PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Continuous glucose monitoring in older people with diabetes and memory problems – a mixed-methods feasibility study in the United Kingdom
AUTHORS	Mattishent, Katharina; Lane, Kathleen; Salter, Charlotte; Dhatariya, Ketan; May, Helen; Neupane, Sankalpa; Loke, Yoon

VERSION 1 – REVIEW

REVIEWER	Steven Trawley Cairnmillar Institute, Melbourne, Australia
REVIEW RETURNED	26-Jul-2019

GENERAL COMMENTS	The authors presented a study on the use of flash monitoring among an older cohort of people with diabetes with a formal diagnosis of dementia or a score <8 on the AMT. This is an important area of research and it is fantastic that the authors have engaged with such a difficult research situation. Overall feedback on the use of the Libre was positive but the issue of participants not scanning at least 3 times a day to provide a complete glycemic picture was highlighted. However, to what extend this was due to memory failure memory or mirrored typical use of flash monitoring among older adults with diabetes is not clear. I think the authors could expand on this point in their manuscript. Further points below. General notes: * Participants were not screened for depression. Potential for depressive pseudodementia? * Mixture of type 1 and type 2 diabetes. Different cognitive profiles have been reported between these patient groups (e.g., Biessels 2008). Worth discussing this I think. * More detail on the severity of cognitive impairment each participant was experiencing would have been helpful. Cognitive profile of the 12 participants was probably quite varied - possibly ranging from MCI to mild/moderate dementia. How this range impacted their use of flash monitoring would be interesting. * The majority of participants lived with someone. How many libre scans were prompted by family members or carers? Analysis of unprompted use of flash monitoring, particularly across different cognitive status, would be of significant value. Future work could specifically ask carers to note when a scan was prompted by

	them. This could be linked to the issue of prospective memory failures among people with diabetes (Trawley 2019). * Is there a cluster of libre scans at specific times? Where they linked to particular events - such as usual times of fingerprick testing / meal times, bedtime, etc. Can the authors extract this data? Was there any learning trend in the daily scan rates? Did participants get more consistant over time? Or peak at start? * Figure 2 is hard to read. Better to redo this stacked barchart without the 3D effect on a white background. Also the x-axis should be labeled - I'm guessing each bar is a participant but that is not obvious (nor is the order as it might be sorted to % of time hypo not participant number). * Time in range data is not discussed fully - probably due to the low capture rate and lack of a comparison period. This could be developed more though I think. * Clarify why scanning 3 times a day is important re the libre (e.g.,sensor memory limitations). Also the issue of those 3 times needing to be 8 hours apart. Relate to scan times cluster issue. Is it correct to say if they scan in the morning (say a few times between 7AM - 10AM) and leave it until bedtime (11PM) there will still be a CGM data capture gap around dinner time (6PM -11PM)? Worth discussing perhaps. * Do the authors have info on number of usual SMBG checks performed by the participants? Maybe the number of scans performed is related to the number of SMBG checks the person usually performs? Seperate it from memory issue. * In the interviews did the participants mention the issue of just forgetting to scan? One participant was quoted as saying "I don't even know it's on" - link between memory problems and forgetting to scan? REF Biessels, G. J., Deary, I. J., & Ryan, C. M. (2008). Cognition and diabetes: a lifespan perspective. The Lancet Neurology, 7(2), 184-190. Trawley, S., Baptista, S., Pouwer, F., & Speight, J. (2019). Prospective memory slips are associated with forgetting to take glucose-lowering therapies among adults with diabetes: results from the second Diabetes MILES–Australia (MILES-2) survey. Diabetic Medicine, 36(5), 569-577.

REVIEWER	Sheila Black University of Alabama, USA
REVIEW RETURNED	01-Aug-2019

GENERAL COMMENTS	Continuous glucose monitoring in older people with diabetes and memory problems – a feasibility study The authors examined the suitability of using a particular Continuous glucose monitoring (CGM) system (i.e., FreeStyle Libre) to track glucose readings among older adults with memory problems. Authors reported that feasibility criteria included numbers of eligible patients, recruitment, attrition, extent of capture of glucose readings and adverse events. They were particularly concerned with tracking hypoglycemia, as it is associated with serious physical and cognitive health outcomes. Participants were recruited from hospitals. To be eligible for the study, participants had to be over 65 and have a score ≤ 8 on the abbreviated mental test or have a preexisting diagnosis of dementia. Although CGM has been shown to be an efficacious way to improve glucose monitoring among children and younger adults, CGM has not been studied extensively among older adults. This study examined the feasibility of a particular type of CGM 'flashglucose monitoring'. One feature of the FreeStyle Libre is that participants or carers swipe the reader over a sensor and obtain both immediate feedback about glucose readings as well as readings from 8 hours earlier. Only 12 of 49 patients actually completed the study. Among the participants who completed the study, 55% of readings were actually captured. Participants and carers also received a qualitative interview. Their assessments of the FreeStyle Libre was mostly positive. The topic of this study is vitally important. Twenty percent of older adults suffer from Type 2 diabetes and many of these individuals find it difficult to manage diabetes—in part because of cognitive decline. Hypoglycemia is a problem for older adults in general, but it is particularly a problem for older adults with memory problems. The FreeStyle Libre, along with other CGMs, may help healthcare providers and carers track hypoglycemia. The authors point out that their study is unique in that both carers and patients participated in the study and because this study examined the efficacy of a particular type of CGM, 'flash glucose monitoring' via the FreeStyle Libre . I believe the study was important. However, I have some concerns about the generalizability of the study, given the low number of participants and the advanced age of the participants (Mean age, 85). As the authors pointed out, a number of individuals dropped out of the study because they found the procedures too cumbersome. In addition, many of the individuals with memory problems had difficulty tracking their glucose at least three times a day. I agree with their conclusion that participants might be better served with real time devices that provided automated data tracking. This manuscript was overall well-written and provided information about the feasibility of the FreeStyle Libre in comparison with automated CGMs. I would like to see it published.

	Minor Concerns: The authors should provide more detail about the abbreviated mental test. The following phrase on page 6 should be stated clearer: “at least eight-hourly in order to achieve complete”

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Steven Trawley

Institution and Country: Cairnmillar Institute, Melbourne, Australia

Please state any competing interests or state ‘None declared’: None

Please leave your comments for the authors below The authors presented a study on the use of flash monitoring among an older cohort of people with diabetes with a formal diagnosis of dementia or a score <8 on the AMT. This is an important area of research and it is fantastic that the authors have engaged with such a difficult research situation. Overall feedback on the use of the Libre was positive but the issue of participants not scanning at least 3 times a day to provide a complete glycemic picture was highlighted.

However, to what extend this was due to memory failure memory or mirrored typical use of flash monitoring among older adults with diabetes is not clear. I think the authors could expand on this point in their manuscript.

Response: We have expanded our Discussion section on page 17 to include the following:
This study has shown that whilst the participants found wearing the sensor acceptable, data capture varied, depending on how many times the reader was used to scan the sensor during the study period. This is in contrast to findings from Reudy et al’s study (a post-hoc analysis of the multi-centre DIAMOND trial) looking at the effectiveness of CGM in adults aged 60 years and older with type1 or type 2 diabetes using multiple daily insulin injections. The authors found that of the 61 participants in the CGM group completing the study, 97% used CGM 6 or more days per week at the six-month follow-up (1).
It should be noted though that these participants were not frail, and the inclusion criteria required a stable diabetes regime for three months prior to study entry, use of SMBG three or more times daily, with no history of recurrent hypoglycaemia (2).
Our study illustrates the real-world difficulties that older people with memory problems and their carers face in glucose self-monitoring. We are aware of other studies using flash glucose monitoring in older people, but these have not reported on the extent of data capture (3) (4).

Further points below.

General notes:

* Participants were not screened for depression. Potential for depressive pseudodementia?

* Mixture of type 1 and type 2 diabetes. Different cognitive profiles have been reported between these patient groups (e.g., Biessels 2008). Worth discussing this I think.

* More detail on the severity of cognitive impairment each participant was experiencing would have been helpful. Cognitive profile of the 12 participants was probably quite varied - possibly ranging from MCI to mild/moderate dementia. How this range impacted their use of flash monitoring would be interesting.

* The majority of participants lived with someone. How many libre scans were prompted by family members or carers? Analysis of unprompted use of flash monitoring, particularly across different cognitive status, would be of significant value. Future work could specifically ask carers to note when a scan was prompted by them. This could be linked to the issue of prospective memory failures among people with diabetes (Trawley 2019).

Response: We accept that participants may have different cognitive profiles depending on the type of diabetes or other psychological issues, however, this does not change the need for a management strategy directed at hypoglycaemia detection and minimisation. Our feasibility study was not about making new dementia diagnoses. Rather, we wanted to identify all patients with memory problems (irrespective of the possible underlying pathology) who might benefit from the use of CGM in detecting out-of-range glucose values.

We fully agree that it would be very interesting to correlate extent of data capture with regards to multiple covariates such as severity of dementia, functional status, cognitive profile, type of diabetes, co-morbid psychological conditions, familiarity with self-monitoring, and involvement of carers. Given the large number of influential variables, however, this would require a large cohort study that is several times the size of our feasibility trial, so that the relative contribution and interaction of all the subgroups and underlying characteristics could be adequately evaluated in a multivariable regression model.

We note that current trial methodology frowns on the use of post-hoc subgroup analyses to evaluate parameters and outcomes that have not previously been pre-specified as part of the analytic plan. This is because of the high risk of bias from spurious and misleading construction of subgroups, and selection of results for reporting based on statistical significance. Hence, it would be methodologically unsound to deviate from the original analytic plan of our feasibility study which was specified for a different purpose, and was never powered to evaluate relative contribution of multiple patient factors in extent of data capture.

We do agree that a large prospective cohort study to identify factors influencing the successful use of continuous glucose monitoring in patients with memory problems would be valuable and we have now added this as a proposal in the Discussion section.

* Is there a cluster of libre scans at specific times? Where they linked to particular events - such as usual times of fingerprick testing / meal times, bedtime, etc. Can the authors extract this data? Was there any learning trend in the daily scan rates? Did participants get more consistent over time? Or peak at start?

Response: The typical times when participants scanned the reader were around mealtimes, and when they might have taken their medication. We did not identify any learning trends or that participants got more consistent over time.

* Figure 2 is hard to read. Better to redo this stacked barchart without the 3D effect on a white background. Also the x-axis should be labeled - I'm guessing each bar is a participant but that is not obvious (nor is the order as it might be sorted to % of time hypo not participant number).

Response: We have amended Figure 2 and added the following sentence on page 12: Figure 2 shows those participants with hypoglycaemic episodes first, followed by the six participants who did not experience hypoglycaemic episodes. The percentage of time spent in the hypoglycaemic range is illustrated in red (below 4 mmol/L), time spent in range in green (4-10 mmol/L), and time spent above range is illustrated in yellow (above 10 mmol/L).

* Time in range data is not discussed fully - probably due to the low capture rate and lack of a comparison period. This could be developed more though I think.

Response: We have added the following sentence on page 18:
Based on a recently published international consensus on clinical targets for CGM data interpretation, only four out of the twelve participants reached the target of 70% or more data capture in fourteen days (5). The consensus statement for CGM targets in older people is that they should spend more than 50% in the target range (3.9-10 mmol/L), less than 1% below the target range (<3.9 mmol/L) and less than 10% above target (>13.9 mmol/L). Of the six participants who experienced hypoglycaemic episodes during the 14 days of wearing the device, only one spent 1% below the target range. Six participants reached the above 50% time in range target.

* Clarify why scanning 3 times a day is important re the libre (e.g.,sensor memory limitations). Also the issue of those 3 times needing to be 8 hours apart. Relate to scan times cluster issue. Is it correct to say if they scan in the morning (say a few times between 7AM - 10AM) and leave it until bedtime (11PM) there will still be a CGM data capture gap around dinner time (6PM -11PM)? Worth discussing perhaps.

Response: We have added the following sentence on page 8: If there is a gap of more than 8 hours between scans, then there will be missing data. For example, if there is a 10-hour gap between two scans, then there will be two hours of lost data.

* Do the authors have info on number of usual SMBG checks performed by the participants? Maybe the number of scans performed is related to the number of SMBG checks the person usually performs? Separate it from memory issue.

Response: We did not collect data on the number of SMBG checks, but have added a column to Table 1 illustrating which participants were conducting daily SMBG checks.

* In the interviews did the participants mention the issue of just forgetting to scan? One participant was quoted as saying "I don't even know it's on" - link between memory problems and forgetting to scan?

Response: The participants did not mention the issue of forgetting to scan. The interview focussed on acceptability of the device, including any negative experiences (such as anxiety) during the study period.

We have changed the last sentence of the Introduction section on page 6 to:

In addition, we asked participants (and their carers) about their experience of using of the device (including anxiety or inconvenience related to wearing the CGM sensor), and whether they experienced any adverse events (pain or skin reactions).

On page 15 we have clarified the following sentence:

Participants and carers overwhelmingly found using the device acceptable. Almost without exception participants reported the device was so unobtrusive that they did not know or were not conscious of wearing the device throughout the two weeks and that it did not interfere with day-to-day activities

REF
Biessels, G. J., Deary, I. J., & Ryan, C. M. (2008). Cognition and diabetes: a lifespan perspective. The Lancet Neurology, 7(2), 184-190.

Trawley, S., Baptista, S., Pouwer, F., & Speight, J. (2019). Prospective memory slips are associated with forgetting to take glucose-lowering therapies among adults with diabetes: results from the second Diabetes MILES–Australia (MILES-2) survey. Diabetic Medicine, 36(5), 569-577.

Reviewer: 2
Reviewer Name: Sheila Black

Institution and Country: University of Alabama, USA

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below Continuous glucose monitoring in older people with diabetes and memory problems – a feasibility study

The authors examined the suitability of using a particular Continuous glucose monitoring (CGM) system (i.e., FreeStyle Libre) to track glucose readings among older adults with memory problems. Authors reported that feasibility criteria included numbers of eligible patients, recruitment, attrition, extent of capture of glucose readings and adverse events. They were particularly concerned with tracking hypoglycemia, as it is associated with serious physical and cognitive health outcomes. Participants were recruited from hospitals. To be eligible for the study, participants had to be over 65 and have a score ≤ 8 on the abbreviated mental test or have a preexisting diagnosis of dementia. Although CGM has been shown to be an efficacious way to improve glucose monitoring among children and younger adults, CGM has not been studied extensively among older adults. This study examined the feasibility of a particular type of CGM 'flashglucose monitoring'. One feature of the FreeStyle Libre is that participants or carers swipe the reader over a sensor and obtain both immediate feedback about glucose readings as well as readings from 8 hours earlier. Only 12 of 49 patients actually completed the study. Among the participants who completed the study, 55% of readings were actually captured. Participants and carers also received a qualitative interview. Their assessments of the FreeStyle Libre was mostly positive.

The topic of this study is vitally important. Twenty percent of older adults suffer from Type 2 diabetes and many of these individuals find it difficult to manage diabetes—in part because of cognitive decline. Hypoglycemia is a problem for older adults in general, but it is particularly a problem for older adults with memory problems. The FreeStyle Libre, along with other CGMs, may help healthcare providers and carers track hypoglycemia. The authors point out that their study is unique in that both carers and patients participated in the study and because this study examined the efficacy of a particular type of CGM, 'flash glucose monitoring' via the FreeStyle Libre .

I believe the study was important. However, I have some concerns about the generalizability of the study, given the low number of participants and the advanced age of the participants (Mean age, 85). As the authors pointed out, a number of individuals dropped out of the study because they found the procedures too cumbersome. In addition, many of the individuals with memory problems had

difficulty tracking their glucose at least three times a day. I agree with their conclusion that participants might be better served with real time devices that provided automated data tracking.

Response: We have expanded on the generalizability of our findings on page 21 with this added text: We believe that older people with memory problems anywhere in the world will face similar hurdles when using a new technological device. However, we had difficulty recruiting eligible participants who had severe dementia needing full-time residential care. Our findings cannot be generalised to this group.

This manuscript was overall well-written and provided information about the feasibility of the FreeStyle Libre in comparison with automated CGMs. I would like to see it published.

Minor Concerns:
The authors should provide more detail about the abbreviated mental test.
The following phrase on page 6 should be stated clearer: "at least eight-hourly in order to achieve complete"

Response: We have now provided more detail about the AMT on page 20:
With regards to the use of the AMT, we acknowledge that its use only covers three cognitive domains (memory, orientation, attention/calculation) and there are more rigorous cognitive tests available. The more rigorous tests do not necessarily lend themselves to being carried out in an acute busy hospital setting (20). Our feasibility study was not about making new dementia diagnoses. Rather, we wanted to identify inpatients with any memory problems (irrespective of the possible underlying pathology) during their hospital admission who might benefit from the use of CGM.

We have amended the sentence on page 8 to: Whilst glucose levels are measured continuously, data are not transmitted continuously from the sensor. Instead, the user has to swipe the sensor with a reader (hence the term 'flash glucose monitoring' used by the manufacturer) at eight-hourly intervals in order to achieve complete capture of data throughout the two-week life-span of a sensor.

References

1. Ruedy KJ, Parkin CG, Riddlesworth TD, Graham C. Continuous Glucose Monitoring in Older Adults With Type 1 and Type 2 Diabetes Using Multiple Daily Injections of Insulin: Results From the DIAMOND Trial. J Diabetes Sci Technol. 2017:1932296817704445.
2. Beck RW, Riddlesworth T, Ruedy K, Ahmann A, Bergenstal R, Haller S, et al. Effect of Continuous Glucose Monitoring on Glycemic Control in Adults With Type 1 Diabetes Using Insulin Injections: The DIAMOND Randomized Clinical Trial. Jama. 2017;317(4):371-8.
3. Alitta Q, Grino M, Adjemout L, Langar A, Retornaz F, Oliver C. Overestimation of Hypoglycemia Diagnosis by FreeStyle Libre Continuous Glucose Monitoring in Long-Term Care Home Residents With Diabetes. J Diabetes Sci Technol. 2018;12(3):727-8.
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5. Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, et al. Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range. Diabetes Care. 2019.

VERSION 2 – REVIEW

REVIEWER	Steven Trawley Cairnmillar Institute
REVIEW RETURNED	29-Sep-2019

GENERAL COMMENTS	The reviewer completed the checklist but made no further comments.