



## RESEARCH ARTICLE

**REVISED** The effects of the glycaemic control on the severity of the delirium in the advanced phase of Alzheimer's disease  
[version 2; peer review: 2 approved]

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**Abstract**

Background: Behavioral and psychological symptoms of dementia (BPSD) and delirium are common in advanced phases of Alzheimer's disease (AD).

Methods: Thirty-eight moderate-severe AD patients were enrolled (n=16 affected by type 2 diabetes). Each patient received a comprehensive geriatric assessment (CGA) (including evaluation of BPSD and frailty), and a complete metabolic evaluation (including the measurement of the glycosylated hemoglobin, HbA1c).

Results: Both the hyper- and hypo-glycemic extremes of the glycemic spectrum worsened BPSD, but delirium was more susceptible to hypoglycemic events. The severity of delirium was significantly related to cognitive function ( $r = -0.585$ ,  $p < 0.001$ ) and frailty ( $r = +0.440$ ,  $p < 0.05$ ).

Conclusions: The measurement of HbA1c was useful for evaluating the risk of delirium in relationship to glycemic control and nutritional status.

**Keywords**

Marigliano-Cacciafesta-polypathology-scale, glycaemic control, Alzheimer's disease, delirium

**Open Peer Review**

Reviewer Status  

Invited Reviewers

1 2

**version 2**



(revision)  
28 Jul 2021

**version 1**

16 Dec 2020

  
report

  
report

1. **Sandra Sigala** , University of Brescia, Brescia, Italy
2. **Takahiko Nagamine** , Director of Sunlight Brain Research Center, Hofu, Japan  
Matsumoto Surgical Hospital, Hofu, Japan

Any reports and responses or comments on the article can be found at the end of the article.

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**Author roles:** **Martocchia A:** Conceptualization, Formal Analysis, Methodology; **Scarienzi M:** Data Curation; **Prunas P:** Data Curation; **Bentivegna E:** Writing – Review & Editing; **Cacciafesta M:** Resources; **Martelletti P:** Resources; **Sesti G:** Resources

**Competing interests:** No competing interests were disclosed.

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**REVISED Amendments from Version 1**

This version of the article has details about the treatment with central nervous system agents in the groups of AD patients with and without diabetes. The references have been increased, considering the suggestions of the reviewers. The introduction and the discussion have been improved.

**Any further responses from the reviewers can be found at the end of the article**

## Introduction

Behavioral and psychological symptoms of dementia (BPSD) and delirium are common in the advanced phases of Alzheimer's disease (AD) and worsen with disease severity, whereas symptoms of cognitive decline may be prevalent in the first phases of the disease<sup>1</sup>.

Both the hyper- and hypo-glycemic extremes of the glycemic spectrum may worsen cognitive functions in AD patients<sup>2-4</sup>, and nutrition plays an important role in the development of the delirium in frail older patients<sup>5</sup>.

The aim of this preliminary report was to evaluate the relationship between delirium and glycemic control in the advanced phases of AD.

## Methods

### Ethical statement

The study involved human participants with metabolic syndrome in aging and it was performed in accordance with the ethical standards of the local institutional committee (S. Andrea Hospital, ID number 67910) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent for participation and evaluation of data was obtained from the individual participants included in this study or from their caregivers, where ability to consent was affected by delirium.

### Participants

We randomly (systematic sampling) enrolled 38 elderly patients ( $n = 11$  males and  $n = 27$  females) from the outpatients of the S. Andrea Hospital of Rome, in 2019. From their medical records, the patients met the criteria for probable AD dementia proposed by the National Institute on Aging-Alzheimer's Association (NIA-AA)<sup>6</sup> (Mini Mental State Examination (MMSE) score of  $12.4 \pm 7.3$ , mean + standard deviation, in the moderate-severe stage of the disease). Prior to inclusion, subjects with other diseases, such as territorial infarction, intracranial hemorrhage, brain tumor, hydrocephalus, or severe white matter hyperintensities (WMH) were excluded from the study. Sixteen of the patients (16/38, 42% of the sample) were affected by type 2 diabetes (T2DM, according to 2020 American Diabetes Association, ADA, criteria)<sup>7</sup>, undergoing treatment with oral glucose lowering agents ( $n = 13$ , one patient with repaglinide) or with insulin ( $n = 3$ ).

## Assessments

Each patient received from our group: a) a comprehensive geriatric assessment (CGA), including the evaluation of the Activity of Daily Living (ADL), the Instrumental Activities of Daily Living (IADL), the Cumulative Illness Rating Scale (CIRS) and the Marigliano-Cacciafesta Polypathology Scale (MCPS)<sup>8,9</sup>; b) an anthropometric evaluation, including height, weight, body mass index (BMI), waist circumference, Mini Nutritional Assessment (MNA)<sup>10</sup>; c) a behavioral and psychological examination, using the Cornell's scale, the Clinical Dementia Rating scale (CDR), the Neuropsychiatric Inventory (NPI) and the Confusion Assessment Method (CAM, with CAM-severity)<sup>11-13</sup>. An assessment of glucose metabolism, including fasting glycaemia and insulinemia (excluded in insulin-treated patients), glycated haemoglobin (HbA1c) and insulin resistance by the means of the HOMA-index (glycemia mg/dl x insulinaemia  $\mu$ U/mol /405) (excluded in insulin-treated patients) and an evaluation of renal function, measuring creatinine and glomerular filtration rate (GFR) estimated using the Chronic Kidney Disease Epidemiology Collaboration formula (CKD-EPI), was performed using a clinical chemistry analyzer (c16000 Architect System, Abbott Laboratories). A continuous glucose monitoring (FreeStyle Libre system) was used in selected patients with a high risk of hypoglycemic events, or with great variability of glycaemia during the day.

## Statistical analysis

For the statistical analysis, carried out using Primer of Biostatistics Version 7, one-way analysis of variance (ANOVA) was used for the evaluation of the differences between the groups of patients. The relationship between two variables was examined by the means of regression analysis. A  $p < 0.05$  was assumed as significant. Data are presented as mean + standard deviation.

## Results

The clinical characteristics of the 38 AD patients with and without T2DM are described in [Table 1](#)<sup>4</sup>.

The percentage of use of drugs (antipsychotics, sleeping pills, antidepressants, antidementia, antiparkinsonian agents, mood stabilizing medications) in AD patients with or without diabetes, were respectively: 37%, 19%, 19%, 6%, 19%, 6%, and 32%, 18%, 23%, 9%, 9%, 9% (differences not significant). One AD patients with diabetes was treated with zolpidem.

The MMSE scores were inversely and significantly related to CAM-S score ( $r = -0.585$ ,  $p < 0.001$ ), while MCPS scores were positively related to the CAM-S score ( $r = 0.440$ ,  $p < 0.05$ ) ([Figure 1a](#) and [1b](#)).

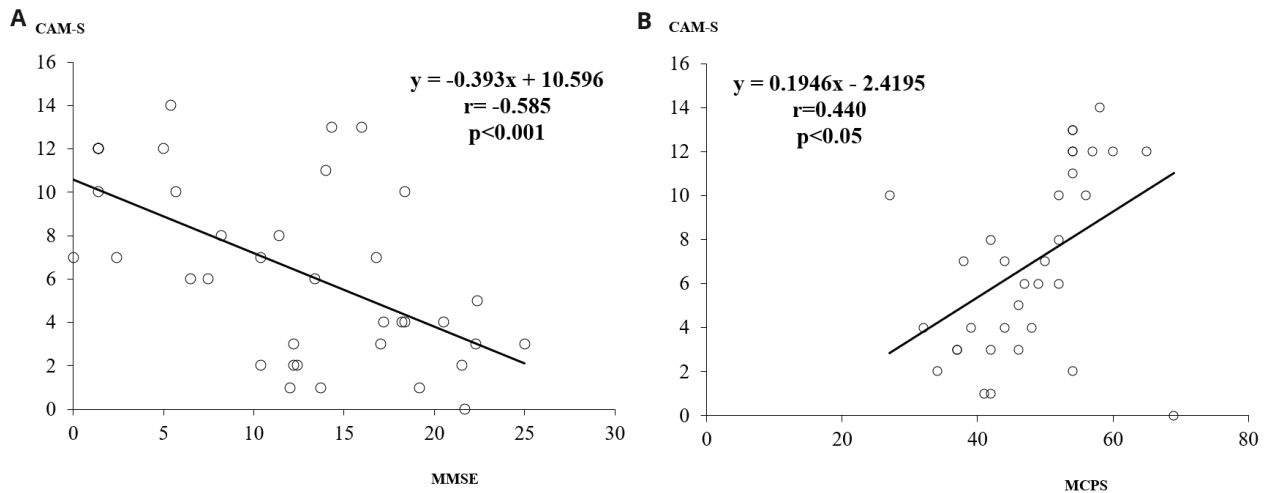
The regression analysis between HbA1c and MMSE score showed a concave downward "∩" parabola (not significant) with apex at HbA1c of 10.5% and MMSE of 13.0. The regression analysis between HbA1c and the psychometric BPSD scales (Cornell, NPI and CAM-S) showed a "U" shape (concave upward

**Table 1. Clinical characteristics in Alzheimer’s disease (AD) patients with (n = 16, females n = 9) and without (n = 22, females n = 18) type 2 diabetes (T2DM) (mean+standard deviation).**

	AD patients without T2DM	AD patients with T2DM
Age (years)	83.3+5.7	82.3+4.2
MMSE	11.6+7.1	12.7+7.5
ADL (IADL M and F)	2.9+2.2 (M: 1.7+1.7; F: 1.2+1.8)	2.7+1.8 (M: 1.4+1.5; F: 0.7+1.0)
MCPS	48.6+10.5	47.4+7.0
CIRS-SI and -CI	2.2+0.6 and 4.8+2.2	2.3+0.4 and 5.6+1.4
BMI	24.4+7.0	26.7+5.7
Waist circumference (cm)	M: 98.7+1.5; F: 90.3+22.6	M: 97.7+8.6; F: 89.1+15.2
MNA	17.4+6.0	18.8+4.8
Cornell	14.2+8.6	11.4+6.0
CDR	2.7+1.4	2.2+1.1
CAM	2.7+1.5	2.2+1.9
CAM-S	7.8+4.1	4.7+3.7*
NPI	53.7+28.5	40.2+20.2
Fasting glycaemia (mg/dl)	94.5+11.2	135.6+58.0**
Fasting insulinaemia (µu/ml)	6.0+2.6	8.9+9.5
HbA1c	5.4+0.4%	6.8+1.1%***
HOMA index	1.4+0.6	3.2+3.4*
GFR (CKD-EPI; ml/min)	66.0+16.9	64.9+23.4

MMSE, Mini Mental State Examination; ADL, Activity of Daily Living; IADL, Instrumental Activities of Daily Living; MCPS, Marigliano-Cacciafesta Polypathology Scale; CIRS, Cumulative Illness Rating Scale; SI, severity index; BMI, body mass index, MNA, Mini Nutritional Assessment; CDR, Clinical Dementia Rating scale; CAM, Confusion Assessment Method; CAM-S, CAM-severity; NPI, Neuropsychiatric Inventory; HbA1c, glycated haemoglobin; GFR, glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration formula; M, male; F, female.

\*p<0.05, \*\*p<0.01, \*\*\*p<0.0001.



**Figure 1. a)** The relationship between MMSE and CAM-S scores. **b)** The relationship between MCPS and CAM-S scores. MMSE, Mini Mental State Examination; CAM-S, Confusion Assessment Method-severity; MCPS, Marigliano-Cacciafesta Polypathology Scale.

parabola) (Cornell  $p < 0.05$ , NPI  $< 0.01$  and CAM-S  $p < 0.0001$ ) (Figure 2). The apices of the parabolas were at HbA1c of 6.9%, 7.6% and 10.3%, the levels that minimized the Cornell, NPI and CAM-S scores, respectively (Figure 2). Therefore, the mean HbA1c that minimized all the behavioural disorders was 8.3%.

Continuous glucose monitoring in selected patients ( $n = 3$ ) showed that, even if HbA1c level was within the normal range, either a great variability in glycaemia during the 24 hours or repeated hypo-glycemic events during the night (up to 26 hypoglycemic events in a single patient) were present (Figure 3).

**Discussion**

In our preliminary study, polyopathy and frailty was associated with the severity of delirium as demonstrated by using the MCPS scale in correlation with the CAM-S scale.

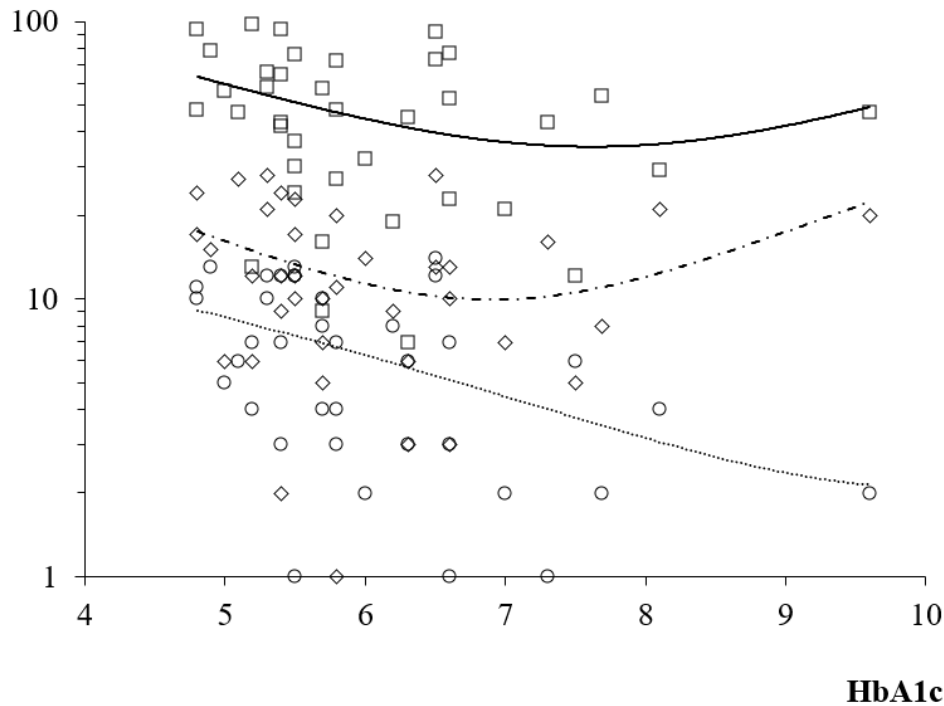
To the best of our knowledge this is the first report about the association of the MCPS and CAM-S scale, whereas the

MCPS was previously evaluated by our group in patients with comorbidities and frailty<sup>9</sup>.

Glycemic control was associated with modification of BPSD and delirium in the advanced phases of AD. In particular, delirium (as indicated by the CAM-S score) was more susceptible to the glycemic control in its low range. As considered by point 7 (Metabolism and Nutritional state) of MCPS, high glucose levels increase the score of the MCPS scale (+25) only in conditions of diabetes mellitus decompensation, with significant risks of development of delirium.

Glycemic control modulated the appearance of BPSD and delirium with a polynomial U-shaped curve, with both the hyper- and hypo-glycemic extremes of the glycemic spectrum worsening BPSD. The regression equations showed that HbA1c levels between 6.9–10.3% (mean 8.3%) minimized BPSD, in agreement with International Diabetes Federation (2020)<sup>15</sup> and ADA (2020)<sup>7</sup> guidelines for managing T2DM in older people. As matter of fact, in healthy older subjects (with few coexisting

**NPI/Cornell/CAM-S**

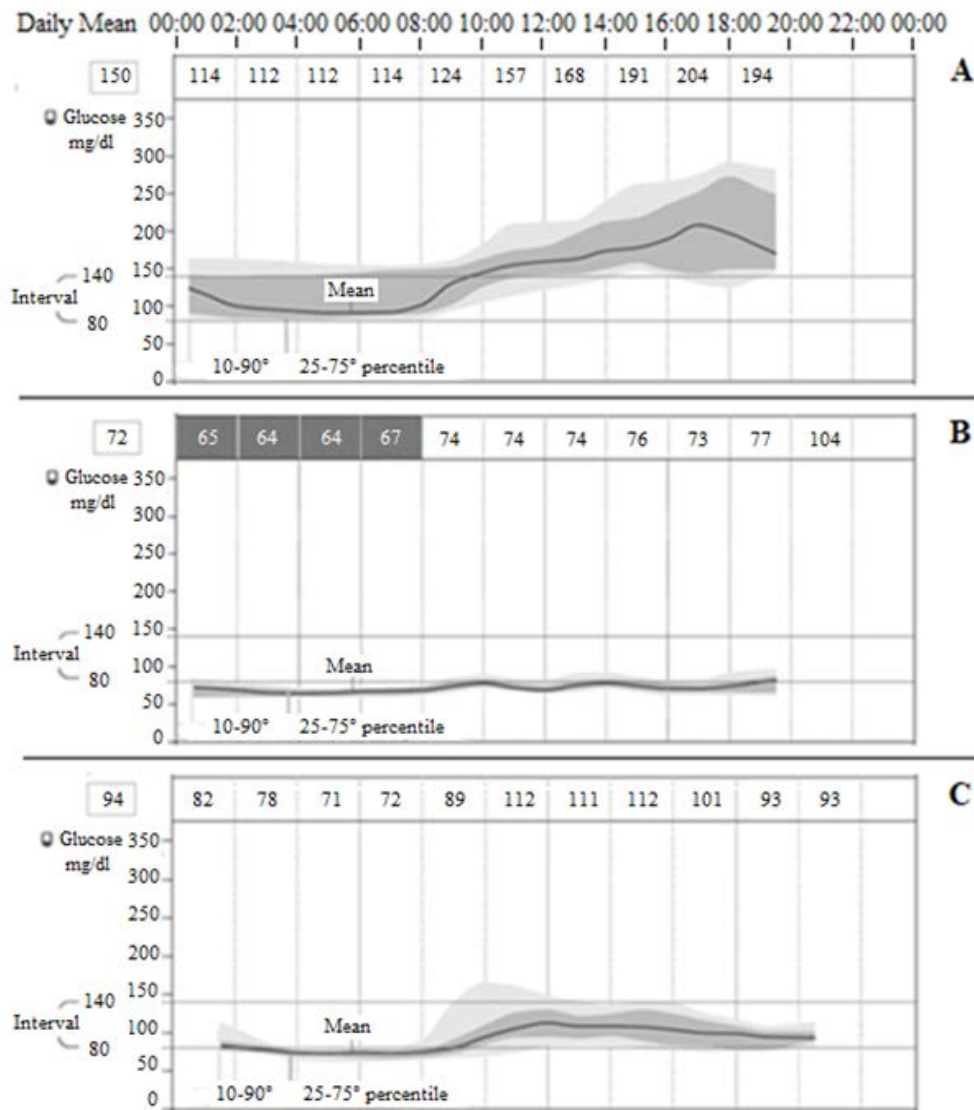


$NPI = 3.7 HbA1c^2 - 53.6 HbA1c + 239.5; R^2 = 0.101, p < 0.01.$  □ — NPI

$Cornell = 1.7 HbA1c^2 - 23.6 HbA1c + 91.5; R^2 = 0.122, p < 0.05.$  ◇ - - - Cornell

$CAM-S = 0.3 HbA1c^2 - 5.1 HbA1c + 27.9; R^2 = 0.175, p < 0.0001.$  ○ ..... CAM-S

**Figure 2.** The relationship between the glycated haemoglobin (HbA1c) and the Neuropsychiatric Inventory (NPI), Cornell's scale and Confusion Assessment Method-severity (CAM-S) score.



**Figure 3. Continuous glucose monitoring in selected cases (n=3).** **A)** Patient A, 81 years, MMSE=1.5, NPI=77, Cornell=13, CAM-S=17, HbA1c=6.6%, glucose mean 150 mg/dl, above/in/under the interval 56/43/1%, event of low glucose=0, mean duration=0, mean duration=0 min. **B)** Patient B, 77 years, MMSE=13.7, NPI=30, Cornell=12, CAM-S=4, HbA1c=5.5%, glucose mean 72 mg/dl, above/in/under the interval 0/16/84%, event of low glucose=26, mean duration=296 min. **C)** Patient C, 82 years, MMSE=10.5, NPI=52, Cornell=18, CAM-S=11, HbA1c=5.7%, glucose mean 94 mg/dl, above/in/under the interval 7/54/39%, event of low glucose=4, mean duration=281 min.

chronic illnesses, intact cognitive and functional status) a reasonable HbA1c goal is <7.5% (with fasting or pre-prandial glucose of 90–130 mg/dl), whereas in complex/poor health patients (with more chronic illnesses, moderate-to severe cognitive impairment or >2 ADL dependencies) the reasonable HbA1c goal rises to <8.5 (with fasting or pre-prandial

glucose of 100–180 mg/dl) to avoid possible overtreatment, hypoglycemic events and fall risk.

The HbA1c value of 6% corresponds to a mean glucose of 126 mg/dl, with 95% prediction limits of 100–152 mg/dl, which includes the lower goals for glycaemia (100–180 mg/dl)

suggested by ADA standard of care<sup>16–18</sup> in older frail patients with moderate-severe dementia. More than half of our patients (22/38, 58%) showed HbA1c levels lower than 6%.

The reduction of one point (%) of HbA1c (from 6.8% to 5.8%) was associated with an increase of +2.2 points in Cornell, +7.0 points in NPI and +0.2 in CAM-S scores. Because of the parabolic profiles of the curves, another reduction of one point of HbA1c (from 5.8% to 4.8%) resulted in an exponential increase of BPSD scores (+5.6 Cornell, +14.4 NPI and +2.6 CAM-S).

The variability of glycaemia seemed to be associated with greater BPSD in AD patients, although it was not possible to carry out a statistical analysis because of the few number of patients in the sample (a limit of the study).

The treatment with central nervous system drugs (antipsychotics, sleeping pills, antidepressants, antidementia, antiparkinsonian agents, mood stabilizing medications) may be a confounding

factor in AD patients<sup>19–21</sup>, but, as above reported, no differences were found in the present study between the two AD groups with and without diabetes.

In conclusion, the measurement of HbA1c in elderly AD patients with advanced dementia (with and without T2DM) is recommended in order to evaluate glycaemic control (and nutritional status). The reduction of mean glycaemic levels (due to malnutrition in non-diabetic patients or overtreatment in diabetic patients) should be avoided by means of a multidimensional approach.

### Data availability

DANS EASY: The Glycaemic Control and the Severity of the Delirium. <https://doi.org/10.17026/dans-xq4-58fq><sup>14</sup>.

Data are available under the terms of the [Creative Commons Zero “No rights reserved” data waiver](#) (CC0 1.0 Public domain dedication).

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# Open Peer Review

Current Peer Review Status:  

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Version 1

Reviewer Report 13 July 2021

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**Takahiko Nagamine** 

<sup>1</sup> Director of Sunlight Brain Research Center, Hofu, Japan

<sup>2</sup> Department of Emergency Medicine, Matsumoto Surgical Hospital, Hofu, Japan

This paper analyzes HbA1c (blood glucose control status) and delirium in patients with Alzheimer's disease. It is interesting to note that both high and low blood glucose levels increase the risk of delirium. The paper is clinically significant because it shows that HbA1c as a predictor of delirium may be valid.

If possible, two points should be considered: one is to conduct a study with separate analysis for the presence or absence of diabetes mellitus, and the other is to design the study to take into account the effects of antipsychotics and sleeping pills on blood glucose and delirium.

Alzheimer's disease is caused by a decrease in neurotransmission in the acetylcholine system. The central acetylcholine nervous system may be less responsive to glucose loading. Older patients with Alzheimer's disease may occasionally experience hypoglycemia. This is due not only to the decline in acetylcholine and other neurotransmitters in Alzheimer's disease itself but also to antipsychotic drugs used for delirium <sup>1</sup>.

The level of HbA1c is also affected by the type of hypoglycemic drug. For example, concomitant use of insulin secretagogues (e.g., sulfonylureas) and dopamine blockers can cause hypoglycemia and delirium-like disturbances in consciousness <sup>2</sup>.

To avoid the effect of diabetic drugs, it is recommended to divide Alzheimer's disease into two groups, one with comorbid diabetes and the other without diabetes, and study the relationship between HbA1c and delirium in each group. Delirium is influenced by Alzheimer's disease, but also by medications used to treat insomnia (e.g., benzodiazepine receptor agonists), so it is advisable to adjust for medications that have a risk of inducing delirium as a background factor <sup>3</sup>.

Even though there are confounding factors, the study of HbA1c as a predictor of delirium is very unique and a good perspective from the point of view that Alzheimer's disease is called diabetes of the brain.



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3. Nagamine T: Long-term preoperative use of zolpidem is associated with postoperative delirium in elderly patients undergoing hip surgery. *Psychogeriatrics*. 2021; **21** (4): 689-690 [Publisher Full Text](#)

**Is the work clearly and accurately presented and does it cite the current literature?**

Yes

**Is the study design appropriate and is the work technically sound?**

Yes

**Are sufficient details of methods and analysis provided to allow replication by others?**

Yes

**If applicable, is the statistical analysis and its interpretation appropriate?**

Partly

**Are all the source data underlying the results available to ensure full reproducibility?**

Yes

**Are the conclusions drawn adequately supported by the results?**

Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** psychopharmacology, emergency medicine, diabetes

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

Author Response 22 Jul 2021

**Antonio Martocchia**, Sapienza University of Rome, ROMA CAPITALE, Italy

Dear Prof Takahiko Nagamine,

We agree with the evidence about HbA1c as a predictor of delirium in Alzheimer's disease and with the interest about the effects of the presence/absence of diabetes mellitus or concurrent therapies (antipsychotics and sleeping pills, as well as insulin secretagogues, e.g. sulfonylureas, and dopamine blockers) on HbA1c and delirium.

In our sample of AD patients with diabetes, one subject was treated with repaglinide (we added a sentence in the text in methods).

The percentage of use of drugs (antipsychotics, sleeping pills, antidepressants, antidementia, antiparkinsonian agents, mood stabilizing medications) in AD patients with or without diabetes, were respectively: 37%, 19%, 19%, 6%, 19%, 6%, and 32%, 18%, 23%, 9%, 9%, 9% (differences not significant) (we added a sentence in the text, results and discussion). One AD patients with diabetes was treated with zolpidem. We added the suggested references in the bibliography's list.  
Yours sincerely, Antonio Martocchia, MD PhD

**Competing Interests:** No competing interests were disclosed.

Reviewer Report 17 May 2021

<https://doi.org/10.5256/f1000research.28717.r85330>

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**Sandra Sigala** 

Section of Pharmacology, Department of Molecular and Translational Medicine, University of Brescia, Brescia, Italy

The Ms entitled "The effects of the glycaemic control on the severity of the delirium in the advanced phase of Alzheimer's disease" by Martocchia and coll is very interesting and gives support to the evidence that glycaemic control in the frail elderly is important in slowing cognitive degeneration/Alzheimer's onset.

Authors highlighted as well the importance in these patients of a comprehensive clinical evaluation, which includes both biochemical and functional values.

The main limit of the study is the sample size, but this point has been taken up and discussed by the Authors themselves.

I have only minor points to underline:

1. The first sentence in the Introduction needs a reference
2. Characters in the Figure legend need to be unified - Figure 3 is hard to read
3. Throughout the Ms, please correct typos and the language style

**Is the work clearly and accurately presented and does it cite the current literature?**

Yes

**Is the study design appropriate and is the work technically sound?**

Yes

**Are sufficient details of methods and analysis provided to allow replication by others?**

Yes

**If applicable, is the statistical analysis and its interpretation appropriate?**

Yes

**Are all the source data underlying the results available to ensure full reproducibility?**

No source data required

**Are the conclusions drawn adequately supported by the results?**

Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Clinical pharmacology; translational oncology

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

Author Response 22 Jul 2021

**Antonio Martocchia**, Sapienza University of Rome, ROMA CAPITALE, Italy

Dear Reviewer Prof Sandra Sigala,

We really appreciated your review, discussing the importance of a comprehensive clinical evaluation in frail elderly with Alzheimer's disease.

We agree that the limit of study is the sample size: we completed the sentence in the manuscript in the Discussion: "The variability of glycaemia seemed to be associated with greater BPSD in AD patients, although it was not possible to carry out a statistical analysis because of the few number of patients in the sample (a limit of the study)".

We added the reference (1) and modified the first sentence: "Behavioral and psychological symptoms of dementia (BPSD) and delirium are common in the advanced phases of Alzheimer's disease (AD) and worsen with disease severity, whereas symptoms of cognitive decline may be prevalent in the first phases of the disease (1)".

We unified the characters in the figure legends.

We modified the figure 3.

We corrected typos and the language style throughout the Ms.

Yours sincerely Antonio Martocchia, MD PhD

**Competing Interests:** No competing interests were disclosed.

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