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Glycemic overtreatment among very old adults with type 2 diabetes mellitus

ABSTRACT

Introduction. In older type 2 diabetes mellitus (T2DM) patients with serious comorbidities, tight glycemic control exceeds the benefits. The aim of the study was to assess glycated hemoglobin A_{1c} (HbA_{1c}) in hospitalized T2DM patients aged ≥ 80 years and to compare the level of HbA_{1c} in diabetics with and without severe hypoglycemia (SH) at admission.

Material and methods. We enrolled 166 consecutive T2DM patients ≥ 80 years of age with a wide spectrum of comorbidities hospitalized between 2009–2013.

Results. Patients' mean age was 83.72 ± 3.19 years and mean diabetes duration was 9.14 ± 5.88 years, body mass index (BMI) was 27.87 ± 4.51 kg/m² and the glomerular filtration rate (GFR) was 58.94 ± 25.87 ml/min/1.73 m². Mean HbA_{1c} for the whole group was 7.61 ± 1.87% (59.77 ± 20.48 mmol/mol). Tight glycemic control with HbA_{1c} < 7.0% (53 mmol/mol) was observed in 77 patients (46%). SH was diagnosed in 19 (11%) patients. Subjects with SH had significantly lower mean HbA_{1c} level than those hospitalized for other reason [6.38 ± 1.22 *vs.* 7.77 ± 1.88% (46.31 ± 13.36 *vs.* 61.51 ± 20.63 mmol/mol), p = 0.002]. A history of myocardial infarction and/or stroke was reported almost two-fold more frequently by the diabetics hospitalized for SH than diabetics without hypoglycaemia (47 *vs.* 28%, χ^2 = 3,03, p = 0.082). SH was diagnosed only in patients receiving insulin (n = 10) or sulfonylurea (n = 9).

Conclusion. Despite the fact, that harms of intensive hypogylcemic treatment exceed the benefits for older patients with T2DM, half of them reached tight glycemic control. Every tenth patient was hospitalized because of SH. Subjects with SH had significantly lower mean HbA_{1c} level than those hospitalized for other reason. Our observations suggest that a substantial proportion of T2DM patients ≥ 80 years may be overtreated. (Clin Diabetol 2018; 7, 2: 102–107)

Key words: type 2 diabetes mellitus, severe hypoglycemia, glycated hemoglobin A_{1c}, very old people

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Clinical Diabetology 2018, 7, 2, 102–107
DOI: 10.5603/DK.2018.0004
Received: 03.12.2017 Accepted: 17.01.2018

Introduction

As the mean life expectancy of modern societies lengthens, it is likely that a large group of geriatric population may have glucose homeostasis disorders, including type 2 diabetes (T2DM) [1]. The International Diabetes Federation estimates that worldwide prevalence of diabetes in people between the ages of 65 and 99 is 18.8% [2]. Information on the safety and efficacy of various regimens of hyperglycemia management in this age group is limited [3]. ACCORD study showed increased mortality from intensive glycemic control, especially in older adults with long duration of T2DM and high cardiovascular risk [4].

Severe hypoglycemia (SH) increases the risk of major cardiovascular events and death [5]. Given that the risk of SH and its serious consequences in the elderly is much higher than in younger T2DM patients, the treatment of hyperglycemia in this group of diabetics should be strictly individualized and less stringent. The main goal of such therapeutic strategy should be to maintain quality of life and minimize the risk of

hypoglycemia. However, due to the lack of evidence for specific targets of blood glucose concentration and glycated hemoglobin A_{1c} (HbA_{1c}) levels in the elderly, available treatment guidelines are based on date extrapolation from younger adults and expert opinions. The latest guidelines emphasize that more careful, conservative management of hyperglycemia in very old people is required due to advanced age-related changes in renal and hepatic functions, cardiovascular diseases and physical and mental limitations. According to the Polish Diabetes Association (PDA), in elderly patients with long-term diabetes and history of myocardial infarction and/or cerebral stroke, the maintenance of $HbA_{1c} \leq 8.0\%$ (64 mmol/mol) is recommended [6]. The American Diabetes Association (ADA) recommends in very complex/poor health status patients (long term care, end stage chronic illness, moderate to severe cognitive impairment) HbA_{1c} target < 8.5% (69 mmol/mol) [7]. The American Geriatrics Society also recommends individualized goals for those ≥ 65 years old, but for patients with comorbidities, poor health status and limited life expectancy even < 9% (75 mmol/mol) [8].

The aim of the study was to assess HbA_{1c} in hospitalized T2DM patients aged ≥ 80 years and to compare the level of HbA_{1c} in diabetics with and without SH at admission.

Material and methods

One hundred and sixty six of T2DM patients in the age 80 years and older (age range 80–98 years) were included in the study. All of them were referred to the internal ward between 2009–2013 because of various diabetes complications including SH or advanced age-related diseases — mainly cardiovascular and respiratory diseases. SH was diagnosed in accordance with recommendations of PDA, as well as ADA by paramedics called for help by the members of patient's family, neighbours or by the nursing homes staff [6, 7]. Immediately after the diagnosis of SH the patients received *i.v.* infusion of 20% glucose solution that caused gradual neurological recovery and the patients were transported to the hospital.

Inclusion criteria were T2DM determined from self-reported diabetes and treatment of chronic hyperglycemia implemented at least 90 days before admission. Patients were excluded if they had advanced dementia, major psychiatric disorders or any severe medical illness which caused that they were unable to participate in this study.

In the emergency room, all participants underwent physical examination and data regarding their medical history, including frequency of hypoglycaemia, were collected. Taken medications were recorded, with particular emphasis on antidiabetic drugs. The treatment regimens were classified into the following categories: (1) sulfonylurea (SU) monotherapy; (2) metformin monotherapy; (3) metformin plus SU; (4) insulin monotherapy, (5) insulin plus metformin; (6) insulin plus SU and (7) only diet.

Venous blood sample was drawn to measure plasma glucose, creatinine and urea concentration, lipids profile, activity of hepatic enzymes, and HbA_{1c} level. Using the Cockroft-Gault formula, the glomerular filtration rate (GFR) was calculated. The body mass index (BMI) was calculated by the individual's weight in kilograms divided by the square of the individual's height in meters.

The next day, the patients hospitalized for SH (group A) were asked about the onset of typical SH symptoms, their duration and intensity, type and dose of glucose-lowering medications, and about the relation between usage of these drugs and time of meal consumption. Moreover, all diabetics with SH were questioning about frequency of previous hypoglycemic episodes, and awareness of hypoglycemia. Due to occasional post-hypoglycemic amnesia some of them were not able to answer all these questions. The data from group A were compared to the data obtained from the patients with T2DM hospitalized for a different reason than hypoglycemia (group B).

This study was approved by the Bioethics Committee and conducted in accordance with the Declaration of Helsinki.

Data are expressed as mean ± standard deviation (SD), the differences between the means were evaluated using the One Way Anova test. The Pearson's χ^2 test was used for categorical variables. A P value of less than 0.05 was considered statistically significant. All statistical calculations were performed using STATISTICA v. 10.0 package (StatSoft, Tulsa, Oklahoma, United States).

Results

The clinical characteristics and laboratory parameters of the entire cohort are shown in Table 1. A total of 166 participants with known T2DM (125 women and 41 men) were included in the study. The mean age of the patients was 83.72 ± 3.19. The mean duration of diabetes was 9.14 ± 5.88 years and mean HbA_{1c} was 7.61 ± 1.87% (59.77 ± 20.48 mmol/mol). Tight glycemic control with HbA_{1c} < 7% (53 mmol/mol) was found in 77 (46%) patients. Nineteen subjects (11%) of the entire group were hospitalized for SH. Hyperglycemia was managed pharmacologically in 154 T2DM patients, while only 12 subjects were on a diet. 21 individuals were receiving hypoglycemic drugs despite the HbA_{1c}

Table 1. Clinical and laboratory characteristics of the whole study group of T2DM patients at admission

Characteristics	Total (n = 166)
Age (years)	83.72 ± 3.19
Gender	F = 125; M = 41
Duration of diabetes (years)	9.14 ± 5.88
BMI [kg/m^2]	27.87 ± 4.51
HbA_{1c} (%)	7.61 ± 1.87
HbA_{1c} [mmol/mol]	59.77 ± 20.48
Glucose at admission [mmol/l]	12.64 ± 13.88*
Creatinine [μmol/l]	108.27 ± 51.28
Urea [mmol/l]	9.76 ± 5.71
GFR [ml/min/1.73 m^2]	58.94 ± 25.87
ALT [U/l]	19.59 ± 13.34
AST [U/l]	23.60 ± 14.22
No. of patients with a previous myocardial infarction and/or cerebral stroke	50

*Note that blood glucose concentrations were measured in the emergency room approximately 20–30 minutes after *i.v.* glucose infusion administered by paramedics. Data are mean ± standard deviation. ALT — alanine aminotransferase; AST — aspartate aminotransferase; BMI — body mass index; F — female; GFR — glomerular filtration rate; HbA_{1c} — glycated haemoglobin A_{1c}; M — male

Table 2. Antidiabetic treatment regimens used by the elderly T2DM patients before hospitalization

Hypoglycemic agent	No. of patients
SU only	48 (29%)
Metformin only	25 (15%)
Metformin + SU	2 (1%)
Insulin only	41 (25%)
Insulin + metformin	27 (16%)
Insulin + SU	11 (7%)
No drugs/diet only	12 (7%)

SU — sulphonylurea

level < 6% (42 mmol/mol). Antidiabetic treatment regimens (types of antidiabetic medications) used by the elderly T2DM patients before hospitalization are shown in Table 2.

The majority of patients with diabetes were receiving SU or insulin. We found that SH was associated with insulin treatment in 10 patients and with SU in 9. It is noteworthy that none of the patients treated with metformin in monotherapy or in combination with insulin or SU developed this serious complication.

There were no significant differences in age, sex, BMI, duration of diabetes and biochemical markers of kidneys and liver function between patients T2DM who suffered episode of SH (group A) compared to those who did not develop this serious complication (group B). Interestingly, the mean level of HbA_{1c} was significantly lower in group A [6.38 ± 1.22 *vs.* 7.77 ± 1.88%, (46.31 ± 13.36 *vs.* 61.51 ± 20.63 mmol/mol), p = 0.002].

The patients with SH reported higher, although not significant, frequency of previous cerebral stroke and/or myocardial infarction (47 *vs.* 28%) compared with diabetic patients hospitalized for other internal diseases (χ^2 =3.03, p = 0.082) (Tab. 3).

The most common symptoms of SH in that age group — as reported by the patients or family members — were somnolence, confusion and loss of consciousness. We found that sixteen of 19 patients with SH declared having lost their ability to perceive symptoms associated with decreasing blood glucose levels and thus they did not undertake any activities to prevent this serious complication. Only three subjects identifying themselves as aware or partially aware.

Discussion

Despite the harms of intensive treatment exceed the benefits for older adults with diabetes [4] half of patients included in our study had HbA_{1c} less than 7% (53 mmol/mol). Every tenth patient was hospitalized because of SH. Our findings are consistent with the observations of other researchers that substantial proportion of older adults with diabetes may be overtreated [9–11].

Bahrmann et al. reported that elderly patients with T2DM and episodes of SH were characterized by a lower level of HbA_{1c} than the level recommended for this age group [12]. In our study we also revealed that older adults hospitalised with SH had not only mean HbA_{1c} lower then recommended for this group but also significantly lower mean HbA_{1c} compare to those hospitalised with other reasons. Moreover, history of myocardial infarction and/or cerebral stroke was reported twice as often among diabetics with SH — in the group, that

Table 3. Clinical and laboratory characteristics of T2DM patients by group

Parameter	A (n = 19)	B (n = 147)	p value
Age (years)	83.26 ± 2.51	83.78 ± 3.27	0.505
Gender	F = 17; M = 2	F = 108; M = 39	0.127
Diabetes duration (years)	8.78 ± 5.01	9.19 ± 5.99	0.776
HbA_{1c} (%)	6.38 ± 1.22	7.77 ± 1.88	0.002
HbA_{1c} [mmol/mol]	46.31 ± 13.36	61.51 ± 20.63	
Glucose level at admission* [mmol/l]	5.60 ± 4.33	13.55 ± 14.43	0.018
BMI [kg/m^2]	27.64 ± 4.20	27.90 ± 4.56	0.814
Creatinine [μmol/l]	100.10 ± 32.94	109.32 ± 53.18	0.462
Urea [mmol/l]	8.83 ± 4.12	9.88 ± 5.89	0.453
GFR [ml/min/1.73 m^2]	56.84 ± 21.26	55.6 ± 24.54	0.834
ALT [U/l]	17.57 ± 9.87	19.86 ± 13.73	0.483
AST [U/l]	23.89 ± 20.58	23.56 ± 13.27	0.924
No. of patients with a previous myocardial infarction and/or cerebral stroke	9	41	0.082

*Serum glucose level after treatment provided by paramedics. Data are expressed as mean ± standard deviation. p value < 0.05 — difference statistically significant. BMI — body mass index; GFR — glomerular filtration rate; HbA_{1c} — glycated hemoglobin A_{1c}

should have the most liberal therapeutic goals. The lack of statistical differences in the frequency of these chronic macrovascular complications of diabetes may be a result of disparities in the number of patients in the compared groups.

Hypoglycemia, especially SH, experienced by elderly people with diabetes is dangerous, particularly for the cardiovascular system and central nervous system. Abnormally low blood glucose concentration leads to excessive activity of the sympathetic nervous system with a secondary catecholamines release. Elevated blood level of catecholamines is responsible for increase of peripheral resistance, hyperactivity of blood platelets, damage of vascular endothelium, oxidative stress, thromboembolic events, inflammation and destabilization of atheromatous plaque, myocardial ischemia, ventricular arrhythmias and sudden death [13–15]. Hypoglycemia, even it is mild, causes cognitive impairment and accelerates the onset of dementia in elderly people [16, 17]. On the other hand, elderly diabetics with cognitive impairment are at three times higher risk of SH requiring health services [18]. Moreover, SH increases the frequency of falls, fractures and necessity of care from other people [19]. Hypoglycemia and the fear of hypoglycemia decrese significantly quality of life. Patients with recurrent hypoglycemia have been found to have chronic mood disorders including depression and anxiety [20], as well as significantly decreased quantity and quality of sleep [21].

Older adults are at higher risk of SH for many reasons. Firstly, it can be related to decreasing mass and function of β cells, in consequence insulin deficiency and necessitating insulin therapy [22]. Secondly, it can be caused of age-related impairment in counter-regulatory hormone responses, especially with respect to glucagon and growth hormone. With long duration of T2DM the glucagon response to hypoglycemia is virtually absent [23, 24]. Moreover, patients with frequent hypoglycemia do not experience the symptoms from the adrenergic response to decreasing glucose level. The onset of neuroglycopenia before the appearance of autonomic warning symptoms is called hypoglycemia unawareness [24, 25]. We found, that high proportion of very old diabetics included in our study reported hypoglycemia unawareness.

Malnutrition is the next crucial risk factor of low glucose levels. Despite the ageing process is associated with hyperglycemic tendency due to the change in body composition, accumulation of visceral fat and increasing insulin resistance, in very old people we observe a tendency towards hypoglycemia due to malnutrition. More attention should be paid to the management of undernutrition in elderly population by improving energy intake and maintaining muscle mass [26, 27]. Our patients with and without SH had similar BMI, but we did not measure their body composition.

Another important risk factor of hypoglycemia is structural and functional disorders of organs playing a decisive role in pharmacokinetic and pharmacodynamics of hypoglycemic drugs. Age-related declines in renal and liver function may interfere with the metabolism of SU and insulin, thereby potentiating their hypoglycemic effects [28]. However in our study, we did not observe worse renal and hepatic parameters in patients with SH episodes.

The episodes of SH in patients included in our study were noted only in those receiving insulin or SU in monotherapy or in combination. These observations are in accordance with other research that usage of these medications is associated with the highest risk of hypoglycemia [9, 28]. According to the Beers List, prohibited medications in long-term care facilities namely short-acting insulin and glyburide (second generation of SU) should be avoided in the elderly diabetics [29]. It should be emphasized that none of SH episodes in very old people with T2DM in our study was associated with the use of metformin. Based on the systematic review that examined the available evidence on the safety and efficacy of metformin in the management of T2DM in older adults, metformin appears to be better, and certainly no worse, than other antidiabetic managements in older adults [30].

The results of our study revealed that none of the elderly patients enrolled in the study was treated with newer antidiabetic drugs with a low hypoglycemic potential [31, 32]. Unfortunately, high prices and no reimbursement limit the use of these agents in Poland, particularly by the elderly who cannot afford them.

Karter et al. indicate possible remission of T2DM in patients over 65. They demonstrated that some T2DM patients are able to maintain normal blood glucose concentration in the long term with no use of hypoglycemic drugs [33]. In our study 12 subjects were treated successfully only with diet. It cannot be excluded that they were in remission of the disease. However, we realised that to confirm our presumption these patients should be observed for long period after discharge.

Canadian researchers recently performed a systematic review in which they demonstrated that deprescribing hypoglycemic agents is feasible and safe in those with low HbA_{1c} level. Canadian Clinical Practice Guidelines recommend deprescribing antidiabetic medications in older adults at high risk of hypoglycemia, in situations where medications might be causing other adverse effects and in patients who are frail, have dementia or have a limited life expectancy [34]. In our study 21 individuals were receiving hypoglycemic drugs despite the HbA_{1c} level < 6% (42 mmol/mol). If we are right, these patients probably did not need any antidiabetic drugs and it seems that non-pharmacological treatment would be sufficient.

T2DM treatment in very old people constitutes an important challenge for those who are responsible for quality of diabetes care. It is generally accepted that the management of hyperglycemia in this group of patients should be individualized considering a benefit-to-risk analysis. It should be outlined that hypoglycemia is an avoidable iatrogenic complication of T2DM management. Effective and safe medical treatment of diabetes can be realized by regular education, dietary and exercise adjustment and careful glucose monitoring. Elderly patients with T2DM should have HbA_{1c} measurements performed more frequently to adjust the intensity of hyperglycemia management and to decrease the risk of hypoglycemia. Physicians need to recognize the changing health status of elderly patients. This situation requires often reduction or even discontinuation of different medications, including antidiabetic agents.

The main strength of our study is the fact that it tackles an important and alarming medical issue among growing number of elderly people with diabetes. Moreover, the study group consisted of very old diabetics, who are often not included in clinical studies Furthermore, it was a real-life, observational study, not precisely designed multicentre clinical trial.

There are some limitations in our study. First, the study population included a relatively small number of subjects. However, given that it was a single centre study and life expectancy of diabetics is reduced by 8–10 years in comparison with people without diabetes, it was difficult to collect significantly larger group of diabetics ≥ 80 years. Second, we included in our study only those patients with whom we could communicate to obtain their medical history. Third, our patients used only older generation of antidiabetic agents with a high hypoglycemic potential. The newer, expensive antidiabetic drugs with a low hypoglycemic potential are still rarely used by very old Polish diabetics.

Conclusions

Despite the fact, that harms of intensive hypogylcemic treatment exceed the benefits for older patients with T2DM, half of them reached tight glycemic control. Every tenth patient was hospitalized because of SH. Subjects with SH had significantly lower mean HbA_{1c} level than those hospitalized for other reason. Our observations suggest that a substantial proportion of T2DM patients ≥ 80 years may be overtreated.

Conflict of interest

The authors declare no conflict of interests.

The paper was created under the statute UM 503/0-077-09/503-01-006

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