Tighter glycemic control is associated with ADL physical dependency losses in older patients using sulfonylureas or mitiglinides: Results from the DIMORA study

Angela M. Abbatecola a,⁎, Mario Bo b, Fabio Armellini c, Ferdinando D’Amico d, Giovambattista Desideri e, Paolo Falaschi f, Antonio Greco g, Gianbattista Guerrini h, Fabrizia Lattanzio i, Clelia Volpe j, Giuseppe Paolillo k

a Alzheimer’s Disease Clinic, ASL Frosinone, Atina, Italy
b University of Turin, Geriatric Section, Department of Medical Sciences, San Giovanni Battista Hospital, Turin, Italy
c Division of Geriatrics, Hospital of Valdagno, Italy
d Azienda Sanitaria Provinciale di Messina, Messina, Italy
e University of Aquila, Aquila, Italy
f Sapienza University of Rome, Rome, Italy
g Geriatric Unit and Gerontology-Geriatrics Research Laboratory, Department of Medical Sciences, IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo (FG), Italy.
h Fondazione Brescia Solidale, Brescia, Italy
i Italian National Research Center on Aging (INRCA), Scientific Direction, Ancona, Italy
j ASL Napoli 1, Naples, Italy
k Second University of Naples, Department of Medical, Surgical, Neurological, Metabolic and Geriatric Sciences, Naples, Italy

ARTICLE INFO

Article history:
Received 8 January 2015
Accepted 23 July 2015

Keywords:
Aging
Glycated hemoglobin
Disability
Anti-diabetic oral agents
Type 2 diabetes

ABSTRACT

Background. There is growing evidence that tight glycemic control may be more harmful than beneficial in older persons with Type 2 diabetes (T2DM). It remains controversial if tight glycemic control (lower glycated hemoglobin A1c (A1c)) is associated with functional impairments in older frail patients with T2DM. We explored associations between A1c and losses in Activities of Daily Living (ADLs) in diabetic nursing home (NH) patients and tested for differences according to anti-diabetic treatment: diet, anti-diabetic oral drug (AOD), insulin, combined insulin + AOD.

Methods. We conducted a cross-sectional study on 1845 older NH patients with T2DM from 150 sites across Italy. Complete evaluations on ADLs, glycemic control, anti-diabetic treatments, comorbidities, and clinical data were recorded. ANOVA was applied to compare clinical characteristics across A1c tertiles. Multivariate regression models evaluated associations between A1c and ADL losses.

Results. Patients had a mean age [SD] = 82 [8] years; BMI = 25.5 kg/m² [4.7]; Fasting Plasma Glucose (FPG) = 7.4 [3.0] mmol/l; Post-prandial glucose (PPG) = 10.3 [3.6] mmol/l;
A1c = 7.0% (54 mmol/mol), ADL losses = 3.7 [1.8]. Compared to higher A1c tertiles, patients in the lower tertile had greater ADL losses, were more likely to use AODs, while less likely to use insulin or insulin + AOD. After adjusting for multiple confounders, impairments in ADLs were associated with tighter A1c levels (B = −0.014; p = 0.002). Regression models according to anti-diabetic treatment showed that tighter A1c levels continued as independent determinants of ADL losses in patients using AODs (B = −0.023; p = 0.001), particularly in those using sulfonylureas (B = −0.043; p < 0.001) or mitiglinides (B = −0.044; p = 0.050).

Conclusions. Tighter glycemic control was associated with ADL physical dependency losses, especially in those using sulfonylureas and mitiglinides.

© 2015 Elsevier Inc. All rights reserved.

1. Introduction

The rapidly rising increase in the prevalence of Type 2 Diabetes (T2DM) in persons over the age of 80 years has been shown to play a pivotal role on the risk of physical decline and functional disabilities [1]. This high prevalence may be a result of diabetes-related comorbidities, including cardiovascular disease, peripheral neuronal damage, vision loss or poor glycemic control [2–5]. Even though strategies aimed at correcting severe hyperglycemia have shown to improve short- and long-term A1c levels and hypoglycemia [6], trials performed in younger and older adults have also indicated that intensive glycemic control (A1c < 6%) is associated with an increased risk of hypoglycemia [7] and mortality [7,8]. There is growing literature that tight glycemic control may be more harmful than beneficial, especially in older persons [9,10]. Due to the lack of evidence for specific glucose control targets in frail elderly at risk of disability [11], available treatment guidelines are based on data extrapolation from younger adults and expert opinion [12–14].

Older nursing home (NH) patients represent a population of frail individuals needing assistance in performing daily activities. These individuals usually have severe cognitive decline, increased rates of bone fracture, and hypoglycemic events, all of which contribute to the complexity of managing diabetes treatment. The number of people using long term care, including NH facilities is projected to rise from 15 million in 2000 to 27 million by 2050 [15,16]. At the moment, no studies have investigated the association between losses in physical functional dependency levels and overall glycemic control according to anti-diabetic treatment regimens in institutionalized elderly with T2DM. Different working parties, such as the European Working Party for Older People have recommended maintaining higher A1c targets in older NH patients, especially with severe losses in physical dependency levels as well as, anti-diabetic treatment algorithms [12,13]. The most important suggestion is to aim at accomplishing an overall flexible glycemic control of A1c between 7% and 8% in complex elderly patients [17]. The risk of functional loss and/or its consequences from specific glucose lowering regimens may also play a role on identifying glycemic control in the very old. Interestingly, NH populations with T2DM can be easily monitored in order to determine associations among physical decline, A1c levels and antidiabetic regimens.

In this study, we aimed at testing associations between A1c levels and physical dependency losses in Activities of Daily Living (ADLs) in a large population of older NH residents with T2DM. We also aimed at testing for these associations according to available anti-diabetic treatment regimens.

2. Methods

The DIMORA (“DIabete MellitO in RsA” (Diabetes Mellitus in the Nursing home)) is an observational cohort study based on data from 150 NHs across different regions of Italy. A total of 2258 NH patients with T2DM aged 65–110 years (mean age: 83 ± 7) were enrolled between 2011 and 2013. Inclusion criteria included: age over 65 years, diagnosis of T2DM of at least 1 year, complete data regarding anti-diabetic treatment, and glycemic control parameters. Exclusion criteria included: age less than 65 years, lack of complete data regarding glycemic control, or refusal to participate in the study. In this report, the study population consisted of 1845 patients with complete data on A1c and ADLs. Information regarding diabetic health status was assessed using a questionnaire on anti-diabetic treatment and laboratory assays of glycemic control from medical nursing home staff (nurses and/or physicians). Data regarding physical and cognitive functional status were also collected. Data collection forms were designed by the Italian Society for Gerontology and Geriatrics (“Società Italiana di Gerontologia e Geriatria” (SIGG)) scientific board and communicated to research foundation Sanofi-Aventis (Italy). The Quintiles company (Milan, Italy) was responsible for data form collection retrievals, performing data entry processing, structuring and testing for data homogeneity during the six-month period following the end of data collection. A scientific SIGG board member, expert in medical statistics, used the provided database to perform all statistical analyses without any potential conflicts of interest relevant to this report.

2.1. Anti-diabetic Treatment

Information regarding the administration of anti-diabetic oral drugs (AODs) included: sulfonylureas, metformin, glinides, α-glucosidase inhibitors, thiazolidinediones, Glucagon-like peptide (GLP-1) analogues, inhibitors of GLP-1 degrading enzyme dipeptidyl peptidase IV (DPP-IV) inhibitors and in combination; and the type of insulin analog treatment: rapid, short, intermediate or long acting, pre-mixed. Information regarding diet therapy was also registered.
At the time of data collection, physical functional status was measured using the Basic Activities of Daily Living (ADLs) and calculated from the questionnaire regarding physical independency levels ranging from 0 to 6 (maximum independency) [18]. All subjects underwent an anthropometrical evaluation, including BMI, calculated as weight in kilograms divided by the square of height in meters.

Information regarding daily glycemic monitoring was based on fasting plasma glucose (FPG) and post-prandial glucose (PPG) concentrations. The most recent glycated Hemoglobin (A1c) was also recorded during this observation period. All sites measured serum glucose levels using an enzymatic colorimetric assay with glucose oxidase-peroxidase method, and A1c by high performance liquid chromatography using DCCT-aligned methods and standardized assays. Intervariability between machines was tested for both glucose and HbA1c measurements and was found to be less 5% for both tests. Severe hypoglycemia events were reported and defined as required documentation of a plasma glucose ≤50 mg/dL (2.8 mmol/L) and symptoms requiring assistance by a third party to administer oral carbohydrate, intravenous glucose, or parenteral glucagon [19,20] during the stay at the NH.

Information was reported regarding the presence of specific comorbidities including heart failure, cardiovascular disease, stroke, chronic obstructive pulmonary disease, cancer, osteoporosis, osteoarthritis, Parkinson’s disease, anemia, chronic respiratory failure, chronic renal failure, liver disease, arterial hypertension, gastrointestinal disease, bone fractures and other (peripheral arterial disease, diabetic neuropathy, diabetic retinopathy, depression, hypothyroidism, prostate hypertrophy). The number of non-diabetic drugs administered daily was also recorded.

The Scientific Review Board of the SIGG in Florence, Italy approved the study protocol. All participating NHs in diverse Italian regions (Abruzzo, Campania, Lazio, Lombardia, Marche, Piemonte, Puglia, Sicilia, Veneto) were informed about the study design and data collection procedures. Patient informed consent was obtained at contributing nursing homes accordingly.

2.2. Statistical Analyses

All statistical analyses were performed using statistical software SPSS version 17.0 (SPSS, Chicago, IL). All data are presented as mean (SD) unless otherwise indicated. To approximate normal distributions, log-transformed values for plasma A1c were used in the analysis and back transformed for data presentation. Pearson product–moment correlations were calculated to test associations between ADL losses, A1c levels, and the number of hypoglycemic events. Partial correlations between ADL losses, A1c and the number of hypoglycemic events were explored after adjusting for age and BMI.

In order to detect for collinearity between A1c and number of severe hypoglycemic events, we calculated the variance inflation factor (VIF) to assess the extent to which the variances of the estimated coefficients were inflated (i.e. VIF = [R²] / (1 – R²)), where R² is the coefficient of determination for regression of the ith independent variable against the remaining variables) [21]. A predictor with VIF > 10 is considered as an indicative of severe collinearity.

Analysis of variance (ANOVA) was applied to test for descriptive continuous variables of clinical characteristics according to A1c tertiles, while categorical data were presented as a number (percentage) and compared using χ² test. ANOVA was applied for comparison between groups followed by a Bonferroni post hoc analysis. Multivariate linear regression models were used to test for associations of ADL impairments and A1c independently of multiple confounders. These models were performed in the entire population and separately according to anti-diabetic regimens (diet, insulin use, insulin + AOD, AOD). Multivariate models were also tested according to specific AOD (biguanide, biguanide + sulfonylurea, sulfonylurea, metgilinitine).

ANOVA models testing and linear regression models excluded patients using α-glucosidase inhibitors (n = 0), thiazolinediones (n = 9), GLP-1 analogues (n = 0) and DPP-IV inhibitors alone and/or combined with metformin (n = 10) due to low power. All linear regression models were adjusted for age, gender, site, comorbidities, BMI, length of NH stay, diabetes duration, A1c and severe hypoglycemia.

3. Results

3.1. Entire Study Population

The study population consisted of 561 men and 1284 women with a mean age of 82 ± 8 years, Fasting Plasma Glucose (FPG) = 7.5 ± 3.0 mmol/l; Post-prandial glucose (PPG) = 10.3 ± 3.6 mmol/l; A1c = 7.0 ± 1.3% (53 ± 14 mmol/l) and ADL impairments = 3.7 ± 1.8. The mean NH stay was 3.0 ± 5.2 years.

Clinical characteristics according to A1c tertiles are reported in Table 1. Patients in the lowest tertile of A1c had significantly higher ADL impairments, were more likely to use AODs and were less likely to use insulin or combined insulin + AOD compared to those in higher tertiles (Table 1). Bonferroni post hoc analysis showed that ADL losses were significantly higher in the first tertile of A1c compared to the second (p < 0.001) and the third tertile (p < 0.001). ADL losses were also significantly higher in the second compared to the second tertile of A1c (p < 0.001).

ADL impairments were negatively associated with A1c levels (r = −0.130; p < 0.001) and positively associated with the number of hypoglycemic events (r = 0.103; p < 0.001). After adjusting for age and BMI, ADL impairments continued to correlate with A1c levels (r = −0.114; p < 0.001) and hypoglycemic events (r = 0.104; p < 0.001).

Multivariate regression analysis performed with ADL impairments as the dependent variable, adjusted for site, age, sex, BMI, number of comorbidities, duration of diabetes, anti-diabetic treatment (oral, insulin or combined oral and insulin) showed that ADL losses were associated with tighter A1c levels (β = −0.014; SE = 0.005; p < 0.001) and hypoglycemic events (β = 0.626; SE = 0.166; p < 0.001). Pearson product correlations showed that A1c values were positively correlated with the number of hypoglycemic events (r = 0.41; p < 0.001). However, in the regression model, VIFs were 1.06 for A1c and 1.10 for hypoglycemic events, thus underlining that no severe collinearity was found.
3.2. Anti-Diabetic Treatment Groups

Table 2 reports ADL impairments tested across A1c tertiles separately according to anti-diabetic treatment groups. Patients using AODs in the lowest A1c tertile, showed a significantly greater number of losses in ADL impairments, while this trend was not statistically significant in those using insulin or combined insulin + AOD (Table 2). Table 2 also shows that those using sulfonylureas or mitiglinides had significantly greater ADL losses across A1c tertiles, while no significant trend was observed in those using biguanide or biguanide + sulfonylureas. Bonferroni post hoc analysis for multiple comparisons in these groups showed that there were significant differences between A1c tertiles tested separately (p < 0.001).

In the next step, we aimed at testing for associations between A1c levels and ADL losses according to specific anti-diabetic treatments. We found an independent association between tighter A1c and ADL losses in patients using AODs (Table 3a). The same regression models were then performed separately according to available AOD classes and we found that tighter A1c levels were independent determinants of ADL losses only in patients using sulfonylureas or mitiglinides (Table 3b).

4. Discussion

This is the first study investigating the association between functional dependency and overall glycemic control in a large population of older NH patients with T2DM according to different anti-diabetic regimens. ADL losses significantly increased across A1c tertiles in patients using AODs and not...
in those using insulin or insulin + AOD. We also found that tighter (lower) A1c levels were associated with a greater number in ADL losses, particularly in patients using sulfonylureas or mitiglinides. This investigation highlights the importance of A1c values with specific anti-diabetic agents on clinical outcomes, such as physical dependency in elderly NH patients.

Long term care facility admissions, especially NH admissions are dramatically rising in older persons with T2DM over 80 years of age [22]. Although the goals of diabetes mellitus care in older NH patients include controlling hyperglycemia, prevention and/or treatment of associated complications, specific anti-diabetic treatment remains challenging due to the higher rates of premature death, comorbidities and functional disability compared to patients without diabetes [23]. At the moment, clinical practice guidelines have suggested that overall glycemic target should be based on functional status in NH patients: A1c ≤ 7% in patients with good functional status and approximately 8% in frail patients (multiple comorbidities, high risk of hypoglycemia, life expectancy < 5 years) [24,25]. In addition, identifying A1c targets according to specific anti-diabetic treatments may also hold a role in protecting against functional decline in this growing population. To date, there are limited data regarding associations between physical functioning and A1c levels in older frail NH patients [26].

The NHANES study showed that poor glycemic control (A1c > 8%) was associated with an increased odds for disability in community dwelling adults over the age of 60 years, but these authors did not test for this association in individuals over 80 years of age [27,28]. In contrast, another study underlined that tighter glycemic control (A1c < 7%) was associated with maintaining better lower extremity function in older adults with T2DM (mean age 76 years) [29]. Interestingly, data from the Health ABC study found that higher A1c levels (≥ 7%) were associated with higher muscle mass (mean age 74 years) [3]. The controversial findings from these studies may be due to heterogeneity of study protocols, thus underlining an urgent need to focus on specific patients at high risk of disability. Indeed, our objective was aimed at investigating physically impaired institutionalized elders with T2DM.

A recent report using retrospective data from 583 NH patients found that the number of falls decreased as A1c levels rose in patients 85 years or older, thus indicating that ideal overall glycemic control significantly varies according to advancing age [26]. This finding may be explained by a lower risk of severe hypoglycemic events when A1c levels are maintained at a higher range. Recently, it has been reported that a higher A1c level was associated with a lower one-year risk of hospitalization due to hypoglycemia [30]. Hypoglycemia is a major adverse consequence of glucose lowering therapy and older patients are at a significantly higher risk due to multiple co-morbidities, polypharmacy (≥ 5 medications), chronic renal or hepatic impairment, poor nutrition, use of sulfonylurea or insulin, acute illness, hypoglycemic unawareness and diminished counter regulatory responses [31].

Tight glycemic control (A1c ≤ 6%) is associated with severe hypoglycemia, which in turn can increase the risk of falls, hospitalization and mortality [20,32]. We found that the number of hypoglycemic events was associated with a greater loss in ADLs. However, in fully adjusted models, severe hypoglycemic events were no longer associated with losses in physical dependency, while A1c levels continued to be independent determinants of ADL losses. Low A1c targets have resulted in an increased risk of hypoglycemia and anti-diabetic oral agents have been shown to confer an additional risk [33].

In our population, one may hypothesize that the negative association found between A1c levels and ADL losses in those using sulfonylureas or mitiglinides may be explained by higher A1c levels associated with separation of the effects of severe hypoglycemia and the role of A1c levels on falls. At the moment, the role of A1c levels on falls is not well understood. It is possible that A1c levels may be associated with the risk of falls, but this association may be confounded by other factors such as frailty, muscle mass, balance, and cognitive function.

### Table 3a - Linear regression models testing the association of ADL impairments with glycemic control according to anti-diabetic treatment among older nursing home patients, DIMORA 2011–2013.

<table>
<thead>
<tr>
<th>Model</th>
<th>Diet</th>
<th>Insulin</th>
<th>Insulin + AOD</th>
<th>AOD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Beta ± SE</td>
<td>P</td>
<td>Beta ± SE</td>
<td>P</td>
</tr>
<tr>
<td>Age</td>
<td>0.011 ± 0.020</td>
<td>0.582</td>
<td>0.028 ± 0.011</td>
<td>0.040</td>
</tr>
<tr>
<td>Gender</td>
<td>−0.607 ± 0.321</td>
<td>0.061</td>
<td>−0.421 ± 0.159</td>
<td>0.008</td>
</tr>
<tr>
<td>A1c</td>
<td>−1.385 ± 0.872</td>
<td>0.115</td>
<td>−0.009 ± 0.006</td>
<td>0.118</td>
</tr>
</tbody>
</table>

* Adjusted for site, anemia, chronic kidney disease, chronic liver disease, BMI, length of NH stay, diabetes duration, severe hypoglycemia.

### Table 3b - Linear regression models testing the association of ADL impairments with glycemic control according to available AOD classes in older nursing home patients, DIMORA 2011–2013.

<table>
<thead>
<tr>
<th>Model</th>
<th>Biguanide</th>
<th>Biguanide + Sulfonylurea</th>
<th>Sulfonylurea</th>
<th>Metiglinide</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Beta ± SE</td>
<td>Beta ± SE</td>
<td>Beta ± SE</td>
<td>Beta ± SE</td>
</tr>
<tr>
<td>Age</td>
<td>0.029 ± 0.011</td>
<td>0.009</td>
<td>0.001 ± 0.018</td>
<td>0.950</td>
</tr>
<tr>
<td>Gender</td>
<td>−0.456 ± 0.161</td>
<td>0.005</td>
<td>−0.723 ± 0.287</td>
<td>0.013</td>
</tr>
<tr>
<td>A1c</td>
<td>−0.012 ± 0.006</td>
<td>0.068</td>
<td>−0.015 ± 0.011</td>
<td>0.194</td>
</tr>
</tbody>
</table>

* Adjusted for site, anemia, chronic kidney disease, chronic liver disease, BMI, length of NH stay, diabetes duration, severe hypoglycemia.

Please cite this article as: Abbatecola AM, et al, Tighter glycemic control is associated with ADL physical dependency losses in older patients using sulfonylureas or mitiglinides: Resu..., Metabolism (2015), http://dx.doi.org/10.1016/j.metabol.2015.07.018
by an increased insulin secretagogue profile of these agents in elderly persons [34,35].

Our study holds strengths and weaknesses. One important strength was that trained medical nursing staff at each NH collected all data regarding drug administration. This is an important issue because most studies use data provided by study participants, thus our study controlled for any erroneous information regarding all drug treatments. This type of approach may explain differences reported by the NHANES survey study that included information based on participant response and not by trained medical staff in a controlled environment. One cannot exclude potential error in reporting daily glycemic measures from nursing staff as a study limitation, however this protocol included highly trained expert staff, thus reducing such potential errors to a minimal [36]. The main limitation of our study is the cross-sectional design that does not allow to explore a cause–effect relationship. Nevertheless, the findings from this study strongly suggest that tighter glycemic control may influence a more rapid functional decline in old NH patients with T2DM using specific AODs. We can also not exclude a potential selection bias because analyses were performed on patients with complete A1c, anti-diabetic treatment and ADL loss data. However, this is the first study investigating associations between overall glycemic control and ADL disability according to specific AODs in a large sample of institutionalized elders. Our findings highlight that overall glycemic control (A1c) is the main target toward improving disability and functional losses. Higher A1c targets may significantly reduce the risk of functional losses in very old frail patients.

5. Summary and Translational Potential of Findings

Our findings strengthen the need for continued surveillance of overall glycemic control using A1c in older persons with T2DM. Even though there are controversial findings in the literature on whether to target lower or higher A1c levels to protect against physical disability in older patients, studies were performed using different criteria. Our study has added a new insight regarding such targets in old patients using specific oral agents, such as sulfonylureas or mitiglinides. One may also hypothesize that anti-diabetic agents may also be working differently in younger T2DM patients with physical disabilities. Therefore, future prospective longitudinal studies and clinical trials in younger and older cohorts of T2DM patients will be necessary for identifying A1c targets that protect against functional disability in different anti-diabetic treatments. This type of research will improve metabolic research for the use of anti-diabetic agents not only in older, but also in younger adults, therefore improving clinical practice guidelines. We believe that our investigation may be a basis for a large spectrum related to geriatric and metabolic research.

Author Contributions

A.M.A collected data, researched the data, performed statistical analyses and drafted manuscript and is the guarantor of the article. M.B., F.A., F.D., G.D., P.F., A.G., G.G., F.L., C.V., participated in data collection organization and reviewed the manuscript. G.P. contributed to the data interpretation and revision of the manuscript.

Funding

The work was supported by an unconditional grant from the research Foundation of Sanofi-Aventis, Italy to the SIGG. The Sanofi-Aventis, Italy had no editorial control over data or manuscript. The Quintiles company from Milan, Italy received all data collection forms, performed data entry processes and created the final database. Quintiles tested for homogeneity of the data before providing the database to the SIGG board. The entire data entry and database production process lasted approximately 6 months.

Conflict of Interest

All authors declare no conflict of interest.

REFERENCES


[22] Rapid Response Reports CADTH. Management of Diabetes in the Long-Term Care Population: A Review of Guidelines [Internet]. Canadian Agency for Drugs and Technologies in Health: Ottawa (ON); 2013 Nov.


