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Original article

Effect of meal timing on postprandial glucose responses to a low glycemic index meal: A crossover trial in healthy volunteers

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SUMMARY

Background & aims: Glucose metabolism is, in part, regulated by the circadian rhythm. Postprandial glucose response is exaggerated and insulin sensitivity is reduced at night compared with the morning. Sustained poor glucose tolerance may be related to the increased risk of type-2 diabetes mellitus and cardiovascular disease experienced by shift workers. Manipulation of meal type may be able to dampen such postprandial excursions. Therefore, the study's aim was to investigate postprandial glucose and insulin responses to a low glycemic index (GI) meal in the morning compared to night in healthy volunteers.

Methods: An oral glucose tolerance test (OGTT), was undertaken to confirm diurnal glucose response. Participants consumed a glucose solution at 0800h (morning) and 2000h (evening). In a separate trial, participants consumed a low GI meal (3.3 MJ, 48% energy (E) from carbohydrate, 40%E from fat and 11%E from protein, 22 g fiber) at 0800h, 2000h and 0000h (midnight). Postprandial glucose and insulin were collected over 3 h. Incremental area under the curve (iAUC) was calculated and significance tested using Wilcoxon-signed rank. A p-value <0.05 was taken as significant.

Results: In the OGTT ($n = 10$), postprandial glucose iAUC was higher in the evening compared to morning ($p = 0.007$). In the low GI meal trial ($n = 9$), postprandial glucose iAUC at evening and midnight were higher than the morning ($p = 0.008$, $p = 0.021$) but not significantly different between evening and midnight ($p = 0.594$). Postprandial insulin iAUC was also higher in the evening and at midnight compared to the morning ($p = 0.008$ for both).

Conclusions: The current study confirms that meal intake at night, even when comprised of low glycemic ingredients, contributes to higher glucose excursions and concomitantly greater insulin levels, compared with an equivalent meal in the morning. This demonstrates that meal timing has an effect on glucose metabolism, which can be observed from as early as 8pm and persists throughout the night. This identifies meal timing as an important modifiable risk factor for metabolic-related disease, which may have implications for high risk populations such as shift workers but also the general population.

Trial registration: Study ID number: ACTRN12616000164493; Website of trial registry: http://www.anzctr.org.au/.

1. Introduction

Numerous physiological processes of the human body are governed by the circadian clock. The central circadian clock is located in the suprachiasmatic nuclei (SCN) of the hypothalamus and responds to cues of the light/dark cycle in the external environment [1]. Clocks are also present in peripheral tissues, such as the liver and gastrointestinal tract. Under normal circumstances, these body clocks ensures metabolic pathways follow a circadian rhythm and occur at the most appropriate time of the day [1]. Glucose metabolism follows such circadian rhythm, reflected through the diurnal

Abbreviations: BASE, Be Active Sleep & Eat Facility of Monash University Australia; GI, glycemic index; h, hour; iAUC, incremental area under the curve; LGI trial, low glycemic index meal trial; min, minute; OGTT, oral glucose tolerance test; T2DM, type-2 diabetes mellitus; %E, Percentage of energy.

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variation of glucose tolerance that peaks during the day light hours (when feeding typically occurs) and reduces during the dark hours (when fasting typically occurs) [2]. Insulin is also subject to diurnal variation, with insulin sensitivity reducing over the course of the 24-h day [3,4].

Night shift workers, especially those working in a rotating shift schedule, are constantly changing their sleep/wake and feed/fast cycle. Such behavioral changes affect their ability to adopt a regular circadian rhythm and may have an influence on metabolic processes [5,6]. A small number of well-controlled simulated shift work studies show that eating at night time, compared to during the day, were associated with poor glucose tolerance and reduced insulin sensitivity [7–9]. Based on this, night time eating may be associated with the increased risks of type-2 diabetes mellitus (T2DM) and cardiovascular disease observed in shift workers, compared to their non-shift working counterparts [10–13].

Avoidance of food intake at night is unrealistic for many people. Therefore, understanding if manipulation of meal composition can favorably impact on postprandial responses is important. This will assist in the management of disease risk factors in the shift worker population. Randomized controlled trials demonstrate that low glycemic index (GI) meals [14] create minimal postprandial glucose responses in healthy individuals and also in those with obesity or T2DM [15–17]. However, in an acute postprandial trial, the beneficial effect of low GI meals on postprandial glycemic response could not be reproduced in the evening [18]. These findings have repercussions for food choice at night in shift working populations.

As such, the current study aimed to examine the postprandial glucose and insulin responses to a low GI meal at 0800h, 2000h and midnight in healthy adults. The addition of a midnight arm enabled the researchers to examine the metabolic responses of a typically healthy meal later in the night, which has not been investigated previously. Based on constant routine studies on meal timing [19,20], we hypothesize that the glucose response at midnight will be more exaggerated compared to at 2000h. A separate trial was also undertaken, comparing the postprandial glucose responses to the oral glucose tolerance test (OGTT) given at 0800h and 2000h. The OGTT is the diagnostic test for T2DM, which allowed us to confirm the temporal difference of postprandial glucose regulation in healthy adults.

2. Subjects and methods

2.1. Study design

The study comprised two separate crossover intervention trials. The first trial utilized a 2-h oral glucose tolerance test (OGTT) to compare glucose response in the morning (0800h) and evening (2000h). In the second trial, low glycemic index meal trial (LGI trial), the OGTT was replaced by a low GI meal given at 0800h, 2000h and midnight; postprandial glucose and insulin were measured for 3 h. Each session (for both OGTT and LGI trial) was completed on a different day. Participants chose the order of session completion based on time of convenience and were not randomized. Time of day was considered the intervention, hence blinding was not possible. The study was conducted at the Be Active Sleep Eat (BASE) Facility at Monash University, Australia.

2.2. Ethics

This study was approved by the Monash University Human Research Ethics Committee (Project Code CF15/1301–2015000620) and complied with the Declaration of Helsinki of 1975 as revised in 1983. It was registered with the Australian New Zealand Clinical Trials Registry (ID: ACTRN12616000164493).

2.3. Participants

Eligible participants were healthy males and females (BMI between 18.5 and 30 kg/m^2) and aged between 18 and 50 years. Recruitment was carried out between July 2015 and February 2016 of which 32 potential participants expressed interest. Eligible participants had to maintain a regular sleep/wake cycle; residing to bed between 2200h and 0000h habitually. Those who were engaged in shift work; diagnosed with impaired fasting glucose (fasting glucose > 6 mmol/L), diabetes mellitus, cardiovascular disease or sleep disorders; taking oral hypoglycemic agents, antihypertensive or lipid-lowering medication were excluded. Eligibility was assessed through a phone interview and confirmed through a screening session at the BASE facility prior to inclusion. Participation was voluntary; written informed consent was obtained from all participants.

2.4. Pre-intervention procedures

Before each study session, participants were asked to maintain their regular sleep/wake cycle for at least three days. One day prior to, and including the day of each session, participants were asked to abstain from alcohol and strenuous exercise. All participants were provided with an identical control meal prior to each session. The participants were instructed to consume the meal at least 10 h prior to the start of each session, i.e. the night before a morning session (2200h), the morning (1000h) of a night session or the afternoon (1400h) of a midnight session. This ensured a 10-h fast period before each session. The control meal contained a total of 2.7 MJ, with approximately 48% of energy (E) from carbohydrate, 34%E from fat and 19%E from protein. Once participants had consumed this control meal, they were asked to refrain from any further food or beverages intake (except water) until arriving at the BASE facility.

2.5. Test meal challenge

2.5.1. OGTT

The glucose solution administered contained 75 g of pure glucose powder (Glucodin, Inova Pharmaceuticals, Australia) diluted in 400 ml of water. The drinks were prepared on the day of each session.

2.5.2. LGI trial

Participants were given a tomato-based vegetarian pasta dish. Each individual ingredient used in the meal was associated with a low GI value (GI < 55), but the meal's overall GI value was not assessed. The low GI meal consisted of 3.3 MJ, with 48%E from carbohydrate, 40%E from fat, 11%E from protein and 22 g of fiber. Nutrient composition of the low GI meal was analyzed using Foodworks (version 7.0.3016, Xyris Software, Brisbane, Australia).

2.6. Procedures

2.6.1. OGTT

For the morning session (0800h), participants reported to the BASE facility at 0730h. Baseline anthropometric measures (height, weight and waist circumference) and blood pressure were obtained using standardized procedures. Fasting blood samples (finger prick) were taken 15 min and immediately prior to administering the OGTT (i.e.: −15 and 0 min measure). The glucose solution was provided at 0800h and participants were asked to consume this within 5 min. Blood samples were then taken at 15, 30, 45, 60, 90 and 120 min after the commencement of the drink. A small drop of capillary blood was obtained from a finger prick and placed on the

target area of the testing strip (Accu-Chek Performa test strip, Accu-Chek, Indiana, USA) and immediately assessed for glucose using an Accu-Chek blood glucose monitor (Accu-Chek Performa II, Accu-Chek, Mannheim, Germany). Readings were recorded to the nearest 0.1 mmol/L. Participants remained in the BASE facility during this period and no other food was consumed, but water was allowed. Participants remained awake and were permitted to undertake sedentary activities such as watching television.

For the evening session (2000h), participants reported to the BASE facility at 1930h. The glucose solution was administered at 2000h and the session concluded at 2200h. All other procedures were the same as the OGTT morning session.

2.6.2. LGI trial

The LGI trial replicated the OGTT except an intravenous cannula was inserted by an experienced nurse or phlebotomist 30 min before the start of the session. For the morning session (0800h), a fasting blood sample was taken (0 min measure), immediately followed by a low GI meal at 0800h, which participants were asked to consume within 15 min. Blood samples were then taken at 15, 30, 45, 60, 90, 120, 150 and 180 min after the commencement of the meal. At each time point, blood for glucose and insulin samples were drawn from the intravenous cannula into a 4 ml EDTA tube (BD Vacutainer, Oxford, UK), centrifuged at 626 × g at 4 °C for 12 min (Eppendorf Centrifuge 5702R, Hamburg, Germany) and plasma was aliquoted and frozen at - 80 °C for future analysis. Participants remained in the BASE facility during this period and permitted activities were the same as during the OGTT session.

For the evening session (2000h), participants reported to the BASE facility at 1930h. The low GI meal was administered at 2000h and the session concluded at 2300h. For the midnight session, participants reported to the BASE facility at 2330h. The low GI meal was administered at midnight and the session concluded at 0300h; participants remained awake for the entire session. All other procedures for the evening and midnight session were the same as the LGI trial morning session.

2.7. Biochemical analysis (LGI trial)

Plasma glucose (Thermo Fisher, 981779) was analyzed using an Indiko™ Clinical and Specialty Chemistry System (Thermo Fisher Scientific™, Vantaa, Finland) as per manufacturer instructions. The multicalibrator Scal (981831) was used to calibrate the machine in conjunction with control serums Nortrol (981043) and Abtrol (981044). Glucose in the sample was phosphorylated to glucose-6-phosphate by hexokinase. The change in absorbance at 340 nm resulting from NAD^+ being reduced to NADH was measured, and the corresponding concentration calculated by referencing the standard curve. Intra-assay coefficient of variation was <5%. Plasma insulin was measured by an in-house enzyme-linked immunoassay (Department of Physiology, Monash University), using an anti-insulin antibody raised in guinea pigs (Antibodies Australia, Australia). The insulin ELISA was calculated to have a sensitivity of 0.2 ng/ml and the following between-assay coefficient of variation: 10.4% at 1.45 ng/ml, 12.3% at 3.43 ng/ml and 7.6% at 4.41 ng/ml. All samples were ran in duplicate, any duplicate sample with a coefficient of variation of more than 10% was rerun.

2.8. Data analysis

A power calculation was conducted *a priori* based on data from a previous study [7] that administered meals at 1300h (day time point) and at 0100h (night time point). Seven participants were required, to provide 80% power and detect a mean difference of 15% in glucose concentration (total area under response curve) at an alpha value of 0.05.

Data from the OGTT and LGI trial were analyzed separately. Statistical analyses were conducted using Statistical Package for Social Sciences (version 21.0, IBM Corp., New York). Statistical significance was considered as $p < 0.05$.

2.8.1. OGTT

Postprandial glucose response, estimated using incremental area under the response curve (iAUC), was the primary outcome measure. The iAUC was calculated by the trapezoid rule, which ignores the area beneath the baseline concentration [21]. Fasting glucose was taken as the mean of the −15 min and 0 min measure. All data are reported as median (IQR), except for the postprandial glucose time course graphs, which are reported as mean ± SEM.

The Wilcoxon signed-rank test was used to analyze the difference in postprandial glucose iAUC, fasting glucose concentration and glucose concentration at 120 min postprandial between the morning and evening sessions.

2.8.2. LGI trial

Postprandial glucose iAUC was the primary outcome measure. Postprandial insulin iAUC was the secondary outcome measure. Fasting glucose and insulin concentration was taken as the 0 min measure. Insulin samples that were below the detection limits of the assay were reported as the lower limit of detection of 0.1 ng/ml. Insulin data were converted to mU/L for analysis. All data are reported as median (IQR), except for the postprandial glucose and insulin time course graphs, which are reported as mean ± SEM.

The Friedman Test was used to analyze the differences in fasting and postprandial measures between the three sessions (morning, evening and midnight). Comparisons were made across the three time points for glucose and insulin iAUC, fasting glucose and insulin concentration, glucose concentration at 180 min postprandial, early phase insulin response (iAUC from 0 to 30 min) and late phase insulin response (iAUC from 30 to 120 min) [22]. The Wilcoxon signed-rank test was used as the *post hoc* test.

3. Results

3.1. Participant enrollment

The study participant flow of both OGTT and LGI trial is shown in Fig. 1. Ten participants completed the OGTT and nine completed the LGI trial; all data were included in analyses. Five participants completed both trials.

3.2. OGTT

3.2.1. Participant characteristics

Seven of ten participants completed the morning session first. Baseline characteristics of participants are presented in Table 1. All participants were within the healthy weight range. Fasting capillary blood were in the normal range of below 5.5 mmol/L [23] and similar between the morning and evening sessions ($p = 0.475$).

3.2.2. Postprandial glycemic response of OGTT administered in the morning and evening

Postprandial capillary blood glucose concentrations after the OGTT are shown in Fig. 2. The Wilcoxon signed-rank test showed that the median postprandial glucose iAUC was significantly greater in the evening compared to the morning (331.88 (166.22) mmol/L.2h versus 181.17 (160.32) mmol/L.2h, $p = 0.007$). Mean (SD) within subject difference of glucose iAUC between the morning and evening sessions are presented in Supplementary Table 1.

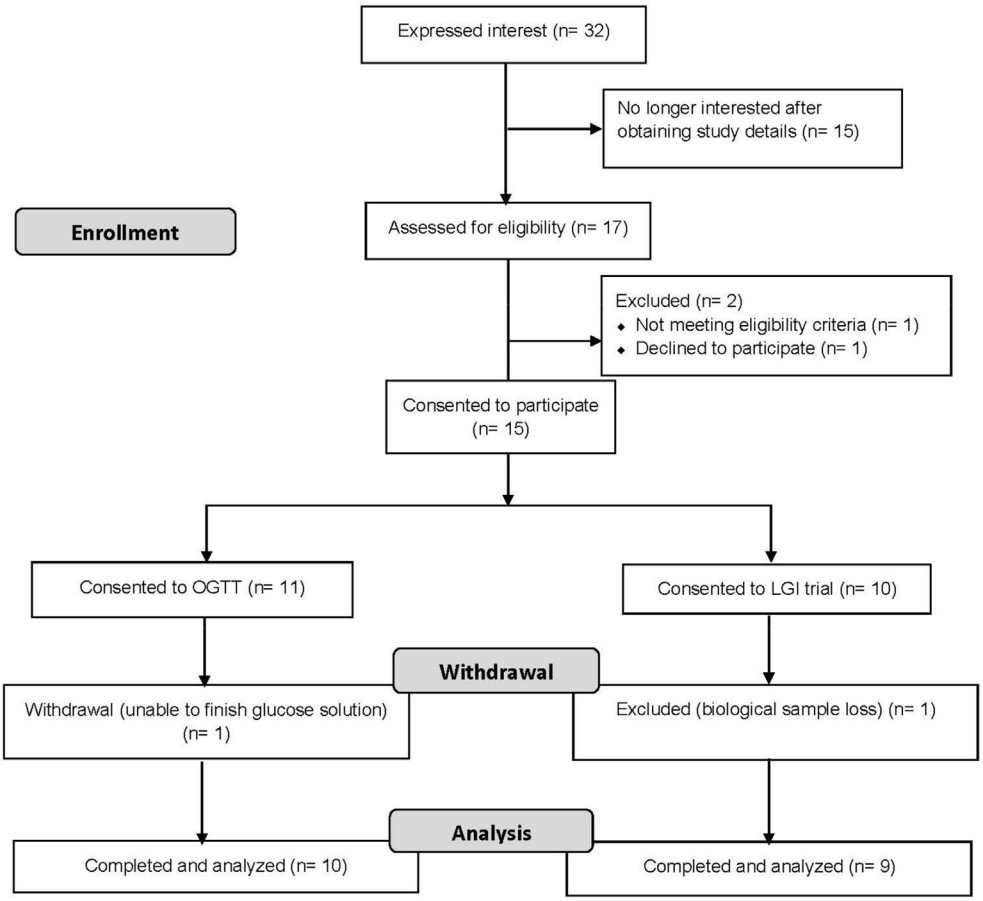

Fig. 1. Participant flow for both OGTT and LGI trial. LGI trial, low glycemic index meal trial; OGTT, oral glucose tolerance test.

Table 1
Baseline characteristics of participants in the OGTT (n = 10). OGTT, oral glucose tolerance test.

Characteristics		
Gender	8 (F), 2 (M)	
	Median (IQR)	
Age (years)	23 (4)	
BMI (kg/m^2)	22.6 (3.0)	
Waist circumference (cm)	72.4 (9.2)	
Systolic blood pressure (mmHg)	109 (7)	
Diastolic blood pressure (mmHg)	71 (6)	
	0800h	**2000h**
Fasting glucose (mmol/L)	4.7 (0.6)	4.8 (0.6)

The median glucose concentration at 120 min postprandial (5.6 (2.1) mmol/L) was not different to the fasting concentration (p = 0.097), indicating that the blood glucose concentration has returned to baseline at the end of the session. Conversely, in the evening session, the median glucose concentration (6.7 (2.9) mmol/L) remained elevated on completion of the study (120 min postprandial) compared to the fasting concentration (p = 0.012).

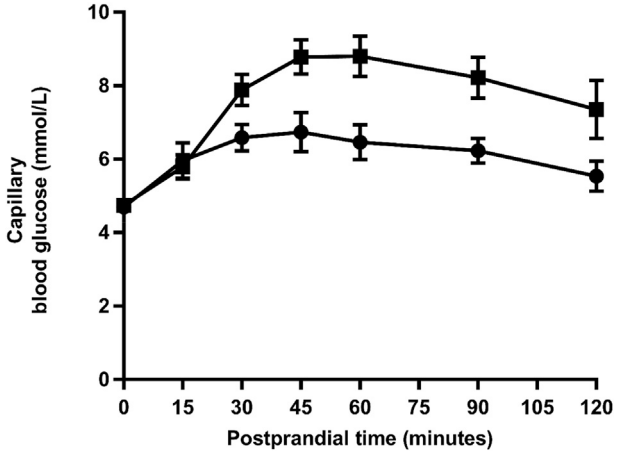

Fig. 2. Postprandial capillary blood glucose concentration after the oral glucose tolerance test (OGTT) at two time points: morning at 0800h (●) and evening at 2000h (■). The Wilcoxon signed-rank test showed significant difference between the morning and evening glucose incremental area under curve (p = 0.007). Values expressed as mean ± SEM, n = 10.

3.3. LGI trial

3.3.1. Participant characteristics

Of the nine participants, three completed the morning session first, while four and two participants completed the evening and midnight session first respectively. Baseline characteristics of participants are presented in Table 2. All participants were within the healthy weight range. Fasting plasma glucose were in the normal range of below 5.5 mmol/L [23] and similar between the three time points (p = 0.819). Fasting insulin were also similar across the three time points (p = 0.196).

3.3.2. Postprandial glycemic response of low GI meal consumed in morning, evening and midnight

Postprandial plasma glucose concentrations after consumption of a low GI meal are shown in Fig. 3a. The Friedman test showed a

Table 2
Baseline characteristics of participants in the LGI trial (n = 9). LGI trial, low glycemic index meal trial.

Characteristics			
Gender	7 (F), 2 (M)		
	Median (IQR)		
Age (years)	26 (15)		
BMI (kg/m^2)	23.6 (3.9)		
Waist circumference (cm)	74.5 (4.8)		
Systolic blood pressure (mmHg)	112 (13)		
Diastolic blood pressure (mmHg)	72 (5)		
	0800h	**2000h**	**0000h**
Fasting glucose (mmol/L)	5.0 (0.7)	4.8 (0.7)	5.1 (0.8)
Fasting insulin (mU/L)	7.4 (6.6)	3.8 (5.5)	4.1 (2.6)

significant difference in postprandial glucose iAUC between the three time points (p = 0.004). Median postprandial glucose iAUC (Table 3) was significantly greater after the evening and midnight sessions compared with the morning session (p = 0.008, p = 0.021). No significant difference was found between the evening and midnight postprandial glucose iAUC (p = 0.594). Mean (SD) within subject difference of glucose iAUC between the three sessions are presented in Supplementary Table 1.

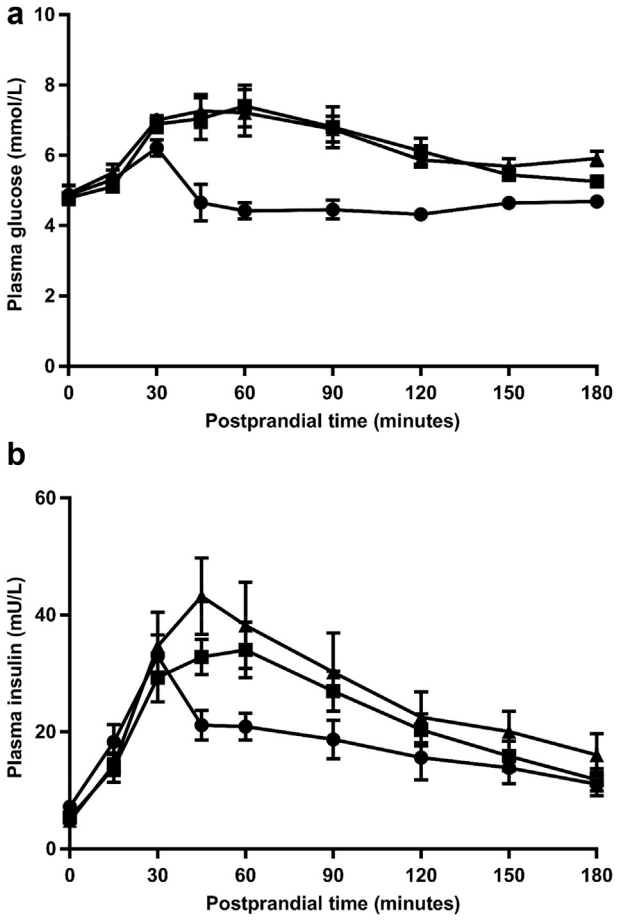

Fig. 3. (**a**) Postprandial plasma glucose concentration after a low glycemic index meal at three time points: morning at 0800h (●), evening at 2000h (■) and midnight at 0000h (▲). The Friedman test showed a significant difference in postprandial glucose incremental area under the curve between the three time points (p = 0.004). Values expressed as mean ± SEM, n = 9. (**b**) Postprandial plasma insulin concentration after a low glycemic index meal at three time points: morning at 0800h (●), evening at 2000h (■), midnight at 0000h (▲). The Friedman Test showed a significant difference in postprandial insulin incremental area under the curve between the three time points (p = 0.001).Values expressed as mean ± SEM, n = 9.

At the completion of both morning and evening sessions (180 min postprandial), median glucose concentration have returned to the fasting concentration (p = 0.138 and p = 0.097 respectively) (Table 3). Conversely, in the midnight session, the median glucose concentration remained elevated on completion of the session (180 min postprandial) compared to baseline (p = 0.012).

3.3.3. Postprandial insulin response of low GI meal consumed in morning, evening and midnight

Postprandial plasma insulin concentrations after consumption of a low GI meal are shown in Fig. 3b. Median postprandial insulin iAUC (Table 3) was significantly greater in the evening and midnight sessions compared with the morning session (p = 0.008 for both); however, no significant difference was found between the evening and midnight postprandial insulin iAUC (p = 0.374). Mean (SD) within subject difference of insulin iAUC between the three sessions are presented in Supplementary Table 1.

The early phase insulin response (0–30 min) was not different between the three different time points (p = 0.717). No late phase insulin response (30–120 min) was observed after the morning meal (Table 3). Conversely, insulin concentration peaked later after the evening and midnight meal (compared to the morning); creating a significantly larger late phase insulin response (p = 0.018 and p = 0.017). There was no significant difference between the evening and midnight late phase insulin response (p = 0.327).

4. Discussion

This study reports exaggerated glucose response to meal challenges at night (8pm and midnight), compared to the morning in healthy participants. The low GI meal was able to improve glycemic response in the morning, but had little impact at night. This may be associated with the effect that the endogenous circadian rhythm have on glucose metabolism [24]. Unexpectedly, glycemic response at 8pm and midnight was similar.

Our study's findings builds on observations from previous postprandial studies [8,25,26]. Gibbs et al. [18], in particular, found that the postprandial glucose response was higher in the evening compared to the morning, for both low GI and high GI meals. Unexpectedly, the glycemic responses between the low GI and high GI meals were not different in the morning. They concluded that further research was required, using “larger meals sizes with different nutritional compositions” [18], to determine whether low GI meals indeed have little benefits in the evening. Therefore, in our study, the low GI meal used was more comparable to a main meal, with a higher total energy load and an even macronutrient distribution. Despite these changes, postprandial glucose response was high at night, as observed previously [18]. However, we showed that this occurred despite an elevation in insulin response, which was not observed in the Gibbs et al. study [18].

The reduced glucose tolerance observed at night may be attributed to reduced insulin sensitivity. This is indicated through higher plasma insulin iAUC measured at both night time points compared to the morning. In particular, higher late phase insulin response observed at night, despite sustained elevation in postprandial glucose concentration, suggests reduced insulin sensitivity [24]. Although we could not prove this in our study, other intervention trials have employed more specific techniques to examine insulin sensitivity of peripheral tissues, including the intravenous glucose tolerance test, intravenous insulin tolerance test and the Triple Tracer Technique [3,27,28]. All studies found a

Table 3
Postprandial glucose and insulin after a low glycemic index meal at three time points (n = 9). Data reported as median (IQR).

	0800h	2000h[a]	0000h[a]
Glucose iAUC (mmol/L.3h)	27.90 (40.98)	176.25 (331.21)[a]	252.75 (84.80)[a]
Glucose concentration at 180 min (mmol/L)[b]	4.7 (0.5)	5.2 (0.8)	5.8 (1.1)[b]
Insulin iAUC (mU/L.3h)	1404.4 (885.2)	3288.0 (1844.8)[a]	2945.1 (3665.2)[a]
Late phase insulin response (mU/L.90min)[c]	0.0 (0.0)	93.8 (811.3)[a]	239.6 (391.6)[a]

iAUC: incremental area under the curve.
[a] Significantly different to concentration observed at 0800h denoted by[a]; determined by the Wilcoxon signed-rank test.
[b] Significantly different to the fasting glucose concentration of the session, denoted by[b], determined by the Wilcoxon signed-rank test.
[c] Late phase insulin response taken as insulin iAUC from 30 to 120 min postprandial.

reduction in insulin sensitivity at night (1800–2130h) compared to the day (0700–0930h) [3,27,28]. This results in less efficient uptake of glucose by peripheral tissues, hence postprandial glucose concentration is maintained at a higher level [29]. Postprandial hyperglycemia has been suggested as an independent risk factor of T2DM and cardiovascular disease [30,31]. Collectively, these findings provide a potential mechanism for the increased risks of cardiovascular disease and T2DM observed in shift workers [10,12,32,33].

Glycemic response at 8pm and midnight was the same. This was unexpected, as constant routine studies utilizing hourly or bi-hourly feeding, have shown that peak plasma glucose and insulin occurs between 2200h and 0600h [19,20]. The difference in findings may be attributed to the continuous wakefulness (for at least 27 h) experienced by participants in the constant routine studies. Nonetheless, it appears that the benefits of healthy low GI meals on glycemic control are masked by the circadian regulation of glucose metabolism during the dark hours, regardless of the hours of the night. This has implications for the general population, as 8pm is a time when many free-living individuals may consume dinner. Therefore, further investigation regarding the optimal macronutrient composition of meals consumed at night is required. Meals higher in protein and/or fat have been observed to have beneficial effects on glycemic control, at least in the morning [34] and warrants investigation at night time.

Our study benefitted from tightly controlled conditions, ensuring that morning and night sessions were conducted on separate days and preceded by the same length of fast; hence the true effects of meal timing could be examined. Furthermore, participants consumed a control meal prior to fasting and were asked to restrict alcohol intake and physical activity prior to each session. A limitation of this study was that there was no direct comparison to a test meal that was energy-matched, but had a macronutrient composition similar to a standard mixed meal. The glucose response to this standard mixed meal at night may have been greater than that of the low GI test meal. Furthermore, our rationale for investigating the effect of meal timing on glucose metabolism was to provide recommendations for shift workers, who often eat at night. However, the nature of our findings suggest that the effect of meal timing on glucose metabolism is evident from the evening, hence have a wider implication.

The current study confirms postprandial glucose excursion begins in the evening, despite concurrent increase in plasma insulin response. This seems to persist, but not worsen, throughout the night. While a low GI meal was able to produce slow and small changes in plasma glucose in the morning, this was not achieved in the evening and night. The observed temporal difference in postprandial glucose response may be associated with the effects of the circadian rhythm. Of note, these findings may be relevant to those trying to minimize daily glucose excursions, both in the shift working population and in the general population.

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Conflicts of interest

The authors of the study have no potential conflicts of interest or financial interest to declare.

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Statement of Authorship: GKWL, MPB, CEH were involved in the design of the study and acquisition of data; GKWL analyzed data and drafted the manuscript. All authors read and approved the final manuscript.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clnu.2017.11.010.

References

[1] Johnston JD. Physiological responses to food intake throughout the day. Nutr Res Rev 2014;27:107–18.
[2] Kalsbeek A, la Fleur S, Fliers E. Circadian control of glucose metabolism. Mol Metab 2014;3:372–83.
[3] Saad A, Man CD, Nandy DK, Levine JA, Bharucha AE, Rizza RA, et al. Diurnal pattern to insulin secretion and insulin action in healthy individuals. Diabetes 2012;61:2691–700.
[4] Van Cauter E, Shapiro ET, Tillil H, Polonsky KS. Circadian modulation of glucose and insulin responses to meals: relationship to cortisol rhythm. Am J Physiol 1992;262:E467–75.
[5] Boivin DB, Boudreau P, Tremblay GM. Phototherapy and orange-tinted Goggles for night-shift adaptation of police officers on patrol. Chronobiol Int 2012;29:629–40.
[6] Folkard S. Do permanent night workers show circadian Adjustment? A review based on the endogenous melatonin rhythm. Chronobiol Int 2008;25:215–24.
[7] Al-Naimi S, Hampton SM, Richard P, Tzung C, Morgan LM. Postprandial metabolic profiles following meals and snacks eaten during simulated night and day shift work. Chronobiol Int 2004;21:937–47.
[8] Holmback U, Forslund A, Forslund J, Hambraeus L, Lennernas M, Lowden A, et al. Metabolic responses to nocturnal eating in men are affected by sources of dietary energy. J Nutr 2002;132:1892–9.
[9] Lund J, Arendt J, Hampton SM, English J, Morgan LM. Postprandial hormone and metabolic responses amongst shift workers in Antarctica. J Endocrinol 2001;171:557–64.
[10] Gan Y, Yang C, Tong X, Sun H, Cong Y, Yin X, et al. Shift work and diabetes mellitus: a meta-analysis of observational studies. Occup Environ Med 2015;72:72–8.
[11] Pietroiusti A, Neri A, Somma G, Coppeta L, Iavicoli I, Bergamaschi A, et al. Incidence of metabolic syndrome among night-shift healthcare workers. Occup Environ Med 2010;67:54–7.
[12] Tenkanen L, Sjöblom T, Kalimo R, Alikoski T, Härmä M. Shift work, occupation and coronary heart disease over 6 years of follow-up in the Helsinki Heart Study. Scand J Work Environ Health 1997;23:257–65.
[13] Vyas MV, Garg AX, Iansavichus AV, Costella J, Donner A, Laugsand LE, et al. Shift work and vascular events: systematic review and meta-analysis. BMJ 2012;345:e4800.
[14] Jenkins DJA, Wolever TMS, Taylor RH. Glycemic index of foods: a physiological basis for carbohydrate exchange. Am J Clin Nutr 1981;34:362–6.
[15] Fleming P, Godwin M. Low-glycaemic index diets in the management of blood lipids: a systematic review and meta-analysis. Fam Pract 2013;30:485–91.
[16] Liu AG, Most MM, Brashear MM, Johnson WD, Cefalu WT, Greenway FL. Reducing the glycemic index or carbohydrate content of mixed meals reduces

postprandial glycemia and insulinemia over the entire day but does not affect satiety. Diabetes Care 2012;35:1633–7.
[17] Silva FM, Kramer CK, Crispim D, Azevedo MJ. A high-glycemic index, low-fiber breakfast affects the postprandial plasma glucose, insulin, and ghrelin responses of patients with type 2 diabetes in a randomized clinical trial. J Nutr 2015;145:736–41.
[18] Gibbs M, Harrington D, Starkey S, Williams P, Hampton S. Diurnal postprandial responses to low and high glycaemic index mixed meals. Clin Nutr 2014;33:889–94.
[19] Morgan L, Arendt J, Owens D, Folkard S, Hampton S, Deacon S, et al. Effects of the endogenous clock and sleep time on melatonin, insulin, glucose and lipid metabolism. J Endocrinol 1998;157:443–51.
[20] Shea SA, Hilton MF, Orlova C, Timothy Ayers R, Mantzoros CS. Independent circadian and sleep/wake regulation of adipokines and glucose in humans. J Clin Endocrinol Metab 2005;90:2537–44.
[21] Chapter 4-The role of glycemic index in food choice. Italy: food and agriculture organisation of the United Nations. http://www.fao.org/docrep/w8079e/w8079e0a.htm#calculation%20of%20glycemic%20index%20of%20meals%20or%20diets. [Accessed 26 May 2015].
[22] Hanefeld M, Koehler C, Fuecker K, Henkel E, Schaper F, Temelkova-Kurktschiev T. Insulin secretion and insulin sensitivity pattern is different in isolated impaired glucose tolerance and impaired fasting glucose: the risk factor in impaired glucose tolerance for atherosclerosis and diabetes study. Diabetes Care 2003;26:868–74.
[23] Phillips PJ. Oral glucose tolerance testing. Aust Fam Physician 2012;41:391–3.
[24] Morris CJ, Yang JN, Garcia JI, Myers S, Bozzi I, Wang W, et al. Endogenous circadian system and circadian misalignment impact glucose tolerance via separate mechanisms in humans. Proc Natl Acad Sci U. S. A. 2015;112:E2225–34.
[25] Biston P, Van Cauter E, Ofek G, Linkowski P, Polonsky KS, Degaute JP. Diurnal variations in cardiovascular function and glucose regulation in normotensive humans. Hypertension 1996;28:863–71.
[26] Owens DS, Macdonald I, Benton D, Sytnik N, Tucker P, Folkard S. A preliminary investigation into individual differences in the circadian variation of meal tolerance: effects on mood and hunger. Chronobiol Int 1996;13:435–47.
[27] Lee A, Ader M, Bray GA, Bergman RN. Diurnal variation in glucose tolerance: cyclic suppression of insulin action and insulin secretion in normal-weight, but not obese, subjects. Diabetes 1992;41:750–9.
[28] Morgan LM, Aspostolakou F, Wright J, Gama R. Diurnal variations in peripheral insulin resistance and plasma non-esterified fatty acid concentrations: a possible link? Ann Clin Biochem 1999;36:447–50.
[29] Saltiel AR, Kahn CR. Insulin signalling and the regulation of glucose and lipid metabolism. Nature 2001;414:799–806.
[30] Gao W, Qiao Q, Tuomilehto J. Post-challenge hyperglycaemia rather than fasting hyperglycaemia is an independent risk factor of cardiovascular disease events. Clin Lab 2004;50:609–15.
[31] Onat A, Can G, Cicek G, Ayhan E, Dogan Y, Kaya H. Fasting, non-fasting glucose and HDL dysfunction in risk of pre-diabetes, diabetes, and coronary disease in non-diabetic adults. Acta Diabetol 2013;50:519–28.
[32] Bøggild H, Knutsson A. Shift work, risk factors and cardiovascular disease. Scand J Work Environ Health 1999;25:85–99.
[33] Knutsson A, Jonsson B, Akerstedt T, Orth-Gomer K. Increased risk of ischaemic heart disease in shift workers. Lancet 1986;328:89–92.
[34] Moghaddam E, Vogt JA, Wolever TMS. The effects of fat and protein on glycemic responses in nondiabetic humans vary with waist circumference, fasting plasma insulin, and dietary fiber intake. J Nutr 2006;136:2506–11.