<table>
<thead>
<tr>
<th>Clock Time</th>
<th>Core Temperature (°C)</th>
<th>Body Temp.</th>
<th>Melatonin (pmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20.00</td>
<td>37.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>08.00</td>
<td>36.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cagnacci et al., J Clin Endocrinol Metab. 1992 Aug;75(2):447-52
Peripheral Clocks

Pancreas
- Insulin secretion

Heart
- Cardiovascular function

Intestine
- Food absorption

Muscle
- Insulin sensitivity

Adipose
- Fat accumulation

Immune
- Inflammation

Insulin secretion, Nature. 2012 Nov 15;491(7424):348-56
Icons made by flaticon.com/authors/smashicons
Circadian Cycle

Behavioural Cycle

Time Since Wake (Hours)

Leptin (% from mean)

Aligned
Misaligned

↓ 17%

Time Since Wake (Hours)

Cortisol (% from mean)

Aligned
Misaligned

σ

% increase when misaligned

Glucose: + 6%
Insulin: + 22%

8am Wake Time – Normal Alignment

~ 5.6 mmol/L
~ 100 mg/dL

8pm Wake Time – Maximal Misalignment

~ 7.3 mmol/L
~ 132 mg/dL

Average 2-h postprandial glucose response to breakfast

2-hr postprandial glucose

Glucose (mg/dL)

Aligned

Misaligned

2-hr postprandial insulin

Insulin (µU/mL)

Aligned

Misaligned

Peripheral Clocks

Pancreas
- Insulin secretion
- Cardiovascular function

Intestine
- Food absorption

Muscle
- Insulin sensitivity

Adipose
- Fat accumulation

Immune
- Inflammation

Diet
- Shift work
- Sleep restriction
- Time-zone travel
- Social jet lag

Insulin secretion
Cardiovascular function
Food absorption
Insulin sensitivity
Fat accumulation
Inflammation

Light
Wake
Feeding
Activity

Dark
Sleep
Fasting
Rest
Chrononutrition
Observations
Mechanistic Rationale
Animal Data
Human Trials (TRF)
Observations

Mechanistic Rationale

Animal Data

Human Trials (TRF)
Individuals consuming more of their daily calories between 4 h before DLMO and sleep onset had a higher percentage of body fat.
Higher % of daily calories consumed here = Higher body fat %

First Caloric Intake of Day

Individual Participants

Monday - Friday
Weekend

“Metabolic Jetlag”

Gill & Panda, Cell Metab. 2015 Nov 3; 22(5): 789–798
Regular

70% of kcal

30% of kcal

Irregular

3 – 9 meals/d
<table>
<thead>
<tr>
<th>Day</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>x 7</td>
</tr>
<tr>
<td>Day 2</td>
<td>x 4</td>
</tr>
<tr>
<td>Day 3</td>
<td>x 9</td>
</tr>
<tr>
<td>Day 4</td>
<td>x 3</td>
</tr>
<tr>
<td>Day 5</td>
<td>x 5</td>
</tr>
<tr>
<td>Day 6</td>
<td>x 8</td>
</tr>
<tr>
<td>Day 7</td>
<td>x 6</td>
</tr>
<tr>
<td>Day 8</td>
<td>x 5</td>
</tr>
<tr>
<td>Day 9</td>
<td>x 9</td>
</tr>
<tr>
<td>Day 10</td>
<td>x 8</td>
</tr>
<tr>
<td>Day 11</td>
<td>x 3</td>
</tr>
<tr>
<td>Day 12</td>
<td>x 4</td>
</tr>
<tr>
<td>Day 13</td>
<td>x 7</td>
</tr>
<tr>
<td>Day 14</td>
<td>x 6</td>
</tr>
</tbody>
</table>

11 women

Irregular

Washout

Regular

14 days

Regular

14 days

Washout

Irregular

14 days

10 kcal/kg = ~550–600 kcal

50% CHO
35% fat
15% pro

3-hour bloods

Irregular

14 days

Regular

93 women with overweight/obesity

**Large Breakfast**
- 700 kcal (50%)
- 500 kcal (36%)
- 200 kcal (14%)

12 weeks
- 38 completed (8 dropouts)

**Large Dinner**
- Breakfast 200 kcal (14%)
- Lunch 500 kcal (36%)
- Dinner 700 kcal (50%)

12 weeks
- 36 completed (11 dropouts)

Jakubowicz et al., Obesity (Silver Spring). 2013 Dec;21(12):2504-12
Jakubowicz et al., Obesity (Silver Spring). 2013 Dec;21(12):2504-12

Graph showing the change in bodyweight (kg) over weeks for Large Breakfast and Large Dinner conditions. The graph indicates a decrease in bodyweight for both conditions:

- **Large Breakfast**: \( \downarrow 8.7 \pm 1.4 \) kg
- **Large Dinner**: \( \downarrow 3.6 \pm 1.4 \) kg
Waist Circumference (cm)

<table>
<thead>
<tr>
<th>Week</th>
<th>Large Breakfast</th>
<th>Large Dinner</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>90</td>
<td>115</td>
</tr>
<tr>
<td>6</td>
<td>108</td>
<td>113</td>
</tr>
<tr>
<td>12</td>
<td>109</td>
<td>115</td>
</tr>
</tbody>
</table>

△ 3.9 cm

△ 8.5 cm

Jakubowicz et al., Obesity (Silver Spring). 2013 Dec;21(12):2504-12
Start

0

Testing Day

Blood Samples every 30 minutes

Visual Analogue Scales

WEEK

2

End

12

Glucose

Insulin

Ghrelin

Hunger

Satiety

Sigma Nutrition.com
Week 2*: Test Meals

Blood Glucose (mg/dL)

- Large Breakfast
- Large Dinner

Hours After Breakfast

Jakubowicz et al., Obesity (Silver Spring). 2013 Dec;21(12):2504-12
Per-Meal Glucose AUC (3hr)

- **Breakfast**
- **Lunch**
- **Dinner**

**Large Breakfast**

**Large Dinner**

Jakubowicz et al., Obesity (Silver Spring). 2013 Dec;21(12):2504-12
420 people w/ overweight/obesity

Weight Loss Program:
~ 20 week intervention

Dietetic treatment based on Mediterranean Diet
Nutritional Education
Moderate physical activity program
Cognitive behavioural therapy

Using food diary from a week that most deemed usual by patient & dietitian

51%  49%

Early Eaters   Late Eaters

Lunch (largest meal) before 3pm

Lunch (largest meal) after 3pm

a) Total daily calories & dietary composition was similar between groups
b) Late eaters for lunch were also late eaters for dinner

Early Eaters

Late Eaters

Circadian disruption = ↑ risk of metabolic disease

- Shift Work
- Breakfast Skipping
- Late night eating
- Metabolic jetlag
- Erratic eating patterns
- Prolonged eating window is typical
- Time of largest meal
- Large breakfast vs. large dinner
Morning vs. Evening

Beta-cell Function: 15% higher

Aligned vs. Misaligned

Insulin Sensitivity: 16% higher

Breakfast vs. Dinner

Insulin Sensitivity: 25% higher
Goo et al., Gastroenterology. 1987 Sep;93(3):515-8

Minutes

% Retention Solids

Morning

Evening

Goo et al., Gastroenterology. 1987 Sep;93(3):515-8
Diet-induced Thermogenesis (kcal/min)

Morning

Evening

DIT 44% lower in evening

Morris et al., Obesity (Silver Spring). 2015 Oct; 23(10): 2053–2058
Post-prandial EE (kcal/min)

- **Morning**: 1.2 kcal/min
- **Evening**: 1.1 kcal/min

Morris et al., Obesity (Silver Spring). 2015 Oct; 23(10): 2053–2058
33 lean people (21 women)

**Breakfast**

≥700 kcal before 11 am
(at least 50% within 2 h of waking)

6 weeks

**Fasting**

Fast until 12 pm
(water allowed)

Calories

**Breakfast**

- Resting Metabolic Rate
- D.I.T
- Physical Activity Thermogenesis

**Fasting**

- Resting Metabolic Rate
- D.I.T
- Physical Activity Thermogenesis

**Energy Expenditure**

- 0
- 1500
- 3000

**Energy Intake**

- 2,730 kcal
- 2,191 kcal


Energy Expenditure

- Breakfast: Resting Metabolic Rate + Physical Activity Thermogenesis
- Fasting: Resting Metabolic Rate + Physical Activity Thermogenesis

Energy Intake

- Breakfast: 2,730 kcal
- Fasting: 2,191 kcal

* indicates statistical significance.
Physical Activity Thermogenesis

Difference explained by difference in “light intensity” PA in the early part of the day

Breakfast: 851 kcal
Fasting: 442 kcal

• Prolonged feeding period leads to fat gain, insulin resistance, and increased liver fat [1]
• When mice without a circadian clock are fed ad libitum, they gain weight. When feeding is kept within a 10-hour window during their active phase, they are protected against weight gain and metabolic syndrome [2]
• Restricting access to a high-fat, high-sugar diet to the time when mice usually sleep tends to lead to greater body fat. Doing so also flattens daily hormone rhythms and reduces energy expenditure and fat oxidation [3]
• Restricting access to high-fat food to only 8–12 hours per day does not reduce overall caloric intake (compared to animals fed ad libitum), but improves circadian rhythms and helps prevent or reverse metabolic diseases [4]

Observations

Mechanistic Rationale

Animal Data

Human Trials (TRF)
13 participants; 2 week habitual diet

10 week intervention

Habitual

TRF

1. Delay breakfast 1.5 hours
2. Advance dinner 1.5 hours

Ad libitum food access

Antoni et al., Journal of Nutritional Science (2018), vol. 7, e22, pg 1
<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 10</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Habitual</strong></td>
<td>~1,900 kcal/d</td>
<td>~1,900 kcal/d</td>
</tr>
<tr>
<td><strong>TRF</strong></td>
<td>~2,150 kcal/d</td>
<td>~1,480 kcal/d</td>
</tr>
</tbody>
</table>

Antoni et al., Journal of Nutritional Science (2018), vol. 7, e22, pg 1
Baseline Study

156 people

3 weeks

8 subjects selected

Intervention Study

16 weeks

Gill & Panda, Cell Metab. 2015 Nov 3; 22(5): 789–798
Baseline

Midnight

TRF

Time

Participant

6 am 7 am 8 am 9 am 10 am 11 am 12 pm 1 pm 2 pm 3 pm 4 pm 5 pm 6 pm 7 pm 8 pm 9 pm 10 pm 11 pm 12 am

Gill & Panda, Cell Metab. 2015 Nov 3; 22(5): 789–798
TRF Intervention
Baseline
1 year follow-up

Bodyweight (kg)

↓ 3.27 kg

Gill & Panda, Cell Metab. 2015 Nov 3; 22(5): 789–798
Weight Loss (%)

TRF vs Control

Week of Study

Gabel et al., Nutr Healthy Aging. 2018; 4(4): 345–353
Control

eTRF

Time

7am 10am 1pm 4pm 7pm 10pm 1am 4am

Awake

Sleep

12 hour fasting window

18 hour fasting window

Continuous Glucose Monitoring

Jamshed et al., Nutrients. 2019 May 30;11(6)
Sutton et al., 2018, Cell Metabolism, 27, 1212–1221

The diagram shows a 24-hour time scale with a 12-hour fasting window for the Control group and a 18-hour fasting window for the eTRF group. The time points are marked as follows: 7am, 10am, 1pm, 4pm, 7pm, 10pm, 1am, and 4am. The Control group has meals at 7am, 10am, and 1pm, while the eTRF group has meals at 7am, 10am, and 1pm. The diagram indicates that the eTRF group maintains a longer fasting period compared to the Control group.
8 men with prediabetes

- **Control**
  - 5 weeks
  - Washout
  - 7 weeks
  - **eTRF**
  - 5 weeks

- **eTRF**
  - 5 weeks
  - Washout
  - **Control**

Sutton et al., 2018, Cell Metabolism, 27, 1212–1221
3-hr OGTT: Change from baseline to intervention end

Change in Mean Insulin (mIU/L)

-60
-40
-20
0
Control

eTRF

Sutton et al., 2018, Cell Metabolism, 27, 1212–1221
3-hr OGTT: Change from baseline to intervention end

Change in beta-cell function (U/mg)

Control  eTRF

Sutton et al., 2018, Cell Metabolism, 27, 1212–1221
3-hr OGTT: Change from baseline to intervention end

Change in Insulin Resistance (U/mg)

-60
-40
-20
0

Control

eTRF

Sutton et al., 2018, Cell Metabolism, 27, 1212–1221
11 overweight adults

Control

Washout

eTRF

4 days

3–5 weeks

Washout

Control

eTRF

4 days

Jamshed et al., Nutrients. 2019 May 30;11(6)
9-hour TRF Protocol

**TRFe**
8 am to 5 pm

**TRFd**
12 pm to 9 pm

Eating Window

2 week washout

7 days

7 days

7 days

7 days

Hutchinson et al., Obesity (Silver Spring). 2019 May;27(5):724-732
Glucose (mmol/L)

- eTRF @ baseline
- dTRF @ baseline
- eTRF @ day 7
- dTRF @ day 7

Hutchinson et al., Obesity (Silver Spring). 2019 May;27(5):724-732
Timing

Calorie Distribution
Consistency
Feeding-Fasting Cycle
Consistency

Calorie Distribution

Feeding-Fasting Cycle
Feeding - Fasting Cycle

Timing

Calorie Distribution

Consistency
Feeding–Fasting Cycle
Nuance, Considerations & Contraindications
Conclusions

1. I don’t know anything
2. Lots of questions remain
3. Circadian alignment matters!
4. Factor in to nutrition decisions
5. But don’t undermine fundamentals