycemia	2.78
ICU patients with diabetes	7	Delirium	Hyperglycemia + glucose variability	NS

NS: not significant.

a. Patients without diabetes and normal glucose levels were the reference category.

Analysis and interpretation of glucose measurements

It is well known that glycated hemoglobin (HbA1c) is an appropriate tool to evaluate antidiabetic therapy in patients with diabetes. It provides insight into the mean glucose concentration over the last 3 months and gives an indication of whether antidiabetic therapy needs to be adapted to lower glucose levels. The HbA1c level is strongly correlated with diabetic complications (7). A higher HbA1c level in older patients is considered acceptable because stricter glucose control has not proven beneficial, while it has been associated with hypoglycemia in this population (8). Because measurement of HbA1c is not suitable for evaluating glucose homeostasis over a short time, we had to choose other parameters in this thesis, as discussed below.

Blood glucose levels

To evaluate glucose homeostasis over a short time, an appropriate approach is to use blood glucose levels (9). However, blood glucose levels are rarely measured in the non-diabetic general population, but are measured more often if fluctuations in blood glucose levels are expected, such as in patients with diabetes or in hospitalized patients (for example, in the case of surgery or corticosteroid use). It is not expensive to measure blood glucose levels and the necessary blood samples can be obtained by venipuncture or finger-prick. Patient-related factors that influence glucose homeostasis are food intake, medications (antidiabetic drugs, insulin and other drugs) (10), illness (11), and sleep (12). Sample-related factors that could introduce bias are the frequency of glucose measurements and fasting versus non-fasting glucose levels. A commonly used method to study glucose homeostasis is to determine changes in glucose levels over time, usually with two measurements (**Chapter 5**), and to analyze change scores (if changes are normally distributed) with Students independent *t* test. A less conservative method of analysis is a multivariate approach with longitudinal data, using generalized estimating equations (GEE) or mixed effects models (MEM). These methods give a rate of change with a regression coefficient and allow correction for baseline differences. The positive skewness of the distribution of glucose levels (13) is completely ignored in the literature, but for small studies this should not be ignored. The approach of GEE and MEM is not advisable for transformed data because these methods generate a ratio of glucose levels after retransformation and not a regression coefficient.

Hyperglycemia and hypoglycemia

The presence of hyperglycemia or hypoglycemia can be established with a single blood glucose measurement. However, for research purposes many different thresholds for hyperglycemia and hypoglycemia are used and each threshold has its own sensitivity. The clinical symptoms of hyperglycemia and hypoglycemia are well known. A glucose level > 8.0 mmol/L meets the definition of hyperglycemia although clinical symptoms are frequently absent. Whether clinical symptoms occur depends on how high glucose levels are in the case of hyperglycemia. Hypoglycemia, on the other hand, is often symptomatic

with malaise and autonomic (sweating, heart palpitations, shaking, dizziness, hunger) and neurogenic (confusion, drowsiness, speech difficulty, odd behavior, incoordination) symptoms (14). Data analysis on hyper- and hypoglycemia could be performed as binary (yes/no) or continuous variable (number of measured dysregulations). The advantage of using a binary variable is that the analysis is less prone to fluctuations in the number of glucose measurements. Glucose levels are not often reported in databases and, if available, it is often not clear whether they are fasting or non-fasting levels. This could introduce misclassification if non-fasting and fasting glucose levels are not randomly distributed. The choice of appropriate threshold should be based on the research question and on the availability of data. We used a proxy for glucose dysregulation in **Chapter 2**, namely, hospitalization for hypoglycemia. This is a crude parameter to study blood glucose fluctuations, mild hypoglycemia will be missed (9,14).

Glucose variability

Glucose variability reflects fluctuations in glucose levels over time and is commonly used in research. The higher the glucose variability, the more likely it is that hypoglycemia or hyperglycemia occurs. There are minor differences in the definition of glucose variability used in studies, and heterogeneous approaches have been adopted to account for confounding (15). All measures have one standard error, thus a degree of intrinsic uncertainty (16). The following measures of glucose variability were used in the studies of this thesis:

1. The arithmetic average of all glucose levels (mean glucose concentration) and its dispersion (standard deviation (SD)) independent of the time interval. This is very easy to calculate and is often presented with the smallest standard errors (16), but outliers, especially when there are few measurements, strongly influence the value of the mean glucose concentration. Minimally two glucose measurements are needed to calculate the mean level. Small and large swings around a central tendency might have different SD values but similar mean glucose concentrations.
2. Coefficient of variation (CV) represents a count between 0 and 1 and shows the dispersion of the mean glucose concentration measured with SD and corrected for the mean glucose concentration (in formula: CV= SD/ mean).
3. Mean daily delta (mean daily Δ) (17) is calculated from minimally two glucose measurements. It provides information about changes in glucose levels over 1 or more days. A large mean daily Δ reflects large changes in glucose levels; however, a small mean daily Δ does not exclude high glucose levels. The mean daily Δ is strongly influenced by the occurrence of hypoglycemia and/or hyperglycemia, but more than one episode of hypoglycemia or hyperglycemia does not have an additional effect on the mean daily Δ.
4. Mean absolute glucose (MAG) change (18) reflects glucose variability over a period of time. The absolute change between glucose levels is summed and divided by the time between the first and last glucose measurements (mmol/L/h). Minimally three glucose measurements are needed to calculate the MAG change. The MAG change is

influenced by the number of glucose determinations and should be corrected for the number of determinations or observation time. Another option is an interpolation strategy to generate a glucose level for each time interval (for example, every hour) to calculate glucose variability. In this case, glucose variability is less dependent on the number of determinations. In the prospective investigation reported in **Chapter 5**, glucose levels were determined at fixed time intervals.

Interpretation of glucose variability

'One size fits all' is not appropriate when investigating glucose variability (19). Extrapolation to other populations is difficult: patients with diabetes have a higher glucose variability and blood glucose levels are measured more often than in patients without diabetes. Moreover, glucose variability is affected by disease severity and the use of glucose regulation protocols (target window glucose level and insulin dosing strategies) in the ICU. Generally, the frequency of glucose measurements reflects the severity of illness. Thus with fixed-time observation periods, as in the studies described in **Chapter 6** and **Chapter 7**, insulin dose and frequency of blood glucose measurements could be addressed as additional measures of glucose variability. In investigations with a variable observation period or relatively long observation period, there is a wider range in the total number of blood glucose measurements, and in this case a better approach is to correct for the total number of glucose measurements or observation period. Beside the frequency of glucose measurements, illness severity also affects glucose variability; however, it should be appreciated that glucose variability can reflect critical illness, the compliance of care givers with the glucose regulation protocol, or a true biological effect (20). Plotting glucose levels in combination with time lines of determinants and outcomes of interest could provide insight into associations and pathophysiological processes. The pathophysiology and consequences of acute changes in glucose levels and chronically high glucose levels are different, and therefore different measures are needed to distinguish between the two. Chronic hyperglycemia can be identified by a high mean glucose concentration with a low SD. Solely the mean concentration does not say anything about acute changes or chronically high glucose levels. The CV and MAG change are not suitable for distinguishing between acute and chronic hyperglycemia. Most measures of glucose variability are highly correlated (16). An approach (as used in **Chapter 7**) is to measure different markers of glucose variability. A disadvantage of this strategy could be the introduction of a type I error, meaning that associations are not based on true association, but by chance. The linearity of the glucose variability measure should always be investigated, and a certain degree of glucose variability is common.

Recommendations for future research

- The complete history of glucose measurements (including self-measurements) in outpatients and their insulin dosing strategy should be recorded in the medical record, which increases the possibility of research into glucose levels in outpatients with diabetes.

- Glucose variability should be reported in a more uniform fashion. Therefore, a gold standard should be developed, taking in account chronic and acute dysregulation of glucose levels.

Barriers to research in the geriatric population

Geriatric patients are still under-represented in clinical trials investigating the risk and benefit of drugs. While patients aged 65 years and older (i.e. older patients) are being increasingly included, these patients are relatively healthy and not representative of the geriatric population seen by geriatricians in clinical practice (21,22). The geriatric population is heterogeneous, and many trials use an upper age limit for trial participation in an attempt to create a more homogenous study population (23). Differences in comorbidity, medication use, visual and hearing impairment, cognitive impairment, and physical function are substantial in the geriatric population. Geriatric patients are often excluded from trials because of multiple comorbidity and polypharmacy. Moreover, they are more sensitive to the adverse effects of drugs because the pharmacokinetics and pharmacodynamics of drugs change with age (24). Another reason to exclude geriatric patients is that they are at higher risk of early dropout and death during follow-up.

To improve evidence-based medicine in the geriatric population, geriatric patients seen in clinical practice should be included in good quality research. Outcomes for younger patients, such as mortality and length of hospital stay, are often not relevant in geriatric patients. Length of stay is a measure to study the efficacy of care (25) and it does not distinguish between a long hospital stay because of complications or social care (26). Better outcomes for geriatric patients are measures to define the quality of life, postoperative complications, or prevention of re-admission. Investigations of geriatric populations with long observation periods should correct for competing risks on mortality (27). For example, if the association between delirium during the hospital stay and re-admission is investigated, mortality after hospital discharge should be taken in account in order to avoid bias.

The best approach to increase our knowledge of the efficacy and safety of drugs in geriatric patients is to insist that the pharmaceutical industry conducts clinical trials with geriatric patients before a new drug is given licensing approval. However, there is lack of knowledge about how existing drugs act in geriatric individuals. Several initiatives have been taken to improve knowledge of drug use in geriatric patients. The Expertisecenter Pharmacotherapy in Old Persons (EPHOR) has been established to achieve improvement on appropriate prescribing of drugs in older patients (www.ephor.nl). The Medicines Evaluation Board (MEB, in Dutch: College ter Beoordeling van Geneesmiddelen (CBG)) addresses pharmacotherapy in older patients as one of their spearheads, although concrete policies are still in development. In addition, there are also issues with administration of drugs in the geriatric population. Therefore, the European Medicines Agency (EMA) has started to investigate the need for pharmaceutical development of appropriate drug use in older patients (e.g. preparations for use in older

patients and administration through oral feeding tubes) (28).

Research involving geriatric patients is particularly filled by investigator initiated research. Some national and international guidelines on research involving older patients have been developed (29-31), there is a need for standardized definitions of frailty and functional status. In addition, patient exclusion because of concomitant drug use should be avoided and instead medication use should be used as an indicator of frailty and comorbidity. Lastly, exclusion criteria should be minimized so that the study population better reflects the population seen by geriatricians in daily practice. The study design needs a good balance between inclusion and exclusion criteria and between generalizability and selection bias. Fewer inclusion criteria would increase the number of potential participants and limit selection bias, but a larger sample size generates higher study costs. A guideline with practical advice on how to perform medical research involving the older population has been developed by the Department of Geriatric Medicine of the RadboudUMC (31) in an effort to stimulate research into older patients in the Netherlands.

The practicalities of research with older patients are more complex than those of research with younger patients. First, it can be difficult to distinguish between serious adverse events caused by an intervention and the natural course of a disease (32). Second, the interpretation of data is complicated by more potential effect modifiers and confounding factors. Complicating factors that negatively influence the willingness of geriatric patients to participate in research are a low health-related quality of life, transport barriers, and a lack of understanding of the potential benefits of research participation (24,33,34). An underexposed issue is valid informed consent. This can only be given if the patient is sufficiently informed about the content and burden of the study, is legally capable of providing consent, and participation is voluntary (35). Factors such as educational level, the acute character of hospitalization, and the complexity of the study design affect how well a potential participant understands the aims of the study and the consequences of participation. While participation is always voluntary, in practice patients are easily influenced by the opinion of their caregivers, the research team, and physicians. An additional problem is that some geriatric patients are no longer able physically to sign their name (and hence the informed consent form). In this case, loss of patients can be prevented by adapting the study procedure (36), by asking informed consent of the potential participant in the presence of a proxy who then signs the informed consent form after approval of the potential participant. Additional barriers are that geriatric patients often do not know their medical history in detail, and visual and hearing impairments make communication difficult. Moreover, these patients are often seen by different medical specialists, which complicates the collection of reliable information. Hospitalized patients who are restricted to bed have decreased writing skills, do not wear their glasses, and their hearing aids are often switched off. Planning a follow-up is more difficult after hospital discharge as geriatric patients are often temporarily admitted to a nursing home or rehabilitation center. Another consequence of the difficult communication makes follow-up using telephone interviews very difficult, so that a face-to-face visit seems the preferred method.

Current evidence-based knowledge of delirium is limited, and treatment strategies are largely based on practical experience. Investigations of delirium have to deal with additional challenges with regard to participation and data collection. Our study (**Chapter 5**) illustrates the difficult balancing act between ethical considerations regarding the protection of vulnerable patients, practical issues in performing delirium research for investigators, and adequate recruitment. First, patients with advanced stages of dementia are at highest risk of developing delirium and they are underrepresented in delirium research. This adversely influences the generalizability of evidence (37). Patients with an advanced stage of dementia are considered to be incapacitated, they are unable to make a well-reasoned decision about medical treatment and therefore cannot participate in medical research. Other groups of incapacitated patients are children, patients with severe psychiatric diseases, mentally disabled patients, and patients who are (temporary) delirious or comatose. In the Netherlands, the Medical Research Involving Human Subjects Act (WMO) covers the participation of human subjects in medical research. The WMO is based on international codes and laws, with the Nuremberg Code and Declaration of Helsinki forming the basis of the Act's ethical principles. Incapacitated patients are not allowed to participate in research unless they may benefit from participation (therapeutic research trials) or, in the case of no potential benefit (non-therapeutic research) and when inclusion is based on group relatedness, if there is negligible risk and minimal burden. Since March 2017, the WMO has been extended to cover non-therapeutic research and now allows the participation of incapacitated patients provided that the risks and burden are minimal compared with those of usual treatment. The group-relatedness argument has been abandoned. Similar guidelines exist in other European countries. This adaption will stimulate the participation of patients with the highest delirium risk. However, interpretation of minimal risk and burden compared to regular care is subjective, and the Medical Research Ethics Committee (MREC) has the final decision about whether incapacitated patients can be included in studies. Second, patient recruitment for studies of delirium has an additional problem in that patients admitted to the emergency department with fractures are at higher risk of delirium than patients with a planned admission. Many of them are admitted after office hours, which means that a research team has to be available, which increases costs, especially when patients need to be included for baseline measurements before emergency surgery. The highest risk of delirium onset is in the first 24-36 hours after surgery. It is a question of balancing manpower and costs. Moreover, geriatric patients often want to discuss participation with their relatives, which causes a delay or results in exclusion from studies because there is too little time to think about study participation if emergency surgery is needed, and relatives are often not present. Furthermore, it is important to identify those patients who are incapacitated during the informed consent procedure. The incapacitated state may be temporary as a result of delirium or related to dementia. The gold standard to determine mental incapacity is not available. Many heterogeneous methods, with their own sensitivity and specificity, have been described, including judgment made by a physician, different scales to determine

patients' cognitive function, such as the Mini-Mental State Examination (MMSE) (38), and interview methods (example: vignette method (39)). For our investigations (**Chapter 5**), we used a combination of these methods, but in retrospect this may have been too stringent. When gaining approval to recruit incapacitated patients, two informed consent procedures are needed for patients' proxy and for the patient after recovery from delirium. Of course, patients are able to withdraw after recovery of delirium. Another challenge is the fluctuating course of delirium and how to monitor it. Generally, delirium is considered to be present or absent. Even though there are several validated scales to establish the presence and severity of delirium (40), it is difficult to establish the onset of delirium exactly because scales are administered only once or twice daily.

Recommendations for research involving older patients

- Collection of data from older persons for research purposes should be integrated in usual care settings. The collection of data for usual care in hospitalized patients should be performed structurally and in a standardized format to facilitate research involving older patients.
- Good clinical practice guidelines and their ethics can be learned by classical training or e-learning. However, putting this knowledge into practice requires clinical experience and is time consuming. Junior researchers should learn from more experienced researchers from different research groups and discuss practical issues and handy hints.
- In order to successfully reduce the barriers to research in older patients, it is of importance to involve potential participants in the process of study design and logistics.
- It is advisable to consult the MREC in an early stage of study design. Patients with the highest delirium risk need to be recruited to delirium research in order to generate a better understanding of the causes and consequences of delirium and glucose homeostasis.
- A geriatrician should be consulted by the MREC to evaluate the risks and benefit of investigations with geriatric patients, especially if it is desirable to recruit patients with a diminished mental capacity. This also has been recommended by the guideline medical research for and with older people in Europe (29). This is in concordance with the policy in research involving children, because pediatricians are involved in the evaluation of research involving children by the MREC.

The interplay between delirium, antipsychotic drugs, and glucose homeostasis

The most widely used antipsychotic drug in patients with delirium is haloperidol, which has a high affinity for the dopamine D2 receptor and affinity for the adrenergic alfa-1 receptor. Blockage of postsynaptic dopamine D2 receptors in the mesolimbic

system seems responsible for the positive effect of the drug on psychotic symptoms in schizophrenia and is the suggested mechanism in delirium (41). However, there are several dopamine pathways in the brain and periphery, and their inhibition may result in harmful effects. For example, blockage of nigrostriatal pathway by dopamine D2 receptor antagonism may be responsible for extrapyramidal adverse effects (42).

Antipsychotic treatment of schizophrenia has been associated with impaired glucose levels in the long term, a component of the metabolic syndrome that increases the risk of cardiovascular events (43-45). The mechanisms by which atypical antipsychotic drugs may induce glucose disturbances are insulin resistance as a result of serotonin 5-HT2a receptor antagonism, increased food intake as a result of serotonin 5-HT1a receptor antagonism, weight gain as a result of histamine H1 receptor antagonism, and impaired insulin secretion as a result of muscarinic M3 receptor and serotonin 5-HT2a receptor antagonism. Furthermore, atypical antipsychotic drugs may have an acute effect on glucose homeostasis. The occurrence of diabetic ketoacidosis early in the course of antipsychotic therapy and impaired glucose levels in schizophrenic patients without obesity suggest an underlying mechanism is active that is independent of weight gain (46). Retrospective research involving older outpatients has found that antipsychotic drugs increase the risk of hospitalization for hyperglycemia, especially early in the course of therapy with either atypical or conventional antipsychotic drugs (47-49). We were the first to report an association between the use of antipsychotic drugs and hypoglycemia, especially early in the course of therapy with higher doses or conventional antipsychotic drugs (**Chapter 2**). In addition, hospital-initiated haloperidol was associated with hyperglycemia (**Chapter 3**). These findings support that antipsychotic drugs acutely disrupt glucose homeostasis, although we have reported opposite effects. Glucose dysregulation happens in a few patients treated with antipsychotic drugs, which suggests that other unknown factors, such as genetic profile, may influence the individual vulnerability to develop glucose dysregulation when antipsychotic drugs are used.

The mechanisms underlying glucose dysregulation are not known. There might be a role for peripheral dopamine pathways via dopamine D2 receptors on pancreatic beta cells. These receptors are involved in glucose-stimulated insulin secretion (50). Dopamine D2 receptor antagonism has been associated with increased insulin production by pancreatic beta cells (51-53). The effect of haloperidol on insulin secretion has been studied previously, but with conflicting results (54-58). Another possibility is the involvement of peripheral adrenergic pathways via adrenergic alfa-1 receptors (responsible for increased and decreased glucose level) in skeletal muscles (59) or an interplay between alfa-1 and dopamine D2 receptors. Furthermore, conventional antipsychotics may elevate extracellular glutamate levels during hypoglycemic episodes, resulting in cognitive impairment that delays recovery from hypoglycemia. In contrast, atypical antipsychotics may be less neurotoxic because they inhibit glutamate release (60).

As mentioned before, little is known about antipsychotic-induced hypoglycemia.

Case reports have been described (Table 2), one of which concerned a patient with diabetes. The incidence of antipsychotic-induced hypoglycemia seems to be low. Only the most serious symptomatic hypoglycemia results in hospitalization to restore the patient to consciousness by means of glucose infusions. Of our cohort (**Chapter 2**), 815 individuals (1.2%) were hospitalized for hypoglycemia, 4.4% of whom used antipsychotic drugs. Severe hypoglycemic episodes are common and often related to treatment with long-acting insulin and long-acting sulfonylurea in older patients. While hypoglycemia has a huge impact on affected individuals, it is difficult to recognize in older patients because it is often non-symptomatic and occurs together with non-specific symptoms, such as dizziness and visual disturbances. Older patients have a delayed counter-regulatory response to hypoglycemia and a slower recovery compared with younger patients (61). Symptoms of decreased consciousness may last longer and more frequently lead to hospital admission. The occurrence of hypoglycemia increases the risk of cardiovascular events and death, but also the risk of dementia and fractures (62). Furthermore, hypoglycemia has a negative impact on the quality of life and social activities (63). Approximately 5% of the patients are responsible for more than 50% of all severe hypoglycemic events (64).

In 2008, Leendertse et al. (65) reported that many hospital admissions were related to adverse drugs events. Almost half of these admissions were preventable and 6% were related to hypoglycemia or hyperglycemia due to the use of antidiabetic drugs. Increased awareness of hypoglycemic symptoms during antipsychotic drug treatment may help prevent hypoglycemic episodes and hypoglycemia-related hospital admission. Patients with polypharmacy, cognitive impairment, and multimorbidity were identified as being most likely to experience preventable medication-related hospital admission. This profile is similar to that of the older population involved in the studies described in this thesis.

Delirium is a disease of acute illness and its pathology is complex and not completely understood. It has been associated with acetylcholine depletion and dopamine excess (76) and is suggested to be caused by an imbalance of neurotransmitters, resulting in disturbances in cognitive function. Other suggested mechanisms of delirium involve proinflammatory markers, electrolyte and metabolic disturbances, physiological stressors, and genetic factors (77). Several studies support the hypothesis that cortisol as end product of the hypothalamic-pituitary-adrenal (HPA) axis is involved in the pathophysiology of delirium (78-81). If a patient is of advanced age and has a diagnosis of dementia (predisposing factors), fewer illness-related factors are needed to precipitate the onset of delirium. Because delirium often occurs during acute illness, it is typically a syndrome that occurs in hospitalized patients. The highest incidence (up to 82%) of delirium is reported in patients in postoperative, ICU, and palliative care settings (82), although outpatients are also susceptible to delirium. A few studies have investigated delirium and its underlying etiology in outpatients compared with hospitalized patients. In 1991, the first study (83) reported a rate of delirium in outpatients of 1%. More recently,

Table 2. Case reports and hypothesized mechanism for antipsychotic-induced hypoglycemia

Author	Year	Environment	APD + duration	Indication	Of note	Hypothesis about mechanism
Buckle et al.	1967	53-year old woman	Chlorpromazine, 2 months	Unknown	Comedication: orphenadrine Normal plasma insulin levels	Summative effect of central hypothalamic-pituitary effect of chlorpromazine and direct peripheral effect of orphenadrine
Kojak et al.	1969	77-year old woman	Haloperidol, 6 days	Prolonged confusion and paranoid delusions	48 hours hypoglycemia High insulin levels	None
Landi et al.	2003	95-year old woman	Olanzapine, 1 single dose	Nocturnal psychomotor agitation	Diagnosis of dementia Comedication: enalapril. High insulin and C-peptide levels	Increased insulin levels with increased sensitivity or direct influence of pancreatic beta cells and insulin secretion or interaction effect between enalapril and olanzapine
Walter et al.	2006	54-year old man	Haloperidol, 18 hours	Delirium	Increased insulin and C-peptide levels	Consistent with insulin-release mechanism
Nagamine	2006	47-year old man	Olanzapine, 4 days	Schizophrenia	Comedication: haloperidol. Increased insulin level	Induced insulin resistance with possibility of delayed insulin hypersecretion and lack of reserve capacity of glucose homeostasis
Suzuki et al.	2009	27-year old man	Quetiapine, 4 months	Schizophrenia	After dose increase (from 400 mg to 600 mg)	None
		53-year old man	Risperidone, unknown	Schizophrenia	After dose increase (from 6 mg to 8 mg)	
		32-year old woman	Olanzapine, unknown	Schizophrenia	After dose increase (from 10 mg to 20 mg)	
Mondal et al.	2012	72-year old man	Aripiprazole, 21 days	Psychosis in Parkinson's disease	Normal glucagon, growth hormone and fasting cortisol levels	Involving lowering energy reservoir. Failed glucose homeostasis (hypoglycemia awareness and blunt counter regulatory responses). Direct glucose-lowering effect
Suzuki et al.	2012	50-year old woman	Quetiapine, 12 days	Hallucinations and delusions	Recent history of risperidone, olanzapine and aripiprazole use	None
Nagamine	2016	77-year old man	Risperidone, 4 weeks	Schizophrenia	Comedication: quetiapine. Risperidone was replaced by blonanserin, which reversed the hypoglycemia	Relatively high insulin. Suggested mechanism is insulin hypersecretion
Nagamine	2017	75-year old woman	Tiapride, 2 weeks	Delusional psychosis	History of diabetes for 20 years	Possibility of hyperinsulinemia

APD: antipsychotic drugs.

delirium rates up to 10-35% have been reported in outpatients (84). A better recognition of delirium in recent years may explain the increase in the reported rate of delirium. Delirium in outpatients is often relatively 'mild' and it can be difficult to distinguish between dementia and delirium (84). In addition, outpatients with dementia have been reported to show different delirium-related symptoms than outpatients without dementia (84).

Delirium is regularly investigated in two separate hospitalized populations, patients who are admitted to non-ICU wards or to the ICU. Extrapolation of risk factors for ICU delirium to delirium occurring on non-ICU wards is difficult, because ICU delirium could have different etiology. This is illustrated in **Chapter 6**, where we investigated the association between the predisposing factor diabetes and the precipitating factor glucose dysregulation and the risk of ICU delirium in multivariate models. The presence of critical illness (precipitating factor) was a very important risk factor for ICU delirium: the SOFA score, APACHE IV score, presence of severe sepsis or septic shock, and hyperglycemia (**Chapter 6**) were associated with ICU delirium (SOFA per 10 points OR 2.55; APACHE IV score per 10 points OR 1.20; presence of severe sepsis or septic shock OR 1.51; data not presented in **Chapter 6**). These markers of critical illness are not measured or present in patients on non-ICU wards, and thus it is difficult to generalize our findings to non-ICU patients. In conclusion, the extent to which diabetes and glucose dysregulation contribute to delirium in non-ICU patients remains unknown.

As delirium is an acute illness, it might also increase the activity of the HPA axis, leading to increased cortisol release and, as a consequence, disturbances of glucose metabolism. We found a higher risk of hypoglycemia in patients with diabetes during ICU delirium (**Chapter 7**). This finding might be generalizable to other delirious populations with diabetes even though the glucose regulation protocol of the ICU is not used on non-ICU wards and it is not known whether ICU delirium is similar to non-ICU delirium.

In non-diabetic ICU patients, acute hyperglycemia and increased glucose variability are associated with a higher mortality risk compared with that of patients with diabetes (85,86). It is hypothesized that diabetic patients are used to chronic hyperglycemia and therefore counter-regulatory mechanisms have a higher threshold (85). In addition, it has been reported that patients with HbA1c > 53 mmol/mol (7.0%) with acute hyperglycemia have a lower mortality risk than patients with HbA1c ≤ 53 mmol/mol (87). Consistent with this, we found that in patients without diabetes, but not in patients with diabetes, acute hyperglycemia was associated with ICU delirium and that diabetes as diagnosis was not associated with delirium (**Chapter 6**). The implications of these findings for antipsychotic drug use and glucose control are not clear. It might be that non-diabetic patients are more likely than diabetic patients to develop hyperglycemia when they use antipsychotic drugs. Or it could be that older patients using antipsychotic drugs who experience hyperglycemia have undetected prediabetes or are at risk of long-term diabetes. Unfortunately, the study described in **Chapter 3** did not have enough power to investigate the associations between antipsychotic drugs and glucose dysregulation in diabetic and non-diabetic patients adequately.

The cause of glucose dysregulation: drug or disease?

On the basis of the results presented in this thesis (Table 1), we were not able to ascertain whether delirium, antipsychotic treatment, or glucose disturbances contributed to the death of the woman in the case described in the introduction. There are arguments for and against antipsychotic drugs having a direct effect on glucose homeostasis. The dose-dependent effect of antipsychotic drugs supports the hypothesis of a drug effect (**Chapter 2**). However, higher doses of antipsychotics are needed to treat more severe delirium, suggesting that it could be an effect of the underlying disease. We found a higher risk of hypoglycemia during delirium in patients on the ICU, supporting the suggestion that the underlying disease causes glucose dysregulation (**Chapter 7**). Finally, the absence of a change in glucose levels (**Chapter 4**) when haloperidol was used as prophylaxis for delirium supports an effect of delirium. Other options are that the associations are based on an additive, synergistic, or inhibitory effect of drug and disease. The lack of clarity whether drug or disease may be responsible for disturbances in glucose homeostasis has also been described in research on antidepressants (9). But for clinical practice, the use of antipsychotic drugs seems to be accompanied by delirium, and thus older patients with delirium and/or using antipsychotic drugs can be considered as being at risk of glucose dysregulation.

Implications for clinical practice and recommendations for future research

- Caregivers should be aware of the risk of glucose dysregulation in older people using antipsychotics. Glucose levels should be monitored in older patients using antipsychotic drugs, in order to prevent severe glucose dysregulation. The summary of product characteristics of conventional antipsychotic drugs should contain information about the potential of antipsychotic drugs to cause glucose dysregulation.
- Large clinical studies should investigate which patient groups are sensitive to antipsychotic-induced glucose dysregulation, taking into account diabetic control with HbA1c, and investigate the consequences on patient relevant outcomes. Prospective studies should collect data on the BMI, dietary intake, physical function, and genetic profile of study participants.
- Clinical studies to investigate glucose variability in patients with and without delirium admitted to non-ICU wards are needed to confirm the hypothesis that glucose variability is altered during delirium.
- The interplay of diabetes and glucose dysregulation as risk factors for delirium should be investigated in older hospitalized patients admitted to non-ICU wards.
- ICU professionals need to be aware of the increased risk of delirium after hyperglycemia in patients without diabetes and the increased risk of hypoglycemia during delirium in patients with diabetes. The use of measures to prevent glucose dysregulation is recommended in the ICU, in order to decrease the risk of delirium. Blood glucose levels should be monitored more often in delirious patients with diabetes in order to prevent hypoglycemia.

Final thoughts and overall conclusion

The studies described in this thesis have increased our knowledge of the interplay between antipsychotic drugs, delirium, and glucose homeostasis in older outpatients, hospitalized older patients admitted to non-ICU wards, and ICU patients. Unfortunately, a prospective observational investigation of delirium and glucose levels in older patients on non-ICU wards had to be stopped prematurely because we were not able to surmount the barriers to research in older patients. However, the findings for ICU patients described in this thesis support the hypothesis that delirium acts on glucose homeostasis and vice versa. The interplay between delirium and glucose was different for patients with and without diabetes, indicating another underlying mechanism. Future research is needed on risk factors for delirium in patients admitted on non-ICU wards and on the ICU and their underlying mechanism.

Glucose dysregulation should be added to the list of adverse events associated with antipsychotic treatment in older patients. While the absolute risk of glucose dysregulation during antipsychotic use seems small, its impact in the frail older population may be huge. Our findings support the advice that antipsychotic drugs should be used with caution in geriatric patients and restricted to those with the most severe psychotic symptoms.

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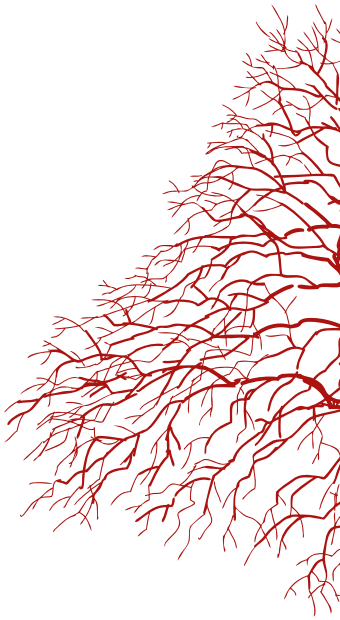


Summary

Summary

Antipsychotic drugs are widely used in older patients to reduce psychotic and behavioral symptoms in dementia and delirium. There is limited evidence of their efficacy, whereas numerous studies have reported adverse effects and safety concerns in the older population. It has been suggested that the cardiometabolic adverse effects of antipsychotic drugs contribute to the increased mortality risk seen in older patients using these drugs. The metabolic effects of antipsychotic drugs in the older population have been poorly studied, whereas in schizophrenic patients, components of the metabolic syndrome are monitored during treatment with antipsychotic drugs. The studies that have evaluated the association between antipsychotic use and metabolic adverse effects in older patients, focused on the risk of new-onset diabetes during antipsychotic drug use, but results are conflicting. Furthermore, three studies report that older antipsychotic drug users have an increased risk of hyperglycemia requiring hospitalization. It is not known to what extent the underlying disease influences the relation between antipsychotic drugs and glucose homeostasis. Even less is known about the mutual relation between delirium and glucose homeostasis. Limited evidence suggests that hyperglycemia, hypoglycemia, and higher fasting glucose levels are risk factors for delirium. Glucose levels were reported to be higher in hyperactive delirium than in non-hyperactive delirium in critically ill patients admitted to the intensive care unit (ICU). As delirium is an acute illness, it might involve the hypothalamic-pituitary-adrenal axis, resulting in increased cortisol release and subsequent changes to glucose metabolism. Both delirium and antipsychotic drug use have been associated with disturbances in glucose levels, but the interplay between antipsychotic treatment, delirium, and glucose has not been clarified. This thesis aimed to answer whether antipsychotic treatment is associated with alterations in glucose levels, whether glucose variability is associated with the onset of delirium and whether glucose variability is altered in delirium in older patients.

Chapter 2 describes the association between the use of antipsychotic drugs and hospitalization for hypoglycemia in older diabetic outpatients. The nested case-control study was conducted in the PHARMO Database Network with drug dispensing data from the community pharmacies and hospital discharge records. The cohort included all patients of 65 years and older with at least one year of valid medication history and at least three prescriptions for insulin and/or oral antidiabetic drugs filled during one year between January 1998 and December 2008 or a hospital discharge diagnosis of diabetes mellitus. Cases were patients from the study cohort with a first hospital admission for hypoglycemia. Up to five comparison subjects from the cohort were sampled for each case. Exposure to antipsychotic drugs before the index date was the primary determinant of interest. Logistic regression analysis was performed to estimate the strength of the association between antipsychotic drug use and hypoglycemia, taking into account potential confounders. 815 patients were admitted to hospital for hypoglycemia. Current use of antipsychotic drugs was associated with an increased risk of hypoglycemia

compared with non-use (adjusted OR: 2.26; 95% CI: 1.45-3.52), especially in the first 30 days of treatment (adjusted OR: 7.65; 95% CI: 2.50-23.41) and with higher doses (adjusted OR: 8.20; 95% CI: 3.09-21.75). Our findings suggest that close monitoring of blood glucose levels is indicated in older outpatients with diabetes treated with antipsychotic agents.

The investigations presented in **Chapter 3**, **Chapter 4**, and **Chapter 5** were conducted in hospitalized patients admitted to non-ICU wards. In **Chapter 3**, we conducted a nested case-control study among older hospitalized patients to assess the risk of hyperglycemia and hypoglycemia associated with antipsychotic drug use. All patients aged 70 years or older admitted to a general community teaching hospital (Tergooi Hospital) between 2010 and 2014 with normoglycemia at admission and at least one glucose measurement during hospitalization were involved. Cases were patients who developed hyperglycemia (glucose level ≥ 11.1 mmol/L) or hypoglycemia (glucose level ≤ 3.5 mmol/L) during hospitalization. Up to five controls were selected for each case. The date of hyperglycemia or hypoglycemia was taken as the index date and each control was assigned an index date. Exposure to antipsychotic drugs before the index date was the primary determinant of interest. Logistic regression analysis was used to estimate the strength of the association between antipsychotic drugs and hyperglycemia or hypoglycemia, taking into account potential confounders including the presence of diabetes and the use of antidiabetic drugs. Of the 2,054 included patients, 483 (23.5%) developed hyperglycemia and 43 (2.1%) developed hypoglycemia. Haloperidol was the most frequently used antipsychotic drug (hyperglycemia: 47 cases and 64 controls and hypoglycemia: 3 cases and 9 controls). Current use of haloperidol was not associated with an increased risk of hyperglycemia (adjusted OR: 1.34, 95% CI: 0.81-2.21) or hypoglycemia (OR: 0.66, 95% CI: 0.17-2.63). We found no evidence for an association between antipsychotic use and hypoglycemia in older hospitalized patients, possibly due to insufficient power. However, hospital initiated haloperidol was associated with hyperglycemia (adjusted OR: 2.02, 95% CI: 1.01-4.03). Our results suggest that closer monitoring of blood glucose levels may be indicated after starting haloperidol in a hospital setting.

The study described in **Chapter 4** aimed to investigate changes in glucose levels during haloperidol use compared with the use of placebo among older hospitalized patients in a substudy of the haloperidol prophylaxis in older emergency department patients (HARPOON) study. In this multicenter, randomized, double blind, placebo-controlled clinical trial, hospitalized patients aged 70 years and older with an increased risk of in-hospital delirium were invited for participation. Participating patients were randomized for treatment and given 1 mg of haloperidol or a placebo twice daily for a maximum of seven consecutive days (14 doses). Exclusion criteria for this substudy were the use of corticosteroids and changes in diabetes medication. Random blood samples to determine glucose levels were collected before day 1 and on day 6 of the study. Student independent sample *t* test was used to determine differences in glucose changes between both groups. Twenty-nine patients were included (haloperidol, n = 14; placebo, n = 15).

The mean glucose level for placebo users was 7.7 mmol/L SD 2.8 on day 1 and 7.8 mmol/L SD 2.8 on day 6, and the mean glucose level for haloperidol users was 7.8 mmol/L SD 3.9 on day 1 and 8.3 mmol/L SD 2.2 on day 6. The change score for placebo users was 0.1 mol/L SD 3.2 and for haloperidol users was 0.6 mmol/L SD 3.2. The difference was not statistically significant ($p = 0.685$).

The aim of the study presented in **Chapter 5** was to determine glucose variability in older patients with and without delirium. A prospective, observational cohort study was performed between February 2015 and February 2016 at the geriatric trauma unit and department of orthopedics in a teaching hospital (Tergooi Hospital, the Netherlands). Patients aged 70 years and older admitted for hip surgery with an increased risk of in-hospital delirium were eligible for participation. Patients were included within 24 hours of hospitalization. Exclusion criteria were diminished cognitive capacity at admission, diabetes and participation in a study of a medical product. Glucose levels were measured four times daily after surgery until hospital discharge, to determine glucose variability, expressed as mean absolute glucose change (MAG change) calculated as the sum of the absolute changes in blood glucose concentrations divided by the time between first and last glucose measurement (in hours). Secondary outcomes were other measures of glucose variability, namely the mean glucose concentration (mmol/L) and its standard deviation (SD, mmol/L) of the mean glucose concentration, coefficient of variation (CV, mmol/L), mean glucose daily delta (mean daily Δ), hypoglycemia (glucose concentration ≤ 3.9 mmol/L), and hyperglycemia (non-fasting blood glucose concentration ≥ 11.0 mmol/L). In total, 123 of the 331 screened patients met the inclusion criteria. Of these patients, 66 were excluded because they were considered to have diminished cognitive capacity, 27 because they had diabetes, and 18 declined participation. Thus 12 patients (10.2% of the expected inclusion rate) were included. This study was ended prematurely because of recruitment problems. In total, 142 glucose measurements were available. We were unable to include the intended number of participants and thus could not determine the association between delirium and glucose variability. The incidence of delirium was 16.7% (2 of 12 patients). One of the two non-diabetic patients with delirium in our study had the highest measured glucose variability (MAG change: 0.44 mmol/L/h, SD: 2.8 mmol/L, CV: 0.32 mmol/L, mean daily Δ: 5.42 mmol/L) and the most episodes of hyperglycemia (4), which supports our hypothesis that delirium may be associated with high glucose variability. This study also illustrates the difficulties encountered when conducting research involving older patients. Broadening the inclusion criteria to allow the inclusion of patients with a diminished cognitive capacity, who are potentially at high risk of developing delirium, is needed in future delirium research.

The investigations presented in **Chapter 6** and **Chapter 7** were conducted in ICU patients. A prospective cohort study was conducted in the 32-bed mixed ICU of the University Medical Centre Utrecht (UMCU), the Netherlands. Patients were included when they stayed for more than 24 hours at the ICU. Patients were excluded in case of admission to the ICU because of a neurological illness, if delirium assessment was hampered due to

deafness or if patients were unable to understand Dutch or English. Their mental status was evaluated using a validated algorithm and each ICU day was classified into the following categories: awake and non-delirious, delirious or comatose.

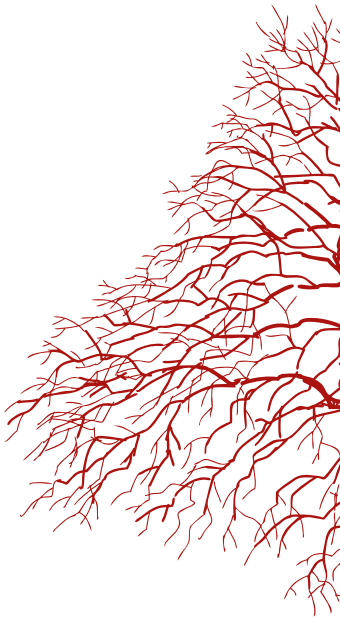
In **Chapter 6**, we investigated whether diabetes and glucose dysregulation (hyperglycemia and/or hypoglycemia) are risk factors for ICU delirium. Critically ill patients admitted to the ICU between January 2011 and July 2016 were selected with a transition of mental status from awake and non-delirious (day *t*) to delirious or remaining awake and non-delirious on the next day (day *t+1*). The determinants of interest were diabetes and glucose dysregulation (hyperglycemia and/or hypoglycemia). The presence of diabetes mellitus at ICU admission was defined as present in the medical record (diagnosis or treatment) or use of insulin and/or oral antidiabetic drugs before hospital admission. Glucose dysregulation was explored in four categories. Hyperglycemia was defined to be present at day *t* if at least one blood glucose level was measured > 8.0 mmol/L on that day (day *t*), and hypoglycemia was defined as at least one measured glucose level < 3.5 mmol/L on day *t*. When both were present on day *t*, the exposure was categorized as both hyperglycemia and hypoglycemia. Day *t* was marked with 'normoglycemia' when none of the determined blood glucose levels met the criteria for hyperglycemia or hypoglycemia. Generalized mixed-effects models with logit link function were performed to study the association between diabetes mellitus, glucose dysregulation and delirium, adjusting for potential confounders. Our study population consisted of 2,745 patients with 1,720 transitions from awake and non-delirious to delirious and 11,421 non-transitions remaining awake and non-delirious. We identified 543 (19.8%) patients with a diagnosis of diabetes of whom 225 (41.4%) had a delirium during ICU stay. Of the 2,202 patients without diabetes, 902 (41.0%) patients experienced delirium during ICU stay. Diabetes was not associated with delirium (adjusted OR: 0.93; 95% CI: 0.73-1.18). In total, 65,727 glucose values were determined on day *t*. Hypoglycemia did not significantly increase the risk of transition to delirium (adjusted OR: 1.86; 95% CI: 0.73-3.71). Only in patients without diabetes the occurrence of hyperglycemia (adjusted OR: 1.41; 95% CI: 1.16-1.68) and the occurrence of both hyperglycemia and hypoglycemia on the same day (adjusted OR: 1.87; 95% CI: 1.07-2.89) were associated with transition to delirium. We did not find that diabetes mellitus was associated with the development of ICU delirium. Hyperglycemia increased the risk of ICU delirium, but only in patients without diabetes. Hypoglycemia increased the risk of delirium non-significantly. This investigation contributes to the understanding of the etiology of delirium and supports the use of measures to prevent hyperglycemia.

In **Chapter 7**, we investigated whether measures of glucose variability are altered during delirious days compared to non-delirious days in critically ill patients with and without diabetes. Critically ill patients admitted to the ICU between January 2011 and June 2013 were selected with at least one delirious and one non-delirious ICU observation day. Glucose variability was measured each observation day, expressed by the mean glucose concentration, its SD, MAG change, daily delta, and the occurrence of hypoglycemia (hypoglycemia: glucose concentration < 3.5 mmol/L and severe

hypoglycemia: glucose concentration < 2.2 mmol/L) and hyperglycemia (hyperglycemia: glucose concentration > 8.0 mmol/L and severe hyperglycemia: glucose concentration > 11.0 mmol/L). We used linear mixed-effects models and generalized mixed-effects models with logit link function as multilevel techniques to test whether delirium was associated with increased glucose variability. From the cohort, 410 patients with 1,233 delirious and 1,775 non-delirious observation days were selected for this analysis. Mean glucose concentrations, its SD, MAG change, daily delta and the risk of hyperglycemia were unaltered during delirious days compared to non-delirious days in non-diabetic and diabetic patients. Furthermore, we demonstrate that in diabetic patients delirium was associated with hypoglycemia (adjusted OR: 2.78; 95% CI: 1.71-6.32). This association was not found for non-diabetic patients (adjusted OR: 1.16; 95% CI: 0.58-2.28). Our findings suggest that glucose levels should be monitored more closely in diabetic patients during delirium at the ICU to prevent hypoglycemia.

In **Chapter 8**, the general discussion, the results of this thesis are discussed in a broader perspective focusing on the analysis and interpretation of glucose measurements, the barriers to research involving the geriatric population, and the interplay between delirium, antipsychotic drugs, and glucose homeostasis.

In conclusion, this thesis has increased our knowledge of the interplay between antipsychotic drugs, delirium, and glucose homeostasis in older outpatients, hospitalized older patients admitted to non-ICU wards, and ICU patients. The findings for ICU patients described in this thesis support the hypothesis that delirium acts on glucose homeostasis and vice versa. The interplay between delirium and glucose was different for patients with and without diabetes, indicating another underlying mechanism. Glucose dysregulation should be added to the list of adverse events associated with antipsychotic treatment in older patients. While the absolute risk of glucose dysregulation during antipsychotic use seems small, its impact in the frail older population may be huge.



Samenvatting

Samenvatting

Antipsychotica worden veel toegepast bij oudere patiënten ter vermindering van psychotische en gedragsproblemen bij dementie en delier. Er is slechts beperkt bewijs voor de werkzaamheid van antipsychotica bij ouderen, terwijl veel onderzoeken bijwerkingen en problemen met de veiligheid rapporteren. Mogelijk draagt het optreden van de cardiometabole bijwerkingen bij aan het verhoogde risico op overlijden bij oudere patiënten die antipsychotica gebruiken. Er is weinig onderzoek gedaan naar metabole bijwerkingen tijdens de behandeling met antipsychotica bij ouderen, terwijl bij patiënten die vanwege schizofrenie behandeld worden met antipsychotica, in de klinische praktijk screening en actieve monitoring van cardiovasculaire risicofactoren plaatsvindt. De onderzoeken die de associatie tussen antipsychotica en metabole bijwerkingen bij oudere patiënten hebben beschreven zijn gericht op het risico op het ontwikkelen van diabetes mellitus tijdens het gebruik van antipsychotica. Deze onderzoeken laten tegenstrijdige resultaten zien. Verder beschrijven drie onderzoeken een associatie tussen de behandeling met antipsychotica en een ziekenhuisopname wegens hyperglykemie bij ouderen. De invloed van de onderliggende ziekte op de relatie tussen antipsychotica en glucose homeostase is onbekend. Nog minder is bekend over de onderlinge relatie tussen delier en de glucose homeostase. Een hyperglykemie, hypoglykemie en een hoog nuchter glucose worden in de literatuur genoemd als risicofactoren voor delier. Bij ernstig zieke patiënten die opgenomen waren op de intensive care (IC) werden hogere glucosewaarden gemeten tijdens een hyperactief delier in vergelijking met een hypoactief delier. Delier is een acute ziekte en daarom is mogelijk de hypothalamus-hypofyse-bijnieras betrokken, leidend tot een verhoogde cortisolafgifte resulterend in veranderingen in het glucose metabolisme. Zowel delier als het gebruik van antipsychotica zijn in verband gebracht met stoornissen in glucosespiegels, maar de relatie tussen de behandeling met antipsychotica, delier en glucose is niet bekend. Het doel van dit proefschrift is het beantwoorden van de vraag of de behandeling met antipsychotica is geassocieerd met veranderingen in glucosespiegels, of glucose variabiliteit is geassocieerd met het optreden van een delier, en of de glucose variabiliteit anders is tijdens een delier bij oudere patiënten.

Hoofdstuk 2 beschrijft het risico op een ziekenhuisopname wegens hypoglykemie bij oudere patiënten met diabetes tijdens het gebruik van antipsychotica. Een patiëntcontroleonderzoek werd uitgevoerd met gegevens afkomstig uit de PHARMO database met aflevergegevens van medicatie uit openbare apotheken en ontslaggegevens uit ziekenhuizen. Het cohort bestond uit patiënten met een leeftijd van 65 jaar of ouder met tenminste één jaar aan medicatiehistorie tussen januari 1998 en december 2008 en minimaal drie receptregels binnen één jaar voor insuline en/of orale bloedsuikerverlagende middelen of diabetes als ontslagdiagnose uit het ziekenhuis. Binnen dit cohort werden 815 patiënten geïdentificeerd die met een hypoglykemie in het ziekenhuis werden opgenomen. Voor iedere patiënt met een hypoglykemie werden maximaal vijf controles uit hetzelfde cohort geselecteerd. Het gebruik van antipsychotica voorafgaand aan de

ziekenhuisopname werd bestudeerd. De associatie tussen antipsychoticagebruik en het risico op een ziekenhuisopname wegens hypoglykemie is onderzocht met behulp van logistische regressie, waarbij rekening is gehouden met potentiële confounders. Huidig antipsychoticagebruik werd geassocieerd met een verhoogd risico op een hypoglykemie in vergelijking met geen gebruik (gecorrigeerde OR: 2.26; 95% betrouwbaarheidsinterval (BI): 1.45-3.52), met name tijdens de eerste dertig dagen van de antipsychoticabehandeling (gecorrigeerde OR: 7.65; 95% BI: 2.50-23.41) en bij hogere doseringen (gecorrigeerde OR: 8.20; 95% BI: 3.09-21.75). Deze bevindingen suggereren dat extra aandacht voor bloedglucosecontrole nodig is na het starten van antipsychotica bij ouderen met diabetes.

In **Hoofdstuk 3**, **Hoofdstuk 4** en **Hoofdstuk 5** worden onderzoeken beschreven onder patiënten die opgenomen zijn in het ziekenhuis op niet-IC afdelingen. **Hoofdstuk 3** beschrijft een patiëntcontroleonderzoek bij oudere patiënten die zijn opgenomen in het ziekenhuis. Het onderzoek bestudeert het gebruik van antipsychotica en het risico op hyperglykemie en hypoglykemie. Alle patiënten met een leeftijd van 70 jaar en ouder die werden opgenomen in een algemeen ziekenhuis (Tergooi) in de periode tussen 2010 en 2014 met een normale bloedglucosewaarde bij ziekenhuisopname en met minimaal één additionele bloedglucosewaarde zijn geïncludeerd. Uit deze groep zijn patiënten geselecteerd met een hyperglykemie (bloedglucosewaarde ≥ 11.1 mmol/L) en met een hypoglykemie (bloedglucosewaarde ≤ 3.5 mmol/L) tijdens ziekenhuisopname. Voor elke patiënt met een hyperglykemie of hypoglykemie werden maximaal vijf controles geselecteerd. Het gebruik van antipsychotica voorafgaand aan de hyperglykemie of hypoglykemie werd bestudeerd. De associatie tussen antipsychoticagebruik en hyperglykemie ofwel hypoglykemie is onderzocht met behulp van logistische regressie, waarbij rekening is gehouden met potentiële confounders als diabetes en het gebruik van bloedglucoseverlagende middelen. In totaal zijn 2.054 patiënten geïncludeerd, waarvan 483 (23,5%) patiënten een hyperglykemie en 43 (2,1%) patiënten een hypoglykemie kregen. Haloperidol was het meest voorgeschreven antipsychoticum (hyperglykemie: 47 cases en 64 controles en hypoglykemie: 3 cases en 9 controles). Huidig gebruik van haloperidol was niet geassocieerd met een hyperglykemie (gecorrigeerde OR: 1.34, 95% BI: 0.81-2.21) of hypoglykemie (OR: 0.66, 95% BI: 0.17-2.63). Mogelijk vonden wij geen bewijs voor een associatie tussen haloperidol en hypoglykemie vanwege een onvoldoende grote steekproef. Wel vonden wij een associatie tussen haloperidol die gestart was in het ziekenhuis en hyperglykemie (gecorrigeerde OR: 2.02, 95% BI: 1.01-4.03). Onze bevindingen suggereren dat extra aandacht voor bloedglucosecontrole nodig is na het starten van haloperidol in het ziekenhuis.

Het onderzoek in **Hoofdstuk 4** beschrijft veranderingen in bloedglucosewaarden tijdens het gebruik van haloperidol in vergelijking met placebo bij oudere patiënten die opgenomen zijn in het ziekenhuis. Dit onderzoek is een onderdeel van het HARPOON onderzoek ('haloperidol preventie in oudere patiënten opgenomen in het ziekenhuis via de spoedeisende hulp'). Alle patiënten met een leeftijd van 70 jaar en ouder met een verhoogd risico op een delier tijdens ziekenhuisopname werden gevraagd voor

deelname aan dit multicenter, gerandomiseerd, dubbel blind, placebo-gecontroleerd klinisch onderzoek. Deelnemende patiënten werden gerandomiseerd voor het gebruik van 1 mg haloperidol of placebo twee maal daags gedurende zeven opeenvolgende dagen (14 giften). Het gebruik van corticosteroïden en veranderingen in het gebruik van bloedglucose verlagende geneesmiddelen waren exclusiecriteria voor deelname aan deze substudie. Bloedglucosewaarden werden bepaald uit venapuncties die op willekeurige momenten op dag 1 en dag 6 van de studie werden afgenomen. Een T-toets werd gebruikt om het verschil in bloedglucosewaarden tussen haloperidol en placebogebruikers te toetsen. Negenentwintig patiënten namen deel aan dit onderzoek (haloperidol n = 14 en placebo n = 15). De gemiddelde bloedglucosewaarde voor placebogebruikers was 7,7 mmol/L standaarddeviatie (SD) 2,8 op dag 1 en 7,8 mmol/L SD 2,8 op dag 6 en voor haloperidol gebruikers 7,8 mmol/L SD 3,9 op dag 1 en 8,3 mmol/L SD 3,2 op dag 6. Het verschil tussen beide dagen voor placebogebruikers was 0,1 mmol/L SD 3,2 en voor haloperidolgebruikers 0,6 mmol/L SD 3,2. Dit verschil was niet significant afwijkend (p = 0.685).

Het doel van **Hoofdstuk 5** was het bepalen van de glucosevariabiliteit bij oudere patiënten met en zonder delier in een prospectief, observationeel onderzoek op de geriatrische trauma unit en de afdeling orthopedie van een algemeen ziekenhuis in de periode tussen februari 2014 en februari 2015. Inclusiecriteria voor dit onderzoek waren een leeftijd van 70 jaar of ouder, een ziekenhuisopname voor een heupoperatie en een verhoogd risico op een delier. Patiënten werden binnen 24 uur na opname geïncludeerd. Exclusiecriteria waren wilsonbekwaamheid bij ziekenhuisopname, diabetes en deelname aan een geneesmiddelenonderzoek. De bloedglucosewaarde werd viermaal daags gemeten met een point-of-care test vanaf de operatie tot ontslag uit het ziekenhuis. De glucosevariabiliteit, gedefinieerd als de gemiddelde absolute glucose verandering ('MAG change') werd bepaald met alle bloedglucosewaarden. De 'MAG change' wordt berekend als de som van de absolute verschillen tussen alle opeenvolgende bloedglucosewaarden gedeeld door de tijd tussen de eerste en de laatste bloedglucosewaardebepaling (in uren). Secondaire eindpunten waren andere maten van glucosevariabiliteit, te weten de gemiddelde bloedglucosewaarde (mmol/L) en SD (mmol/L), variatiecoëfficiënt (CV, mmol/L), gemiddelde dagelijkse delta, hypoglykemie (bloedglucosewaarde ≤ 3,9 mmol/L) en hyperglykemie (niet-nuchtere bloedglucosewaarde ≥ 11.0 mmol/L). Van de 331 gescreende patiënten voldeden 123 patiënten aan de inclusiecriteria. Hiervan werden 66 patiënten geëxcludeerd vanwege wilsonbekwaamheid bij ziekenhuisopname, 27 patiënten omdat ze diabetes hadden en 18 patiënten hadden geen interesse in deelname. Er werden 12 patiënten geïncludeerd (10,2% van het verwachte aantal patiënten) voordat de studie voortijdig werd beëindigd vanwege inclusieproblemen. Tijdens het onderzoek werden 142 bloedglucosewaarden bepaald. Dit aantal was onvoldoende om de associatie tussen delier en glucosevariabiliteit te toetsen. Twee van de 12 patiënten ontwikkelden een delier (incidentie: 16,7%). Eén van deze twee patiënten liet de hoogste glucosevariabiliteit ('MAG change': 0,44 mmol/L/uur, SD: 2,8 mmol/L, CV: 0,32 mmol/L, gemiddelde dagelijkse delta: 5,42 mmol/L) en het vaakst een hyperglykemie (4) zien.

Deze bevinding ondersteunt de hypothese dat een delier mogelijk is geassocieerd met een hogere glucosevariabiliteit. Verder laat deze studie de moeilijkheden zien die spelen bij de uitvoering van wetenschappelijk onderzoek onder oudere patiënten. Voor toekomstig delieronderzoek is het nodig dat mogelijkheden om patiënten met het hoogste delierrisico, de wilsonbekwame patiënten, te includeren worden verruimd.

Het onderzoek dat wordt beschreven in **Hoofdstuk 6** en **Hoofdstuk 7** is uitgevoerd bij IC-patiënten. Een prospectief cohort onderzoek werd uitgevoerd op de medische en chirurgische IC van het Universitair Medisch Centrum Utrecht (UMCU). Patiënten werden geïncludeerd bij een IC opname langer dan 24 uur. Patiënten werden geëxcludeerd bij neurologische ziekten, bij doofheid (omdat doofheid de delierbeoordeling bemoeilijkt) of als communicatie in het Nederlands of Engels onmogelijk was. De mentale status werd dagelijks op de IC geëvalueerd met behulp van een gevalideerd algoritme en geclassificeerd als wakker en niet delirant, delirant of comateus.

In **Hoofdstuk 6** onderzochten we of diabetes en glucoseontregelingen (hyperglykemie en/of hypoglykemie) risicofactoren zijn voor een delier op de IC. We selecteerden ernstig zieke patiënten die waren opgenomen op de IC in de periode tussen januari 2011 en juli 2016 met een mentale status van wakker en niet delirant op één willekeurige IC-dag (dag *t*) en de volgende dag delirant waren geworden of wakker en niet delirant bleven. Diabetes en glucoseontregelingen werden bestudeerd op dag *t*. Diabetes werd gedefinieerd als bij IC-opname de medische status diabetes (aandoening of behandeling) vermelde of wanneer de patiënt voor ziekenhuisopname bloedglucose verlagende geneesmiddelen in gebruik had. Glucoseontregeling werd onderzocht in vier categorieën. 'Hyperglykemie' was aanwezig wanneer minimaal één bloedglucosewaarde > 8.0 mmol/L werd gemeten op dag *t* en 'hypoglykemie' was aanwezig wanneer minimaal één bloedglucosewaarde < 3.5 mmol/L werd gemeten op dag *t*. 'Zowel hyperglykemie als hypoglykemie' was positief wanneer aan de voorwaarden voor hyperglykemie en hypoglykemie op dag *t* werd voldaan. Dag *t* was gecategoriseerd als 'normale bloedglucosewaarden' wanneer geen van de bloedglucosewaarden voldeed aan de definitie van hyperglykemie of hypoglykemie. Gegeneraliseerde mixed-effects-modellen met logit-link-functie werden gebruikt om de associatie tussen diabetes, glucoseontregelingen en delier te onderzoeken waarbij rekening werd gehouden met potentiële confounders. De onderzoekspopulatie bestond uit 2.745 patiënten. Er werden 1.720 transities van wakker en niet delirant naar delirant geïdentificeerd en 11.421 dagen waarbij patiënten wakker en niet delirant bleven. Van de onderzoekspopulatie hadden 543 (19.8%) patiënten diabetes en van deze groep hadden 225 (41.4%) patiënten een delier tijdens IC-opname. Van de 2.202 patiënten zonder diabetes hadden 902 (41.0%) patiënten een delier gehad tijdens IC-opname. Diabetes was niet geassocieerd met een delier (gecorrigeerde OR: 0.93; 95% BI: 0.73-1.18). In totaal werden 65.727 bloedglucosewaarden bepaald op dag *t*. Hypoglykemie liet geen significant verhoogd risico op een transitie naar een delier zien (gecorrigeerde OR: 1.86; 95% BI: 0.73-3.71). Alleen bij patiënten zonder diabetes was het optreden van een hyperglykemie (gecorrigeerde OR: 1.41;

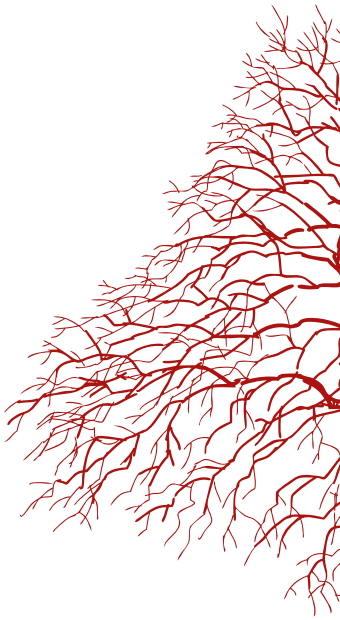
95% BI: 1.16-1.68) en het optreden van zowel een hyperglykemie als hypoglykemie op dezelfde dag (gecorrigeerde OR: 1.87; 95% BI: 1.07-2.89) geassocieerd met een transitie naar delier. We vonden geen associatie tussen diabetes en het optreden van een delier op de IC. Hyperglykemie verhoogde het risico op IC delier, maar alleen bij patiënten zonder diabetes. Ondanks dat de associatie tussen hypoglykemie en delier niet significant was, was de OR 1.86 op de transitie naar delier de volgende dag. Dit onderzoek draagt bij aan het begrip van de etiologie van een delier en suggereert het gebruik van middelen om hyperglykemie te voorkomen.

In **Hoofdstuk 7** onderzochten we of maten van glucosevariabiliteit tijdens delierdagen anders zijn in vergelijking met niet delierdagen bij ernstig zieke patiënten met en zonder diabetes. We selecteerden ernstig zieke patiënten die werden opgenomen op de IC tussen januari 2011 en juni 2013 met minimaal één delirante en minimaal één wakker en niet delirante IC dag. De glucosevariabiliteit werd van elke dag bepaald met de gemiddelde bloedglucosewaarde en SD, 'MAG change', dagelijkse delta en het optreden van hypoglykemie (hypoglykemie: bloedglucosewaarde < 3.5 mmol/L en ernstige hypoglykemie: bloedglucosewaarde < 2.2 mmol/L) en hyperglykemie (hyperglykemie: bloedglucosewaarde > 8.0 mmol/L en ernstige hyperglykemie: bloedglucosewaarde > 11.0 mmol/L). We gebruikten de multilevel analyse technieken lineaire mixed-effects-modellen en generaliseerde mixed-effects-modellen met logit-link-functie om de associaties tussen delier en glucosevariabiliteit te onderzoeken. Voor deze analyse werden 410 patiënten geselecteerd met 1.233 delierdagen en 1.775 niet delierdagen. We vonden geen verschil in glucosevariabiliteit op delierdagen in vergelijking met niet delierdagen gemeten met de gemiddelde bloedglucosewaarde, SD, 'MAG change', dagelijkse delta en het optreden van hyperglykemie in patiënten met en zonder diabetes. Verder hebben wij laten zien dat delier is geassocieerd met hypoglykemie in patiënten met diabetes (gecorrigeerde OR: 2.78; 95% BI: 1.71-6.32), maar niet in patiënten zonder diabetes (gecorrigeerde OR: 1.16; 95% BI: 0.58-2.28). Deze bevindingen suggereren dat bloedglucosewaarden nauwkeurig moeten worden gemonitord bij patiënten met diabetes op de IC tijdens een delier om een hypoglykemie te voorkomen.

In **Hoofdstuk 8**, de algemene discussie, worden de bevindingen uit dit proefschrift in een breder perspectief geplaatst. De onderwerpen die aan bod komen zijn het analyseren en de interpretatie van bloedglucosemetingen, de belemmeringen van het doen van onderzoek in de geriatrische populatie en de wisselwerking tussen delier, antipsychotica en de glucose homeostase.

Concluderend heeft dit proefschrift de kennis vergroot over de wisselwerking tussen antipsychotica, delier en de glucose homeostase in de oudere algemene populatie en bij oudere patiënten opgenomen in het ziekenhuis op niet-IC afdelingen, en bij IC-patiënten. De beschreven bevindingen bij IC-patiënten ondersteunen de hypothese dat delier werkt op de glucose homeostase en andersom. De wisselwerking tussen delier en glucose was anders bij patiënten met diabetes in vergelijking met patiënten zonder diabetes, wat een

ander onderliggend mechanisme waarschijnlijk maakt. Glucoseontregelingen mogen worden toegevoegd aan de lijst met bijwerkingen die optreden tijdens het gebruik van antipsychotica bij oudere patiënten. Het absolute risico op deze bijwerking lijkt klein, maar de gevolgen voor de individuele patiënt kunnen groot zijn.



Dankwoord

Dankwoord

Met het schrijven van het dankwoord gaan de laatste woorden van dit proefschrift op papier. Net na de start van mijn opleiding tot ziekenhuisapotheker was het mijn opleider Rutger Stuffken die bij mij polste of ik geen interesse had in het doen van promotieonderzoek. Ik was nieuwsgierig en enthousiast, al had ik toen geen idee welk pad ik exact in zou slaan. Een brainstorm met Rutger Stuffken, Paul van der Linden en Toine Egberts volgde over mogelijke onderwerpen binnen de geriatrie en de eerste zaadjes werden geplant medio 2011. Al is het een individueel pad dat je bewandelt, het is onmogelijk dit pad alleen te bewandelen. Velen hebben direct of indirect een bijdrage geleverd aan dit proefschrift. Een aantal personen wil ik graag persoonlijk bedanken.

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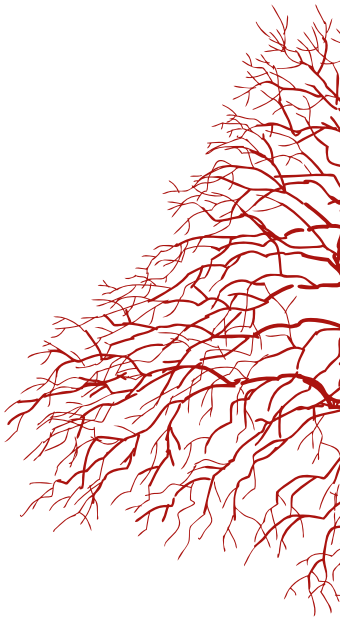
Kris, februari 2018.



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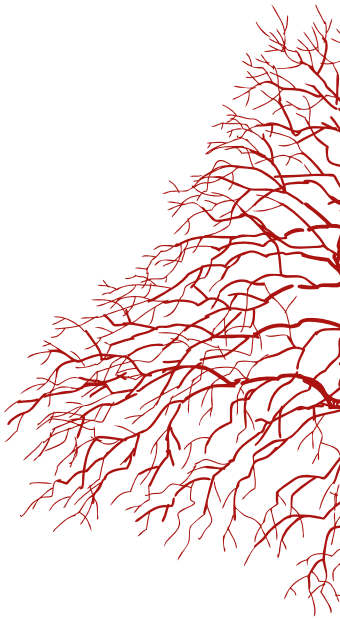

List of publications

Publications related to this thesis

Risk of hospitalization for hypoglycemia in older patients with diabetes using antipsychotic drugs.
K. van Keulen, P.D. van der Linden, P.C. Souverein, E.R. Heerdink, A.C.G. Egberts, W. Knol.
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K. van Keulen, P.D. van der Linden, P.C. Souverein, E.R. Heerdink, A.C.G. Egberts, W. Knol.
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Hyperglycemia and hypoglycemia in older hospitalized patients using antipsychotic drugs.
K. van Keulen, P.D. van der Linden, L.C. Sijtsma, A. de Jonghe, A.C.G. Egberts, E.R. Heerdink, W. Knol.
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K. van Keulen, P.D. van der Linden, A. de Jonghe, A.C.G. Egberts, E.R. Heerdink, W. Knol.
Submitted

Diabetes and glucose dysregulation and transition to delirium in intensive care unit patients.
K. van Keulen, W. Knol, S.V. Belitser, P.D. van der Linden, E.R. Heerdink, A.C.G. Egberts, A.J.C. Slooter.
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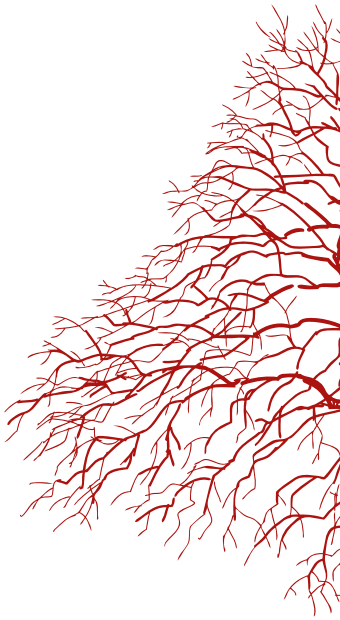

Curriculum Vitae

Curriculum Vitae

Kris van Mastrigt-van Keulen was born on September 15th 1982 in Zwolle and grew up in Wijhe, the Netherlands. After graduating in 1999 from the secondary school at the Florens Radewijns College (HAVO) in Raalte, she studied 'Agroproduktkunde', a study on food technology and marketing at the Van Hall Larenstein in Velp. She obtained her first year certificate in 2000.

Thereafter, she started Pharmacy at the University of Groningen. After graduation in 2007, she started her professional career as a pharmacist at the department of Clinical Pharmacy of Tergooi Hospital (locations Hilversum and Blaricum), the Netherlands. In October 2010, she started her training as hospital pharmacist in the same hospital, and a short year of the traineeship was conducted at the department of Clinical Pharmacy of the University Medical Center Utrecht, the Netherlands. From 2012 onwards she has been working on the studies described in this thesis parallel, to her training as hospital pharmacist, in collaboration with the Division of Pharmacoepidemiology and Clinical Pharmacology on the Utrecht Institute for Pharmaceutical Sciences of the Utrecht University and the department of Clinical Pharmacy of the University Medical Center Utrecht, the Netherlands. She finished her traineeship successfully in 2014, and from then she worked as a hospital pharmacist-clinical researcher in Tergooi Hospital.

Since June 2017, she works as a hospital pharmacist at the department of Clinical Pharmacy in the Amstelland Hospital in Amstelveen, the Netherlands.

Kris van Mastrigt-van Keulen lives together with Peter van Mastrigt in Amersfoort, and they are the proud parents of their son Tijn.