A randomized controlled trial comparing treatment with oral agents and basal insulin in elderly patients with type 2 diabetes in long-term care facilities.

Francisco J Pasquel, Emory University
Winter Powell, Emory University
Limin Peng, Emory University
Theodore Johnson II, Emory University
Shadi Sadeghi-Yarandi, Emory University
Christopher Newton, Emory University
Dawn Smiley, Emory University
Marcos T Toyoshima, Emory University
Pedram Aram, Emory University
Guillermo Umpierrez, Emory University

Journal Title: BMJ Open Diabetes Research and Care
Volume: Volume 3, Number 1
Publisher: BMJ Publishing Group: Open Access | 2015-08, Pages e000104-e000104
Type of Work: Article | Final Publisher PDF
Publisher DOI: 10.1136/bmjdr-2015-000104
Permanent URL: https://pid.emory.edu/ark:/25593/q456b

Final published version: http://dx.doi.org/10.1136/bmjdr-2015-000104

Copyright information:
© 2015 by the BMJ Publishing Group Ltd.
This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (http://creativecommons.org/licenses/by-nc/4.0/), which permits distribution of derivative works, making multiple copies, distribution, public display, and publicly performance, provided the original work is properly cited. This license requires copyright and license notices be kept intact, credit be given to copyright holder and/or author. This license prohibits exercising rights for commercial purposes.

Accessed December 2, 2019 12:20 AM EST
A randomized controlled trial comparing treatment with oral agents and basal insulin in elderly patients with type 2 diabetes in long-term care facilities

Francisco J Pasquel,1 Winter Powell,1 Limin Peng,2 Theodore M Johnson,1 Shadi Sadeghi-Yarandi,1 Christopher Newton,1 Dawn Smiley,1 Marcos T Toyoshima,1 Pedram Aram,1 Guillermo E Umpierrez1

INTRODUCTION
Diabetes is an increasing global health burden with a highest age-specific prevalence in people 60–79 years of age.1 The estimated prevalence of diabetes in long-term care facilities is around 15% to 34%.2-8 Nursing home residents with diabetes have higher rates of serious comorbidities and have greater activity of daily living dependencies than residents without diabetes.9 In addition, persons with diabetes have higher risk of hypertension, heart disease, stroke depression, cognitive impairment and cardiovascular disease than individuals without diabetes.9

Management of hyperglycemia is challenging in the geriatric population in long-term facilities.10 Numerous factors place hospitalized patients at increased risk for hyperglycemia including aging, sedentary life, stress of medical and surgical comorbidities and changes in antidiabetic regimen.11 In addition, elderly patients often experience changes in their nutritional intake and organ dysfunction; these changes increase the risk of hypoglycemic events. In general, therapy is aimed at attaining optimal levels of serum glucose while avoiding the acute complications of hypoglycemia or uncontrolled
We conducted a prospective, randomized controlled trial to assess the difference between the two treatment groups. We conducted χ² tests (or Fisher’s Exact tests) to analyze discrete secondary outcomes including hypoglycemic or hyperglycemic events, cardiac complications and acute renal failure. A p value of <0.05 was considered significant. Statistical analysis was performed using SAS (V.9.2, Cary, North Carolina, USA).
RESULTS
A total of 150 patients with T2D gave consent and were randomized to basal insulin (n=75) and OAD (n=75) therapy. The clinical characteristics of study patients are shown in Table 1. Groups were well matched without significant differences in mean age, gender, racial distribution, BMI, duration of diabetes, previous diabetes therapy and comorbidities. In the OAD treatment group, 21 (28%) patients received treatment with metformin alone, 12 (16%) patients were treated with a combination of metformin and sulfonylurea, and 6 (8%) patients were treated with a combination of metformin and other agents. A total of 20 (26.7%) patients were treated with sulfonylurea alone and 6 (8%) were treated with a combination of sulfonylurea and a DPP-4 inhibitor. Six (8%) patients were treated with diet alone, 2 (2.7%) patients were treated with a TZD and 2 (2.7%) were treated with meglitinides.

Patients randomized to the basal insulin group had a higher hemoglobin HbA1C compared to the OAD group (6.9±0.9% vs 6.5±0.7%, p=0.049). Most patients were admitted for a subacute rehabilitation program (SAR). The duration of admission was similar between groups (32±40 days vs 31±44 days, p=0.30).

The admission BG (144±42 mg/dL vs 137±44 mg/dL, p=0.27) and randomization BG (198±40 mg/dL vs 192±35 mg/dL, p=0.20) were similar between basal insulin and OAD groups. Both treatment regimens resulted in a sustained improvement in mean daily BG concentration during the LTC stay (figure 1). Mean fasting BG during therapy was not significantly different between basal insulin and OAD groups (131±27 mg/dL vs 123±23 mg/dL, p=0.06). The overall mean daily BG level was lower in patients treated with OAD compared to basal insulin (138±27 mg/dL vs 163±39 mg/dL, p<0.05). Overall daily BG did not differ between groups (figure 1). As expected, the total daily insulin dose was higher in the insulin group compared to the OAD group (0.2±0.2 vs 0.1±0.3 U/kg/day, respectively, p<0.001).

The rate of hospital complications including cardiovascular (acute myocardial infarction, cardiac arrhythmia requiring medical treatment and congestive heart failure), acute kidney failure, infection (pneumonia, urinary tract infections, bedsores and diabetic foot infection), falls, emergency room (ER) visits, hospital admissions or mortality (death occurring during admission) was similar between groups (figure 2).

There were no differences in the frequency of hypoglycemia between patients treated with basal insulin or with OADs. BG values <70 were reported in 27% of patients with basal insulin and in 31% of patients treated with OADs. Nine (12%) patients in basal and 13 (17%) in OAD had ≥2 episodes of hypoglycemia. A non-statistically significant excess in the total number of hypoglycemic events was observed in the OAD group compared to basal plus supplements (62 events vs 43 events, p=0.4). In addition, there were no differences in the frequency of hypoglycemia in either group in patients treated with insulin or OADs (see online supplementary table).

Table 1 Clinical characteristics of study patients

<table>
<thead>
<tr>
<th></th>
<th>Basal insulin</th>
<th>OAD</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>75</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>Gender, n (F/M)</td>
<td>49/26</td>
<td>47/28</td>
<td>0.73</td>
</tr>
<tr>
<td>Age, years</td>
<td>79±8</td>
<td>79±8.1</td>
<td>0.97</td>
</tr>
<tr>
<td>Race: black/white/other, n</td>
<td>24/49/1</td>
<td>29/44/2</td>
<td>0.28</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>30±6</td>
<td>30±7</td>
<td>0.73</td>
</tr>
<tr>
<td>Diabetes duration, years</td>
<td>8.6±4.9</td>
<td>7.7±5.2</td>
<td>0.15</td>
</tr>
<tr>
<td>HbA1C, %</td>
<td>6.9±0.9</td>
<td>6.5±0.7</td>
<td>0.05</td>
</tr>
<tr>
<td>Previous diabetes therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin, n (%)</td>
<td>19 (25)</td>
<td>21 (28)</td>
<td>0.95</td>
</tr>
<tr>
<td>Sulfonylurea (SU), n (%)</td>
<td>21 (28)</td>
<td>20 (27)</td>
<td></td>
</tr>
<tr>
<td>DPP-4i, n (%)</td>
<td>8 (11)</td>
<td>6 (8)</td>
<td></td>
</tr>
<tr>
<td>Other, n (%)</td>
<td>27 (36)</td>
<td>28 (37)</td>
<td></td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>68 (91)</td>
<td>61 (81)</td>
<td>0.16</td>
</tr>
<tr>
<td>Coronary heart disease, n (%)</td>
<td>25 (36)</td>
<td>22 (29)</td>
<td>0.11</td>
</tr>
<tr>
<td>Heart failure, n (%)</td>
<td>29 (39)</td>
<td>21 (28)</td>
<td>0.17</td>
</tr>
<tr>
<td>Acute kidney injury, n (%)</td>
<td>21 (28)</td>
<td>23 (31)</td>
<td>0.72</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>34 (45)</td>
<td>33 (44)</td>
<td>0.87</td>
</tr>
<tr>
<td>Dementia, n (%)</td>
<td>27 (36)</td>
<td>18 (24)</td>
<td>0.11</td>
</tr>
<tr>
<td>Mental illness, n (%)</td>
<td>33 (44)</td>
<td>25 (33)</td>
<td>0.18</td>
</tr>
<tr>
<td>Admission area</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subacute Rehab</td>
<td>70 (93)</td>
<td>69 (92)</td>
<td></td>
</tr>
<tr>
<td>Long-term care</td>
<td>5 (7)</td>
<td>6 (8)</td>
<td></td>
</tr>
</tbody>
</table>

HbA1C, glycated hemoglobin; BMI, body mass index.
In the OAD group, there was a higher but not statistically significant difference in the incidence of hypoglycemia between patients receiving sulfonylureas alone or in combination with other agents (34%) versus no-sulfonylurea use (28%), p=0.5. Severe hypoglycemia defined as a BG <40 mg/dL was uncommon (figure 1). Patients with hypoglycemia (n=43) had more episodes of acute kidney injury (12% vs 2%, p=0.02) and a higher rate of a composite of complications (40% vs 22%, p=0.033) compared to patients who did not develop hypoglycemia (n=107).

**DISCUSSION**

This prospective randomized clinical trial compared glycemic control, clinical outcome and frequency of hypoglycemic events in elderly patients with T2D treated with basal insulin and OADs in LTC facilities. Most of the patients enrolled in our study were admitted to LTC facilities for subacute rehabilitation. We observed that both treatment regimens resulted in a rapid and sustained improvement in glycemic control without significant differences between patients treated with basal insulin or with OADs. In addition, we observed no differences in the frequency of hypoglycemia, length of stay, need for ER visit, hospital admission or mortality between treatment groups.

Few prospective randomized studies have reported on the safety and efficacy of different treatment strategies in elderly patients with diabetes admitted to LTC facilities. In general, recommendations for the management of diabetes in this population are extrapolated from studies in the hospital setting or from ambulatory patients with diabetes. Most nursing home residents with T2D are managed with insulin and/or oral antidiabetic agents, with basal insulin being recommended as the first-line therapy, and OAD agents usually considered to be less safe and effective than insulin therapy. In contrast to previous beliefs, our results indicate no significant differences in efficacy and safety of insulin and OAD treatment in elderly nursing home patients with type 2 diabetes.

A major finding in our study is that treatment with a low dose of basal insulin and OAD resulted in a similar...
frequency of hypoglycemia, with ~30% of patients in both groups. A higher but non-significant proportion of patients receiving sulfonylureas alone or in combination with other agents (34%) develop hypoglycemia compared to participants not exposed to sulfonylureas (28%). Previous studies have highlighted the importance of avoiding hypoglycemia in the elderly, as it may be associated with increased risk of complications and mortality. Data from the National Health and Nutrition Examination Survey (NHANES) gathered from 2001 through 2010 suggest that a large proportion of older adults with diabetes are potentially overtreated. Of the older adults with an HbA1C level of less than 7%, more than half were treated with either insulin or sulfonylurea, agents that may lead to severe hypoglycemia. In 1409 LTC residents, we reported that 42% of patients had ≥1 episodes of hypoglycemia and patients with hypoglycemia were more likely to require emergency room, hospital transfers and had higher mortality, than patients without hypoglycemia. In agreement with these studies, we found that patients with hypoglycemia experienced more episodes of acute kidney injury and a higher rate of complications compared to patients without hypoglycemia. These results emphasize the need for prevention of hypoglycemia with agents not associated with hypoglycemia in this vulnerable population. In this regard, a multicenter study is currently underway comparing the safety and efficacy of DPP-4 inhibitors and low-dose basal insulin in LTC facilities (NCT02061909).

Our study confirmed the results of previous studies that showed that glycemic control in elderly nursing home residents with diabetes is more often tight than poor. The average HbA1C levels reported in numerous nursing home studies have ranged between 5.9% and 7.5%, with HbA1C goals achieved in more than three-fourths of nursing home patients. Current guidelines for older residents with diabetes mellitus suggest that HbA1C goals be individualized with an HbA1C target of <7.5% in residents with good cognitive and functional status and without significant hypoglycemia. A target of 8–8.5% may be appropriate in residents with a history of severe hypoglycemia, limited life expectancy, comorbid conditions and longstanding diabetic complications. In our study, we randomized most patients with persistent fasting and premeal hyperglycemia. It is not known if tailoring therapy guiding for correction of fasting or daily hyperglycemia has the same impact in improving outcome or in reducing the frequency of hypoglycemia compared to a targeted HbA1C level in elderly participants with type 2 diabetes.

The main limitations of our study include its small sample size, and the relatively well-controlled population enrolled in the study based on HbA1C alone. The fact that patients were selected based on their previous regimen, including diet with or without oral agents, likely skewed our sample towards a better-controlled population, which probably does not reflect the overall glycemic control spectrum among all institutionalized patients with diabetes. Our study does suggest, however, that a significant proportion of patients are potentially overtreated in LTC or SAR (>50% were treated with sulfonylureas before enrollment). Another limitation is the relatively shorter length of stay (over a month) of most patients. Given the above limitations, the generalization of our results to all older adults with diabetes, in LTC or SAR facilities, is not possible, as patients treated with insulin or combinations of insulin with oral agents who are potentially more fragile (LTC residents particularly), might be at an even higher risk for hypoglycemia than the patients enrolled in our study. Larger and longer studies are needed to address these additional questions.

In summary, our randomized controlled study indicates that elderly residents with relatively well controlled T2D in LTC facilities and subacute rehabilitation settings can achieve and maintain similar glycemic control, and experience a similar rate of hypoglycemic events, when treated with either a low dose of basal insulin or with oral antidiabetic agents. Further studies that include patients with a wider range of glycemic control, including previous treatment with insulin are needed to further understand different therapeutic regimens, and to develop strategies aimed at preventing hypoglycemia in this vulnerable population.
REFERENCES