

COMMENTS TO AUTHORS (Reviewer 1)

In Table 4., percentage of FPG >11mmol increased during IF phase. Is this caused by increase in evening meal size of part of the subjects during IF?

RESPONSE:

We were unable to determine any significant relationship between meal size and SMBG, as the sample size of participants who effectively completed both the dietary records and the SMBG records concurrently was too small.

Given the results of Beebe et. al (1990), which showed no increase in morning glucose when 70% of calories were consumed after 1900h, we feel that evening meal size did not have a significant impact on morning glucose levels.

Moreover, the increase in the incidence of FPG > 11.0 mmol during the morning phase of IF was attributable solely to a single participant.

Lastly, there was no increase in the occurrence of FPG > 11.0 mmol in postprandial evening SMBG readings during IF. If the size of evening meals during IF had an impact on morning SMBG, one would predict that evening SMBG would be elevated as well.

Total energy intake is indicated in Table 6, however change in each meal size is not shown.

RESPONSE:

A direct comparison of meal size was not completed for several reasons:

- 1) Caloric intake for breakfast would always be zero during the IF phase, and would not be comparable to Baseline or Follow-up phases. Some participants even chose to fast over lunch, which would cause similar problems when comparing meal sizes between phases.
- 2) Meal patterns varied greatly between participants. Some participants broke their fast as early as 11AM, while others broke their fast as late as 5PM. Participants were not told to eat in any particular fashion outside of daily intermittent fasts and high protein intake. This makes distinguishing and synchronizing meals between participants impossible.

All the subjects did 3 times a day SMBG for 42 days. This may result in self-teaching effect for the meal selection and blood glucose after eating. The decrease in variance of FPG in the follow-up period may show the result of better skill for choosing evening

meals. Therefore this study may show the mixed effect of IF and 3 times-a-day-SMBG. Do you believe IF is still effective without SMBG?

RESPONSE:

This is a valid point and one of concern to us as well. Currently the Canadian Diabetes Association recommends the use of frequent SMBG in individuals who have not yet achieved glycemic control ($\text{HbA1c} > 8.0\%$), but does not recommend frequent SMBG for individuals with a level of glycemic control ($\text{HbA1c} < 8.0\%$). There is certainly a distinct possibility that self-monitoring may have led to enhanced glycemic control. A note has been added to the limitations section of our manuscript to address your point.

However, our study showed a distinct increase in the occurrence of fasted morning SMBG at target (below 7.0 mmol), and this was not retained in the follow-up phase. If self-measurement had a significant impact on glycemic control, then one would suspect this improvement to be retained in the follow-up phase. Ergo, it is possible that IF would still be effective without the concurrent use of SMBG.

COMMENTS TO AUTHORS (Reviewer 2)

Same as above. The Study is valuable and of interest as intermittent fasting is a hot topic regarding weight loss and related benefits including treatment of diabetes. However, one concern is including 1 male in the study which could skew the data, especially regarding the waist circumference parameter where the mean was calculated collectively including the male. As a reviewer, I wonder if removing the male from the study would affect the results in any way affecting significance. For example, removing the male may contribute to finding significance, or more reliable data, regarding waist reduction. Usually abdominal obesity in females that are pre-menopausal is subcutaneous abdominal rather than omental or visceral. Therefore weight loss may affect their waist circumference more. The authors need to comment on this aspect. It is also not clear regarding the mean age if the age of the male was affecting the mean age and if the women were post or pre-menopausal as this largely affects fat distribution and weight loss trends. The age and waist circumference of males and females need to be specified separately and results described accordingly.

RESPONSE:

The single male in the study was not an outlier regarding age, BMI, or waist circumference. He had a BMI of 31.71 kg/m^2 (avg. 36.9 ± 8.3), WC of 106.5cm, (avg. 109 ± 11.1) and was 59 years old (avg. 53.8 ± 9.1). His biochemical and anthropometric changes in response to IF were also unremarkable. Had there been more males in the study it would have merited exploring sex differences, however, with only one male presenting even basic statistical information such as standard deviation would not be feasible.

Although the majority of the women in the study were above the age of 55, the menopausal status of the women was not recorded during the intake of the study, as it was not considered a factor at the beginning of the study.

COMMENTS TO AUTHORS (Reviewer 3)

The authors examined short-term biochemical and behavioral effects of a popularized version of intermittent fasting (IF) in adults with Type 2 Diabetes Mellitus (T2DM). The increased fasting duration improved at-goal (< 7.0 mmol/L) morning SMBG to 34.1%, from a baseline of 13.8%. The results from this pilot study indicate that short-term daily IF may be a safe, tolerable, dietary intervention in T2DM patients that may improve key outcomes including body weight, fasting glucose and postprandial variability. The findings are interesting, however, I have several concerns.

1. Was the study protocol approved by the ethics committee of the institution?

RESPONSE: Yes. A statement is included in the manuscript indicating this.

2. The HFD and OLR models showed a significant association between change in HFD with lowered morning SMBG but not for afternoon or evening SMBG. Please add the afternoon or evening SMBG.

RESPONSE:

Basic statistical information regarding SMBG and HFD for the OLR model is now added for afternoon and evening SMBG in a new table (Table 5).

3. Did several medications influence the present results?

RESPONSE:

No. All of the participants were on metformin, and only 1 patient was on gliclazide and 1 patient was on liraglutide. The diabetes medication profile did not influence the results.

4. The levels of CRP (4.3 ± 3.8 mg/L) seem to be high. Did the subjects have several inflammatory disease?

RESPONSE:

The presence of inflammatory disease was part of the exclusion criteria for the study, so no participants in the study had any suspected or diagnosed inflammatory diseases.

5. in the table4B, did the levels of SMBG (7.0 - 9.05 mmol/L at baseline) increased during follow-up period?

RESPONSE:

Yes, this was partially due to decreases in SMBG < 7.0mmol and SMBG > 11.1mmol. This is further corroborated by the reduction in evening SMBG variability observed in Figure 2C.

6. IF may improve key outcomes including body weight, fasting glucose and postprandial variability. However, the effects subsequently and quickly returned in the follow-up phase. It means that the effect of IF on glucose metabolism is only short-term?

RESPONSE:

This is possible, yes. One hypothesis is that actively practicing IF promotes unique glycemic control independent of weight loss, but permanent improvement in glycemic control irrespective of dietary patterns likely requires significant weight loss.