High Prevalence of Hypoglycemia in People Above the Age of 75 without Diabetes Mellitus

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Abstract

Background: Hypoglycemia, especially at old age, can lead to several major problems, such as falls and cognitive deficits. The aim of our study was to detect hypoglycemia in older persons with and without diabetes mellitus type 2 (T2DM).

Methods: The frequency and duration of hypoglycemia/hyperglycemia was studied in ambulatory geriatric (>75 years), non-diabetic persons (Group 1, n=10), using real time Continuous Glucose Monitoring (CGM, Dexcom G6), and in age- and sex-matched cognitively-healthy, T2DM patients having HbA1c levels < 9.0% (Group 2, n=10). The device was used during 20 days per person, who was blinded for the values on the receiver (except in case of severe hypo- or hyperglycemia). Data were stored for further analysis on the Dexcom Clarity Portal.

Results: Hypoglycemia occurred frequently in older persons without T2DM, despite absence of hypoglycemia-inducing medication. In this group, people had 0.50% (median value) of the time glycemic values below 70 mg/dL, most of the episodes happened during nighttime.

Conclusions: Our study demonstrates that hypoglycemia occurs frequently in non-diabetic older persons. Further studies are needed to determine whether this could be part of the normal aging process, and to determine if hypoglycemia might contribute to cognitive deterioration.

Background

The occurrence of hypoglycemia is a well-known problem in the treatment of patients with diabetes mellitus (DM) type 1 (T1DM) and type 2 (T2DM), but little is known about hypoglycemia in elderly people without DM.

Older individuals with DM are at a notably higher risk for severe hypoglycemia due to age, duration of DM, duration of insulin therapy, and higher prevalence of hypoglycemia unawareness [1, 2]. Hypoglycemia is often underdiagnosed and can lead to several complications, such as falls, fall-related fractures, epileptic seizures, cognitive deficits, and persistent frailty [3, 4]. Also, the similarity between symptoms of hypoglycemia and symptoms of dementia, such as confusion, agitation and behavioural changes, may lead to missed diagnosis of hypoglycemic episodes in older people [5].

Prevention of hypoglycemia is especially important for elderly persons with long-lasting DM and associated complications, who are prone to asymptomatic hypoglycemia [6, 7]. HbA1c levels give an indication of the average glycemic value, but not of the glycemic variability. Appropriate treatment is essential using specific target values for metabolic control. Different target values for HbA1c for different age groups have been proposed [6, 8]. Hypoglycemia is associated with cognitive and functional decline in older people with diabetes. Identification of individuals at risk and prevention of hypoglycemia is therefore an important task in the management of diabetes in home-dwelling older people with diabetes [5].

It is well known that T2DM increases the risk for cognitive decline and dementia such as Alzheimer's disease (AD) and vascular dementia [9, 10, 11]. It has been established that increased prevalence of hypoglycemia

can worsen cognitive decline in T2DM patients.

Continuous Glucose Monitoring (CGM) can be used to measure hypoglycemia rate, duration and glycemic variability. Several devices for CGM are available: Dexcom (G4, G5 and G6), Medtronic (Guardian Connect and Guardian Sensor 3), Senseonics Eversense and Abbott (FreeStyle Libre and FreeStyle Libre 2). Safe and effective therapeutic decision-making can be facilitated by establishing target percentages of time in the various glycemic ranges, hoping to meet the specific needs of special diabetes populations. The primary goal for effective and safe glucose control is to increase the Time in Range (TIR), while reducing the Time Below target glucose Range (TBR). These CGM-based targets must be personalized if applied to individual DM patients [1].

Very little is known about the occurrence of hypoglycemia as part of the normal ageing process in non-diabetic elderly people and secondly, if the incidence of hypoglycemia is associated with cognitive decline. There is one report by Adolfsson et al. showing a lower fasting glucose in persons with AD [12]. In addition, it has been demonstrated that hypoglycemia occurs in non-DM hospitalized patients [13]. Blood glucose levels also need to be screened in other settings, and especially during common infections, also in nondiabetics, to identify persons at high risk for infection-related hypoglycemia (IRH). Arinzon et al. made a comparative study of diabetic and nondiabetic persons and IRH seems to indicate a poor general health status rather than being the cause of death [14].

Various physiological mechanisms are involved to prevent hypoglycemia: glucagon and norepinephrine play an important role in correcting hypoglycemia in normal human physiology. It could be possible that the impairment of the central sympathetic autonomic nervous system negatively facilitates the occurrence of hypoglycemia [15].

If present, autonomic neuropathy in normal ageing could contribute to a higher risk of hypoglycemia and subsequently enhance cognitive decline. To our knowledge, no studies are available that have addressed this issue.

The aim of our study was to detect hypoglycemia in elderly non-DM people using CGM and to compare this to a DM control group.

Methods

Study participants

This study analyzed the frequency and duration of hypoglycemia in older non-DM persons (Group 1) compared to an age- and sex-matched DM control group on oral anti-DM and/or insulin therapy (Group 2) using real time CGM. Persons using only metformin were included in Group 1, since this therapy is not associated with a risk for hypoglycemia.

In this study, each Group consisted of 10 subjects, aged 75 years or older. Participants of Group 1 and 2 were selected by screening the consultation lists and the list of “robust” subjects who already finished the

BUTTERFLY study (BrUssels sTudy on The Early pRedictors of FrailtY), a longitudinal observational cohort study with a two-year follow-up [16]. Participants were recruited between September 2020 and May 2021.

The inclusion criteria for Group 2 were T2DM based on the ADA-criteria, and HbA1c less than 75 mmol/mol.

Participants selected for both Groups were excluded, if they had a neurocognitive dysfunction, confirmed by an MMSE-score ($\leq 24/30$) or if they were diagnosed with cancer the previous six months prior to the study.

Data collection

The following clinical data were collected for both Groups: age, sex, weight, medical history, clinical findings, medication, HbA1c-level and MMSE-score.

The data regarding glycemia were obtained using the Dexcom G6 device. CGM has repeatedly been described in previous studies [17, 18]. Glucose is measured in interstitial fluid using the glucose oxidase method through fluorescence by using a subcutaneous sensor. The values are sent to a receiver with Bluetooth technology [17, 18]. The participants were monitored for a period of 20 days. After 10 days, the sensor was changed. The CGM-data were uploaded and stored for further analysis after the study period of 20 days on the Dexcom Clarity Portal.

During the entire study period, the participants were not able to observe the actual values of their glucose measurements. This blinded use avoided any influence in lifestyle of the participants concerning exercise, food intake or medication. No adjustments were made to the treatment in Group 2 during the study period, unless severe hypo- or hyperglycemia was observed (glucose < 54 mg/dL or > 250 mg/dL).

Outcomes

The CGM data were analyzed by measuring the following variables: total number of hypoglycemic episodes and duration (glucose <70 mg/dL); the number of nocturnal hypoglycemic episodes (between 22.00 h pm and 7.00 h am); the severity of hypoglycemia (<70 mg/dL or <54 mg/dL); glucose variability; TIR (70-180 mg/dL [1]); HbA1c.

The ethical committee of the University Hospital of Brussels approved the study. Participants received all necessary information and gave a written informed consent.

All methods were performed in accordance with the relevant guidelines and regulations.

Statistical analysis

Data are given as median values and interquartile range. An unpaired t-test was used for comparison of Group 1 and 2.

Results

Demographic information

Table 1 shows the demographic information for all participants. The study was completed by 19 participants; one participant from Group 1 dropped out. No significant differences were noted between the Groups for median age, weight, or MMSE. There was a statistical difference ($p < 0.0001$) in mean HbA1c between the Groups 1 and 2.

Table 1
Patient demographic information: median [IQR]

Median [InterQuartile Range]		
	Group 1 (10 patients)	Group 2 (10 patients)
Age	82 [79 – 87]	85.5 [82 – 86]
Gender (Male / Female)	6/4	5/5
Bodyweight (kg)	75 [68 – 85]	70.5 [65 – 82]
MMSE-score	28 [26 – 29]	28 [25 – 29]
HbA1c (%)	5.55 [5.4 – 5.6]	7.1 [6.6 – 7.3]
Medication (N)		
- Metformin	1	3
- Insulin	0	5
- SU	0	3
- Glinides	0	2
- DPP-4 inhibitor	0	3
- GLP-1 analog	0	0
- SGLT-2 inhibitor	0	2
IQR = InterQuartile Range; N= Number		

Hypoglycemia

Table 2 shows CGM outcomes and HbA1c levels for all participants. Table 3 shows the median values for Group 1 and 2. Hypoglycemia was detected in both groups (median values: 0.50 % of the time vs 0.00 % of the time for Group 1 and 2 respectively, $p = 0.551$).

Table 2
CGM outcomes for Group 1 and Group 2.

Group 1									
	Gender	% Time CGM Active	HbA1c	TIR (70-180 mg/dL)	High (>180 mg/dL)	Very high (>250 mg/dL)	Low (<70 mg/dL)	Very Low (<54 mg/dL)	Coefficient of Variation
ID 1	Male	75.80%	5.40%	97.00%	2.90%	0.00%	0.10%	0.00%	20.4%
ID 4	Female	84.40%	5.00%	95.20%	3.70%	0.00%	1.00%	0.30%	22.70%
ID 5	Female	97.50%	5.60%	98.30%	1.10%	0.00%	0.60%	0.10%	19.00%
ID 7	Male	99.50%	5.40%	99.50%	0.00%	0.00%	0.50%	0.10%	15.20%
ID 8	Male	99.60%	5.60%	99.10%	0.80%	0.10%	0.10%	0.00%	16.00%
ID 9	Female	99.60%	5.20%	96.90%	0.40%	0.00%	2.70%	0.40%	19.80%
ID 10	Female	99.40%	5.50%	98.30%	1.70%	0.00%	0.00%	0.00%	18.20%
ID 11	Female	99.20%	5.60%	98.50%	0.20%	0.00%	1.30%	0.30%	18.00%
ID 12	Male	96.60%	6.20%	88.50%	11.30%	0.70%	0.10%	0.00%	27.40%
ID 19	Male	98.80%	6.10%	90.10%	9.40%	0.10%	0.50%	0.20%	24.90%
Group 2									
	Gender	% Time CGM Active	HbA1c	TIR (70-180 mg/dL)	High (>180 mg/dL)	Very high (>250 mg/dL)	Low (<70 mg/dL)	Very Low (<54 mg/dL)	Coefficient of Variation
ID 2	Male	99.30%	7.40%	40.40%	59.60%	17.60%	0.00%	0.00%	23.80%
ID 3	Male	100.00%	7.80%	61.60%	37.70%	8.70%	0.70%	0.20%	35.60%
ID 6	Male	98.60%	7.30%	41.20%	55.20%	20.20%	3.50%	0.60%	37.10%
ID 13	Male	99.50%	7.20%	28.90%	71.10%	32.50%	0.00%	0.00%	29.40%
TIR: Time In Range									

Group 1									
ID 14	Male	97.80%	6.90%	71.10%	28.80%	4.50%	0.00%	0.00%	24.30%
ID 15	Female	87.00%	7.40%	57.60%	42.40%	8.80%	0.00%	0.00%	23.20%
ID 16	Female	85.9%	7.40%	63.70%	36.20%	9.00%	0.20%	0.10%	30.60%
ID 17	Female	64.80%	7.00%	71.60%	28.40%	1.20%	0.00%	0.00%	18.00%
ID 18	Male	99.00%	6.20%	80.10%	19.90%	1.40%	0.00%	0.00%	20.20%
ID 20	Female	76.80%	5.60%	34.60%	65.40%	13.00%	0.00%	0.00%	20.00%
TIR: Time In Range									

Table 3
Median values for Group 1 and Group 2

Median [IQR]								
	% Time CGM Active	HbA1c	TIR (70-180 mg/dL)	High (>180 mg/dL)	Very high (>250 mg/dL)	Low (<70 mg/dL)	Very Low (<54 mg/dL)	Coefficient of Variation
Group 1	99.00 [96.60 – 99.50]	5.55 [5.4 – 5.6]	97.65 [95.20 – 98.50]	1.40 [0.40 – 3.70]	0.00 [0.00 – 0.10]	0.50 [0.10 – 1.00]	0.10 [0.00 – 0.30]	19.40 [18.00 – 22.70]
Group 2	98.20 [85.90 – 99.30]	7.1 [6.6 – 7.3]	59.6 [40.40 – 71.10]	40.05 [28.80 – 59.60]	8.90 [4.50 – 17.60]	0.00 [0.00 – 0.20]	0.00 [0.00 – 0.10]	24.05 [20.20 – 30.60]
p-value	0.354	<0.0001	<0.0001	<0.0001	0.0008	0.551	0.497	0.017
TIR: Time In Range								
IQR: InterQuartile Range								
p-value: using the unpaired T-test								

In Group 1, periods of hypoglycemia were detected in nine participants, of whom six had values less than 54 mg/dL. Most of the episodes happened during the nighttime. In Group 2, there were only three participants with hypoglycemic values, of which one had frequent hypoglycemia. This latter participant had

hypoglycemic values during the daytime as well as during the night. In Group 2, participants with a high Coefficient of Variation had more hypoglycemia. This correlation was not seen in Group 1.

The median value and IQR for TIR were significantly lower in Group 2 compared to Group 1 ($p < 0.001$). There was a large variation in values for TIR in the diabetic group despite similar HbA1c levels. Hyperglycemia was significantly more present in Group 2 (especially during daytime, $p < 0.0001$).

Discussion

To our knowledge, this study is the first to demonstrate that hypoglycemia occurs in elderly persons without DM using CGM despite absence of hypoglycemia-inducing medication. It was demonstrated that participants in the non-DM Group reached glycemic values below 70 mg/dL during 0.5% of the time. The DM Group 2 showed in general a greater glucose variability. Nevertheless, they had no higher percentage of time spent in hypoglycemia.

The strengths of this study are that two well-defined groups of elderly persons were evaluated and almost all participants wore their sensor during the whole study period. A weakness is the small number of participants in both study Groups and the relatively short duration of the study. Therefore, the results should be explored in larger groups and for longer periods.

Most interestingly is the finding that hypoglycemia occurs in the non-DM group. This has not been demonstrated previously in studies using CGM. One could speculate whether hypoglycemia is an intrinsic characteristic of the natural aging process, although no tests were done to rule out secondary causes for hypoglycemia. If hypoglycemia is part of the natural aging process, it may also play a role in the development of Mild Cognitive Impairment and its progression to AD [19].

It is well known that T2DM increases the risk for cognitive decline and dementia such as AD and vascular dementia [9, 10, 11]. Some studies described even a form of dementia named DM-related dementia, a dementia subgroup associated with specific DM related metabolic abnormalities. It is characterized by less well-controlled glycemia [8, 18]. Some of these people showed neither significant medial temporal lobe atrophy on magnetic resonance imaging (MRI), nor parietotemporal hypoperfusion on single-photon emission computed tomography (SPECT), which are characteristic features of AD. In addition, they show no cerebrovascular disease lesions on MRI that could be responsible for cognitive impairment [9, 20, 21]. Ogawa et al. [9] found that MMSE scores correlated significantly and inversely with mean glucose, HbA1c, and the percentage of time in hyperglycemia in people with DM-related dementia. These people showed significantly greater glucose variability and significantly higher percentage of time spent in hypoglycemia than people with AD and DM. Additionally, Ogawa et al. [9] observed that glycemic controls can improve some domains of cognitive function, such as attention and executive functions, determined by the Trail-Making Test Part A and B [22]. A study by Biessels et al [19] showed that many patients with MCI progress to dementia and that the coexistence of DM may increase the risk for progression of cognitive deterioration.

Hypoglycemia is a frequent complication of DM treatment, and it is considered an independent risk factor for dementia in patients with T2DM [23]. The possible pathophysiological processes include post-hypoglycemic

neuronal damage, inflammatory processes, coagulation defects, endothelial abnormalities, and synaptic dysfunction of hippocampal neurons during hypoglycemic episodes [23].

Few data are available if hypoglycemia occurs in elderly persons, and if it plays a role in promoting cognitive decline: Adolfsson et al. compared the fasting glucoseemia in AD patients, in patients with distal gangrene, with cerebrovascular disease and non-DM controls. They found that the fasting glycemia was significantly lower in people with AD than in the other three groups [12]. On the other hand, Cukierman-Yaffe et al. concluded that hypoglycemia did not increase the risk of incident cognitive dysfunction in middle-aged individuals with dysglycemia [24]. It has recently been demonstrated that hindbrain astrocytes stimulate catecholaminergic neurons to counteract hypoglycemia [25]. One could speculate whether impairment of this system due to aging, could impair the response to hypoglycemia.

Conclusions

We observed that hypoglycemia is common in non-DM persons. Very little is known about the prevalence of hypoglycemia in the normal aging process, where it could occur perhaps as part of central autonomic neuropathy and impaired contra-regulatory mechanisms to prevent hypoglycemia in the elderly. Hypoglycemia could well contribute to cognitive decline in both MCI and AD patients.

In the future, larger prospective trials with different populations (DM vs. non-DM, dementia vs. MCI vs. no known cognitive decline) should be performed in order to evaluate the influence of ageing on glucose values and the effect of hypoglycemia on cognition.

Abbreviations

T2DM = Type 2 Diabetes Mellitus

CGM = Continuous Glucose Monitoring

DM = Diabetes Mellitus

T1DM = Type 1 Diabetes Mellitus

HbA1c = Glycosylated hemoglobin

AD = Alzheimer's Disease

TIR = Time In Range

TBR = Time Below target Range

IRH = Infection-related Hypoglycemia

BUTTERFLY = BrUssels sTudy on The Early pRedictors of FrailtY

ADA = American Diabetes Association

MMSE = Mini-Mental State Examination

IQR = Interquartile Range

MRI = Magnetic Resonance Imaging

SPECT = Single-Photon Emission Computed Tomography

Declarations

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Authors' contributions

JG, SL, BB, and TM contributed in preparing the manuscript and reviewing the literature. JG and BB prepared the figures and edited the report. JG, SL, BB, TM, IB, SE and SL read and approved the final manuscript.

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Availability of data and materials

The protocol and dataset are available from the corresponding author on reasonable request

Ethics approval and consent to participate

The ethical committee of the University Hospital of Brussels approved the study. Participants received all necessary information and gave a written informed consent.

Consent for publication

Not applicable.

Competing interests

All authors state that they have no conflicts of interest.

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