PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Does intensive glycaemic control promote healing in diabetic foot ulcers? A feasibility study
AUTHORS	Dissanayake, Ajith; Vandal, Alain C.; Boyle, Veronica; Park, Diane; Milne, Bobbie; Grech, Roger; Ng, Anthony

VERSION 1 – REVIEW

REVIEWER	Nestoras Mathioudakis, MD MHS Johns Hopkins University Baltimore, MD USA
REVIEW RETURNED	07-Feb-2019

GENERAL COMMENTS	This is an important study designed to assess feasibility of a future RCT to evaluate the impact of glycemic control on wound outcomes in patients with DFUs. The study adds important information in this field, particularly the correlation between change in ulcer area and change in fasting blood glucose. Comments/Questions: 1. A main area of confusion for me in reading this paper relates to the Phases in Substudy 1. I had a difficult time understanding the two phases. Perhaps the authors should consider inclusion of a figure or study flowchart to make this more clear. 2. Please use fasting blood glucose (rather than sugar) consistently throughout the manuscript. 3. Spelling errors: Page 4 line 29 (relationship); page 13, line 8 (hereafter) 4. Diabetes as an adjective- line 6, page 3. Consider switching either to patients with diabetes or diabetic patients. 5. Please put exact study dates for the studies on page 7 (i.e. February 1, 2016 to...) 6. Why was change in A1C not analyzed or reported in addition to change in fasting BG? The authors should consider referencing the following paper (Feeseha BK et al, Association of Hemoglobin A1C and Wound Healing in Diabetic Foot Ulcers, Diabetes Care, 2018 July; PMID: 29661917) 7. For clarity- consider labelling the substudies in the table to guide the reader. There is a lot information presented in this manuscript and this could help with readability. Also, please add N's to the tables with associations or table legends. 8. Page 11, line 46: Why was the 95% CI reported for the actual 24 participants recruited? Isn't this an exact number? I understand that 95% CI's can be used when showing estimated probabilities from the models, but the actual numbers are exact. 9. Page 9: Methods- How was the cox proportional model assumption verified?

REVIEWER	Uma Gunasekaran University of Texas Southwestern
REVIEW RETURNED	14-Feb-2019

GENERAL COMMENTS	I have attached my specific comments. I think that this topic is a very important one in the field of diabetic foot ulcers, a whole in the literature that has yet to be rectified. I am exciting that this group is taking this on. Unfortunately, I feel that there are major flaws in this paper, especially surrounding large assumptions being made that detract from the work that was conducted. I feel that this paper cannot be published without major revisions. Use of FCBS as a surrogate marker for glycemic control and medication adherence Because FCBS is being used as a marker for both glycemic control and medication adherence (page 8), it needs a reference that shows that this alone is an adequate marker to make assumptions about both factors. I would think that a 4 point glucose would be more effective in gaining this information or potentially using a pharmacy refill history. Without a reference, I find this to be an inadequate surrogate. Additionally, in looking at Table 2, the median Hba1c in Substudy 2 was 94mmol/mol which would be roughly equivalent to an average blood sugar of 14.5mmol/L, but the median FCBS in Substudy 2 is 9mmol/L. This makes me question the use of FCBS as a marker of glycemic control. The previously referenced studies and guidelines are all based on Hba1c targets as opposed to FCBS so it is hard to make this argument. Mean vs. Median in examining FCBS and Hba1c In Table 2, median values are provided for baseline values. On page 12, the mean difference from baseline to endpoint is provided. I would want to see the baseline and endpoint values for the mean if that is the measure that is going to be used to determining glycemic improvement. Use of log ulcer area vs ulcer area Though it is stated on page 13 that the log ulcer area is more sensitive, I am unclear as to why this is the case and would ask for more explanation on this point as well as a reference where this measure is used in examining foot ulcers. Rate of absolute ulcer area change vs. Rate of relative ulcer area change On page 13, it states that the absolute ulcer change area showed a significant change. This is not congruent with Table 2 where there is a significant change with rate of relative ulcer area change. Discussion As this is a feasibility study looking to potentially lead to a RCT, it is very important to consider the inclusion criteria. In the discussion section on page 14, there is a comment about potentially relaxing IC2 (need to have diabetes for one year or more with a Hb1c of 60mmol/L or more). I think that it is important to think about whether patients who are recently diagnosed are really the same as patients who have had diabetes longer, more changes due to hyperglycemia- specifically around healing factors. I would advocate that they not dismiss IC2 without mentioning this. Further commentary discussed medication burden being a cause of dissatisfaction and rectifying this may lead to improved medication adherence. First, there has been no mention of what the medication regimen was for the 20 patients enrolled in Substudy 2 to understand what these patients considered to be a

	“medication burden.” Furthermore, on page 8, there was a mention that FCBS was going to be used as a marker for medication adherence and yet there is no mention of this in the discussion section. Relationship to other studies Once again, it is mentioned that intensive insulin therapy led to improved ulcer healing in this study. The intensive insulin regimen needs to be defined or described. Also intensive insulin therapy does not automatically equate to improved control. Though it was mentioned in the results section that both FCBS and Hba1c were reduced, further discussion in this section along with direct comparison of glycemic control in the other referenced studies is needed. Implications for a full study The first sentence of this section states that because the log ulcer area correlates well with glycemic control and the quality of life questionnaire, it is a valid measure. I think the only way this statement works is that the authors would like for intensive glycemic control (need numbers to prove this) and patient satisfaction to correlate with the log ulcer area. They have yet to prove this as a valid measure in the paper and therefore I cannot agree that I am convinced. The basic assumption in that statement is that if patients are happy and blood sugars are doing well then obviously, the ulcer should be healing better. This is what is yet to be determined in the literature. Implications for a full study Once again on page 16, there is more discussion about how glycemic control was better in the first 4-6 weeks and more variable after that. Figures/tables should present the glycemic data. Also, it is stated that the medication burden correlated with adherence (no clear understanding of how adherence is measured beyond the FCBS which I feel is inadequate) and attendance to clinic visits. A correlation does not necessarily mean cause and effect and this should be more clearly stated. Because it is mostly based on expert opinion, there should be consideration made as to what Hba1c level should be the target for optimal wound healing in a full study- < 53mmol/mol? <64mmol/mol? This would be of additional benefit to treating providers to know, especially balanced against the burden of hypoglycemia. Limitations The fact that substudy 2 did not actually reach its power is a very big problem with this study. I find it difficult to agree with any of the conclusions made if they did not actually reach their intended participant target, especially when using statistical analysis. Interestingly the study population in Substudy 1 and Substudy 2 were actually different in terms of ethnicity and this should be mentioned. Other limitations that should be mentioned include exclusion of chronic ulcers and non-adherent patients. In the real world, chronic ulcers are common in the diabetes population with foot ulcers as is non-adherence to treatment regimens. Therefore, it should be clearly stated that the feasibility trial was used to understand glycemic control in acute ulcers in adherent patients. It is generally understood that research participants are different from the average patient. Finally, there should be a better measure of medication adherence and more transparency in the “intensive insulin management” protocol used. There are always 2 sides to suboptimal glycemic

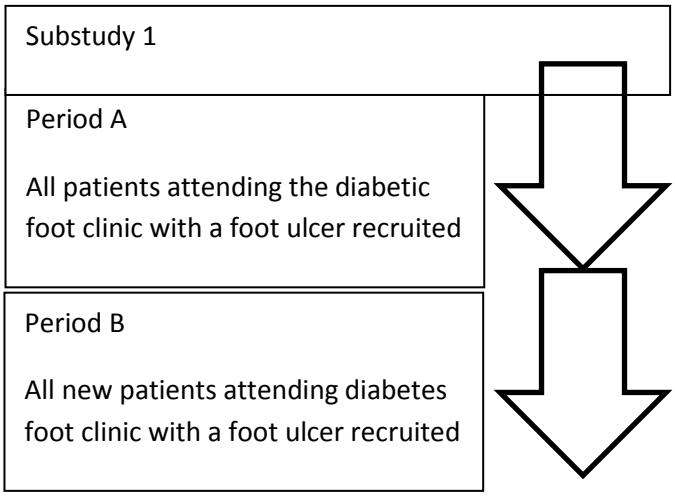
	control- patient adherence and the appropriate prescription from the provider. This study uses the FCBS to state that patients are not adherent if their FCBS does not improve when there is no information as to whether they were prescribed an appropriate insulin regimen. Issues with references Lines 24-31 on page 5 state that a meta-analysis was performed using 9 RCTs but reference 11 does not have this meta-analysis (perhaps reference 18?). Lines 29-34 on page 8 state that using fasting or mean daily capillary blood sugars could provide information on acute glycemic control in a short-term trial. Reference 18 is a Cochrane review of studies conducted on the effect of intensive vs. non-intensive glycemic control on diabetic foot ulcers. I am unclear as to where it states that fasting capillary blood sugars could be used as a marker of improvement in glycemic control. I would suggest a full review of all of the references to ensure that they are correct.

VERSION 1 – AUTHOR RESPONSE

Response to reviewers' comments

1. A main area of confusion for me in reading this paper relates to the Phases in Substudy 1. I had a difficult time understanding the two phases. Perhaps the authors should consider inclusion of a figure or study flowchart to make this more clear.

We have made the following figure to clarify the study design. We have also amended the relevant text in the Method section as follows: During the first period of recruitment (Period A) all patients attending the diabetic foot clinic were to be recruited. Period A was to finish from the moment patients already attending the clinic were recruited, at which only newly enrolled clinic patients started to be recruited in the study, giving way to Period B.



2. Please use fasting blood glucose (rather than sugar) consistently throughout the manuscript. *Each instance of blood sugar has been changed to blood glucose*. *The shorthand FCBS has been changed to FCBG*

3. Spelling errors: Page 4 line 29 (relationship); page 13, line 8 (hereafter) *These have been corrected*

4. Diabetes as an adjective- line 6, page 3. Consider switching either to patients with diabetes or diabetic patients. *This has been changed to "the healing of foot ulcers in patients with diabetes"*

5. Please put exact study dates for the studies on page 7 (i.e. February 1, 2016 to...). *The exact dates have been added under the heading Setting and Study Design now on page 8*

Response to editors' comments

Because FCBG is being used as a marker for both glycemic control and medication adherence (page 8), it needs a reference that shows that this alone is an adequate marker to make assumptions about both factors. I would think that a 4 point glucose would be more effective in gaining this information or potentially using a pharmacy refill history. Without a reference, I find this to be an inadequate surrogate.

We agree with the reviewer that the addition of blood glucose testing throughout the day is a superior measure of glycaemic control compared to fasting blood glucose alone. However, morning fasting blood glucose was the measure our patients were consistently able to provide. While we accept the limitation, we believe the fasting blood glucose to be an adequate marker of glycaemic control.

We have made the addition of the following references to justify this choice "Contribution of fasting and post-prandial plasma glucose increments to the diurnal hyperglycaemia of type 2 diabetes patients: Variation with increasing levels of HbA1c. Monnier L et al Diabetes Care 2003 Mar;26(3):881-5" and "Blood glucose control and medication adherence among adult type 2 diabetic Nigerians attending a primary care clinic in Eastern Nigeria N Am J Med Sc : 2012 Jul;4(7):310-315"

Additionally, in looking at Table 2, the median Hba1c in Substudy 2 was 94mmol/mol which would be roughly equivalent to an average blood sugar of 14.5mmol/L, but the median FCBG in Substudy 2 is 9mmol/L. This makes me question the use of FCBG as a marker of glycemic control. The previously referenced studies and guidelines are all based on Hba1c targets as opposed to FCBG so it is hard to make this argument.

As per our answer above, we agree with the reviewer that the addition of post-prandial blood glucose would provide more information in blood glucose control. However, we maintain that fasting blood glucose is still a marker of glycaemic control and is adequate for the purposes of this study. While we did use HbA1c, given the study time period HbA1c alone may not have provided a true reflection of glycaemic control improvement. We did not have post-prandial blood glucose measures available to analyse. The discrepancy between expected mean blood glucose based on the HbA1c and the fasting blood glucose is adequately explained by fasting blood glucose usually being the lowest blood glucose concentration of the day. Post-prandial blood glucose is expected to be higher than fasting blood glucose even in a patient with well controlled type 2 diabetes.

Mean vs. Median in examining FCBG and Hba1c In Table 2, median values are provided for baseline values. On page 12, the mean difference from baseline to endpoint is provided. I would want to see the baseline and endpoint values for the mean if

that is the measure that is going to be used to determining glycemic improvement.

Thank you for this suggestion. We have made this change.

Use of log ulcer area vs ulcer area

Though it is stated on page 13 that the log ulcer area is more sensitive, I am unclear as to why this is the case and would ask for more explanation on this point as well as a reference where this measure is used.

Log ulcer area has been validated as a surrogate marker of ulcer healing by Margolis et al "Surrogate End Points for the treatment of diabetic neuropathic foot ulcers, Diabetes Care 2003 26(6) 1 696-1700". This reference has been added to the section on substudy 2 on page 9.

As Margolis et al explain, one of the main factors leading to a paucity of clinical trials in foot ulcers is the time it takes for ulcers to heal. Their aim in the above referenced paper was to find surrogate markers that adequately predict wound healing. Their explanation as to why log ulcer area performs better as a surrogate is because it may take into account irregularities in wound shape compared to absolute area.

Rate of absolute ulcer area change vs. Rate of relative ulcer area change

On page 13, it states that the absolute ulcer change area showed a significant change. This is not congruent with Table 2 where there is a significant change with rate of relative ulcer area change.

Thank you for noticing this discrepancy. The table is correct. We have corrected the text

Discussion

As this is a feasibility study looking to potentially lead to a RCT, it is very important to consider the inclusion criteria. In the discussion section on page 14, there is a comment about potentially relaxing IC2 (need to have diabetes for one year or more with a Hb1c of 60mmol/L or more). I think that it is important to think about whether patients who are recently diagnosed are really the same as patients who have had diabetes longer, more changes due to hyperglycemia- specifically around healing factors. I would advocate that they not dismiss IC2 without mentioning this.

Thank you for this suggestion. We agree that those with new onset diabetes are likely to have differences to those who have had diabetes for a long time. There are two other important considerations. Pre-diabetes is also a risk factor for neuropathy and those with diabetes and prediabetes share metabolic syndrome predisposition to vascular disease. Diabetes may precede many years before the diagnosis of diabetes and therefore those with a diagnosis within the past year may have had diabetes for longer.

The following sentence has been added at the beginning of page 15 to acknowledge these considerations ***"Those with recent onset diabetes maybe different to those with long standing diabetes in ways that impact upon ulcer healing. On the other hand, those with recently diagnosed diabetes will likely have years of exposure to risk factors they share with those with long standing diabetes that predispose them to ulcer formation also [Lee CC, Perkins BA, Kayaniyil S et al Peripheral neuropathy and nerve dysfunction in individuals at high risk for type 2 diabetes: the PROMISE cohort. Diabetes Care 2015; 38: 793-800].***

Further commentary discussed medication burden being a cause of dissatisfaction and rectifying this may lead to improved medication adherence. First, there has been no mention of what the medication regimen was for the 20 patients enrolled in Substudy 2 to understand what these patients considered to be a "medication burden." Furthermore, on page 8, there was a mention that FCBG was going to be used as a marker for medication adherence and yet there is no mention of this in the discussion section.

An addition has been made under the subheading "Intervention" on page 8.

Relationship to other studies Once again, it is mentioned that intensive insulin therapy led to improved ulcer healing in this study. The intensive insulin regimen needs to be defined or described. Also intensive insulin therapy does not automatically equate to improved control. Though it was mentioned in the results section that both FCBG and Hba1c were reduced, further discussion in this section along with direct comparison of glycemic control in the other referenced studies is needed.

The intensive insulin regimen is described on page 8 under the heading "intervention" and is as follows "The goal was to maintain FCBG at 4-7 mmol/L, with ≤2 episodes of mild hypoglycaemia per week. This was achieved by a combination of oral hypoglycaemics (metformin, sulphonylurea) and intermediate or long acting insulin.

Additional text has been added to the section headed "relationship to other studies". The paragraph now reads

"Over a similar timeframe, much lower healing rates have been reported with standard care (e.g. 31% at 20 weeks in a meta-analysis [31]). Even when standard care included insulin, a retrospective cohort study found that only 30% of ulcers had healed after 1.1 month [32]. The baseline mean HbA1c was lower in the participants of that study (7.9% or 63mmol/mol) compared to our own (10.8% or 94mmol/mol). While this finding is promising, a randomised controlled trial is needed to confirm that this is the effect of intensive blood glucose control. There are other factors that may account for more rapid ulcer healing in our study such as the high (weekly) frequency of the first four visits in Substudy 2, allowing more opportunities for treatment such as wound debridement, and orthotic or medication adjustments."

Implications for a full study

The first sentence of this section states that because the log ulcer area correlates well with glycemic control and the quality of life questionnaire, it is a valid measure. I think the only way this statement works is that the authors would like for intensive glycemic control (need numbers to prove this) and patient satisfaction to correlate with the log ulcer area) They have yet to prove this as a valid measure in the paper and therefore I cannot agree that I am convinced. The basic assumption in that statement is that if patients are happy and blood sugars are doing well then obviously, the ulcer should be healing better. This is what is yet to be determined in the literature.

We have made the addition referencing prior validation of log ulcer healing as a surrogate marker of ulcer healing (Margolis et al). We acknowledge that whether intensive glycaemic control improves ulcer healing it is yet to be determined in a randomised control. Our estimate for the numbers required to achieve that follows. We have altered the text to the following

"The log of the ulcer area outcome proved sensitive to glycaemic control even controlling for time since study entry, and was correlated with DFS-SF subscores supporting the use of this measure. This is consistent with prior validation of log ulcer area as a surrogate end point for ulcer healing (Margolis et al)"

Implications for a full study

Once again on page 16, there is more discussion about how glycemic control was better in the first 4-6 weeks and more variable after that. Figures/tables should present the glycemic data.

We have added the figure below.

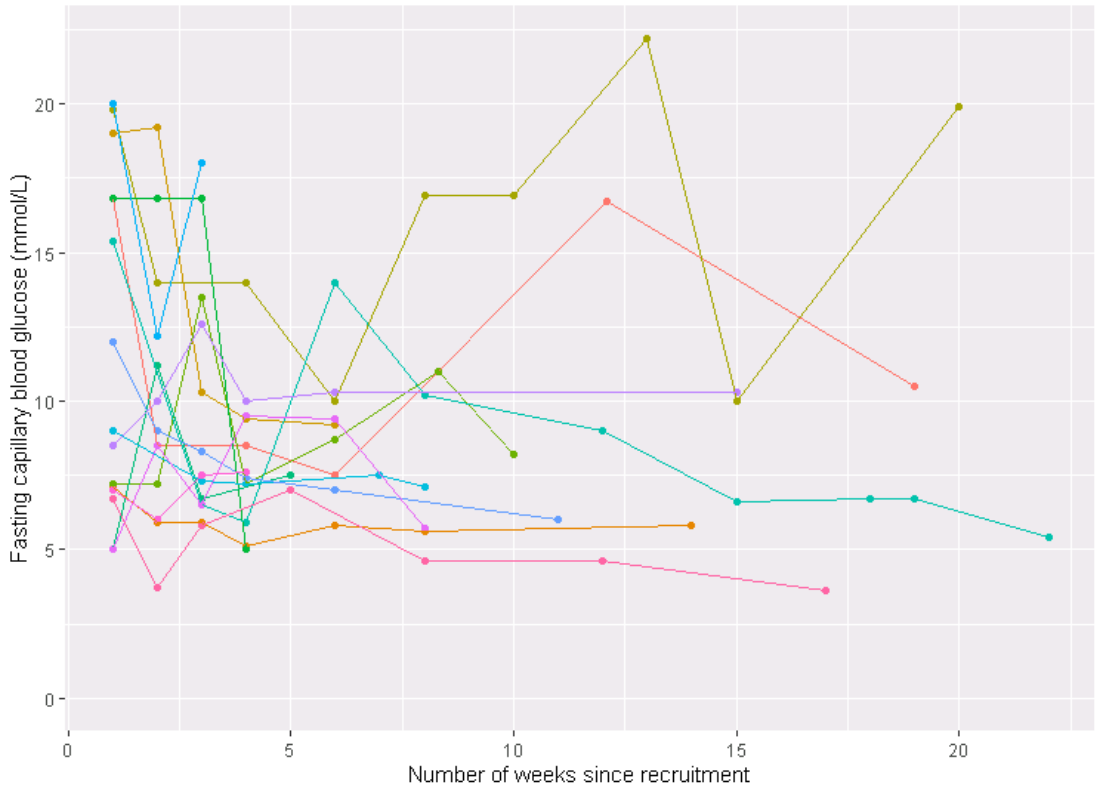


Figure 4. Fasting capillary blood glucose against time from study entry during intensive insulin therapy in the 15 participants of substudy 2

Also, it is stated that the medication burden correlated with adherence (no clear understanding of how adherence is measured beyond the FCBG which I feel is inadequate) and attendance to clinic visits. A correlation does not necessarily mean cause and effect and this should be more clearly stated.

While we accept the inferiority of FCBG alone as a measure of glycaemic control and adherence we do believe it is an adequate surrogate for the purposes of this study. The text has been altered to say ***"Our findings showed that our participants' perception of diabetes medication burden was strongly associated with adherence (as determined by the surrogate marker FCBG) and attendance, suggests, although does not prove, that intervening on burden may promote attendance."***

Because it is mostly based on expert opinion, there should be consideration made as to what Hba1c level should be the target for optimal wound healing in a full study- < 53mmol/mol? <64mmol/mol? This would be of additional benefit to treating providers to know, especially balanced against the burden of hypoglycemia.

We agree with the reviewer that evidence is lacking in this area. This is why a clinical trial such as is being explored here would fill an important gap in the literature. A target HbA1c for improved ulcer healing could be included as a secondary objective in the randomised trial for which this feasibility study was designed to explore. However, this objective may require more participants than feasible in one study.

Limitations

The fact that substudy 2 did not actually reach its power is a very big problem with this study. I find it difficult to agree with any of the conclusions made if they did not actually reach their intended participant target, especially when using statistical analysis. Interestingly the study population in Substudy 1 and Substudy 2 were actually different in terms of ethnicity and this should be mentioned.

*The text has been altered to say "**the most important limitation was that Substudy 2 did not reach target sample size of 20**." We also note that the sample size was not based on power, this study being a feasibility study, but on bounding the coefficient of variation of the various candidates for the primary outcome. Given that we have been able to identify two area-based outcomes sensitive to FCBG, we do not consider the failure to reach sample size invalidates the study, although it is a relevant finding from a full feasibility standpoint.*

We do not find the ethnicity make-up between substudy one and two to be different. (Asian 6.4% vs 6.7%, European 34.6 vs 26.7%, Maori 16.7% vs 13.3%, Pacific 42.3% vs 46.7%).

Other limitations that should be mentioned include exclusion of chronic ulcers and non-adherent patients. In the real world, chronic ulcers are common in the diabetes population with foot ulcers as is non-adherence to treatment regimens. Therefore, it should be clearly stated that the feasibility trial was used to understand glycemic control in acute ulcers in adherent patients. It is generally understood that research participants are different from the average patient.

*Thank you for this suggestion. The following has been added to the text **"Non-adherence to standard care was an exclusion criterion of this study. This was included so that the impact of glycaemic control would be the focus of this study. However, this criterion limits the application of the study to the real world as non-adherence is a major issue in most real-life clinical settings"***

Participants with chronic ulcers were included in this study

Finally, there should be a better measure of medication adherence and more transparency in the "intensive insulin management" protocol used. There are always 2 sides to suboptimal glycemic controlpatient adherence and the appropriate prescription from the provider. This study uses the FCBG to state that patients are not adherent if their FCBG does not improve when there is no information as to whether they were prescribed an appropriate insulin regimen.

*The following has been added **"Another limitation of this study is that FCBG was the only surrogate for medication adherence. The addition of other surrogates such as a record of whether prescriptions had been filled would. Furthermore, in a study aiming to evaluate the four times a day blood glucose testing is preferable to FCBG and HbA1c."***

Issues with references

Lines 24-31 on page 5 state that a meta-analysis was performed using 9 RCTs but reference 11 does not have this meta-analysis (perhaps reference 18?

This has been corrected

Lines 29-34 on page 8 state that using fasting or mean daily capillary blood sugars could provide information on acute glycemic control in a short-term trial. Reference 18 is a Cochrane review of studies conducted on the effect of intensive vs. non-intensive glycemic control on diabetic foot ulcers. I am unclear as to where it states that fasting capillary blood sugars could be used as a marker of improvement in glycemic control. I would suggest a full review of all of the references to ensure that they are correct

This has been corrected

VERSION 2 – REVIEW

REVIEWER	Uma Gunasekaran University of Texas, Southwestern, USA
REVIEW RETURNED	28-Aug-2019

GENERAL COMMENTS	This is a very important question that needs to be answered and has yet to be answered in the literature. That being said, I feel that there are some flaws in the study presented that still need to be addressed. In this iteration of this paper, the inclusion exclusion criteria have been modified. I think that this was a very good change as it included patients with higher Hba1c levels. There does need to be a correction made on p.6 line 28-29 as the Hba1c inclusion value differs from what is stated in Table 1. There needs to be consistency with these 2 numbers. I think though that there should be some caution in removing ulcer size limits as a very small ulcer may not be comparable to a large sized ulcer. I believe that this is a bigger issue with the new criteria that states that ulcers do not also have to be chronic. I would suggest mitigating this issue by comparing acute ulcers to acute ulcers and chronic ulcers to chronic ulcers. I appreciate the updated references for 2 key points- use of fasting blood sugar as surrogate for glycemic control and the reference on using improved glycemic control as a surrogate for medication adherence. On the first reference (#22) the studied population was similar to the study group and was appropriate. A specific point should be made that the authors of study #22 showed is that if the Hba1c was less than 7.3% then the fasting plasma glucose was not a good correlate but this has been resolved with the inclusion criteria change. But, reference #23 did not actually confirm that improved glycemic control equates medication adherence as the study was done in a very limited population in one clinic but more importantly, it specifically excluded patients who were on insulin therapy. Because the pilot study was to introduce intensive insulin therapy for tighter glycemic control, there is inadequate evidence that this could be used as a surrogate for medication adherence. In terms of glycemic targets in Substudy 2, on p9 lines 24-25, it states that the goal fasting plasma glucose target would be 4-7 mmol/L in the pilot study. This would translate to roughly a Hba1c of <47mmol/mol which is not a suggested target in any population by the American Diabetes Association unless it was a patient who was more recently diagnosed with few if any comorbidities and in whom hypoglycemia risk would be acceptable- I do not feel that the study population meets this criteria. If there is a deviation from the guidelines, there should be a justification and reference for this. Though the study was conducted in 2015, these were still not in the society guidelines.

	In terms of the Substudy 2 results, the mean baseline Hba1c was 93mmol/mol and the mean baseline fasting blood sugar was 11.3mmol/L. Based on the mean baseline fasting blood sugar, this should equate to an mean Hba1c of 70mmol/mol showing a strong discordance between the extrapolated value and the actual value. There should be some discussion on why this is (perhaps because of low number of study participants or potentially a need to use another marker of glycemic control). This is concerning because one would expect that the fasting blood sugars should be higher in the setting of the ongoing infection but they are less. A note should also made that 50% of study participants already had a fasting plasma glucose of 7mmol/L or less at the start of Substudy 2 which shows that only 50% actually needed glycemic management. This once again goes back to the baseline Hba1c values being higher and the protocol for glycemic management is not taking this into account. Need more explanation on these points. In terms of ulcer area results, I was confused by the statement that for each 0.08 mmol/L increase in fasting plasma glucose there was an increase in ulcer area. Because this is such a small number there should be a comment about the accuracy of glucometer precision. It is known that glucometers have to meet a certain standard to be approved as being accurate within a margin of error. This value seems small enough to fall into this category and may not be clinically useful statement for this reason. I would suggest just using the information that to reduce the ulcer by 30%, the fasting plasma glucose needs to be improved by 3mmol/L. Overall, I believe that this paper has had significant improvements compared to the previous version. I am still not convinced of glycemic control as a surrogate for medication adherence and at this point would suggest taking this out and just discussing glycemic control alone and leaving the question of adherence for followup. I would also re-examine the justification for such a low plasma glucose target in Substudy 2. The discordance between using a Hba1c and fasting plasma glucose needs to be reconciled. I do think that the inclusion criteria are improved and more clinically pertinent but I still don't advocate for removing any of them to make recruitment better as it detracts from the question being answered. I would definitely mention that 3 patients had Type 1 diabetes and this is a good representation in such a small study population.

REVIEWER	Larisa Tereshchenko Oregon Health and Science University
REVIEW RETURNED	24-Nov-2019

GENERAL COMMENTS	Dissanayake et al conducted a pilot study to determine the feasibility of an RCT of glycaemic control with intensive insulin therapy in diabetic foot ulcer patients. Intensive insulin therapy with standard podiatry care was an intervention in a single-arm study. The pilot study determined the feasibility of the proposed RCT and suggested the definition of an end-point and provided a reliable estimation of statistical power and sample size, suggesting the number of enrolling centers. This is a well-thought and well-conducted pilot study, which fulfilled the study objectives. The manuscript is well-written. Performed statistical analyses are sound and appropriate. Congratulations with the well-conducted study.

VERSION 2 – AUTHOR RESPONSE

Thank you for giving us the opportunity to revise our manuscript "**Does intensive glycaemic control promote healing in diabetic foot ulcers? A feasibility study**". We have made a revised version of the manuscript with the corrections that can be seen as tracked changes. Below is a response to the editors and reviewers' comments. The reviewer's comment is italicised and the response is in bold.

There does need to be a correction made on p.6 line 28-29 as the Hba1c inclusion value differs from what is stated in Table 1.
Thank you for identifying this discrepancy. This change has been made.

I think though that there should be some caution in removing ulcer size limits as a very small ulcer may not be comparable to a large sized ulcer. I believe that this is a bigger issue with the new criteria that states that ulcers do not also have to be chronic. I would suggest mitigating this issue by comparing acute ulcers to acute ulcers and chronic ulcers to chronic ulcers.
We agree with this comment, that comparing ulcers of similar size and chronicity is ideal and improves the validation of the study. The decision to remove size and chronicity as criteria was made in order to recruit enough patients to power the study. The study is not powered to do a separate analysis on comparing acute to acute and chronic to chronic.

But, reference #23 did not actually confirm that improved glycemic control equates medication adherence as the study was done in a very limited population in one clinic but more importantly, it specifically excluded patients who were on insulin therapy. Because the pilot study was to introduce intensive insulin therapy for tighter glycemic control, there is inadequate evidence that this could be used as a surrogate for medication adherence.
As per your recommendation at the end of your comment we have removed references to medication adherence and have referred only to improvement of capillary blood glucose.

In terms of glycemic targets in Substudy 2, on p9 lines 24-25, it states that the goal fasting plasma glucose target would be 4-7 mmol/L in the pilot study. This would translate to roughly a Hba1c of <47mmol/mol which is not a suggested target in any population by the American Diabetes Association unless it was a patient who was more recently diagnosed with few if any comorbidities and in whom hypoglycemia risk would be acceptable.
While not identical to the ADA guidelines recommendation for fasting blood glucose targets (4.4-7.2 mmol/L vs 4.0-7.0 mmol/L) they are not dissimilar. The decision was made in order to simplify the targets for the patient population. Blood glucose targets are individualised according to the patients risks for hypoglycaemia as per the statement "The goal was to maintain FCBG at 4–7 mmol/L, with ≤2 episodes of mild hypoglycaemia per week. Within these parameters the choice of regimen was determined by the Diabetes Nurse Specialist." **In addition, we have added "**if >2 episodes of mild hypoglycaemia occurred the target FCBG was raised**" to make it clear that regimens were adjusted according to the patient's risk of hypoglycaemia.**

In terms of the Substudy 2 results, the mean baseline Hba1c was 93mmol/mol and the mean baseline fasting blood sugar was 11.3mmol/L. Based on the mean baseline fasting blood

sugar, this should equate to an mean Hba1c of 70mmol/mol showing a strong discordance between the extrapolated value and the actual value.
While HbA1c and FCBG correlate strongly, any model used to predict HbA1c from a single fasting capillary blood glucose will never be perfect for the very reason that we use HbA1c in combination with CBG in the clinical setting. This discrepancy is due to the variability of FCBG day to day and post-prandial blood glucose not being taken into account. Furthermore, there is no model developed specifically for the Auckland population which is unique, even when compared to the rest of New Zealand, let alone the rest of the world. The following has been added to the discussion to clarify this.
"The mean HbA1c of substudy group 2 prior to the intervention was 93 mmol/mol and the mean FCBG was 11.3 mmol/L. Depending on the model used to estimate HbA1c from FCBG there may appear to be a discrepancy in these results. However, this is explained by the small number of participants, and the variability of contribution between FCBG and post-prandial capillary blood glucose between individuals and at higher HbA1c concentrations**." In support of this the reference** Monnier L, Lapinski H, Colette C. Contributions of Fasting and Postprandial Plasma Glucose Increments to the Overall Diurnal Hyperglycemia of Type 2 Diabetic Patients. Diabetes Care [Internet]. 2003 Mar 1;26(3):881 LP – 885 **has been added**.

In terms of ulcer area results, I was confused by the statement that for each 0.08 mmol/L increase in fasting plasma glucose there was an increase in ulcer area. Because this is such a small number there should be a comment about the accuracy of glucometer precision. It is known that glucometers have to meet a certain standard to be approved as being accurate within a margin of error. This value seems small enough to fall into this category and may not be clinically useful statement for this reason. I would suggest just using the information that to reduce the ulcer by 30%, the fasting plasma glucose needs to be improved by 3mmol/L.
We agree that the statement "Using this measure as primary endpoint, a target reduction in ulcer size of 30% would correspond to a 3 mmol/L average difference in FCBG" is more translatable and presents the results in a more clinically relevant way. We have included this statement "This corresponds to a 30% reduction in ulcer area with a 3mmol/L improvement in FCBG." **in the results section as well as in the discussion section where it was previously. We do however prefer to continue to include the full model as this explains how we arrive at this result.**

I am still not convinced of glycemic control as a surrogate for medication adherence and at this point would suggest taking this out and just discussing glycemic control alone and leaving the question of adherence for followup.
See our response above

We hope that you find these responses satisfactory