Simposio: Dieta, Dislipidemia e NAFLD

Focus 1 «Crono-nutrizione»

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DISCLOSURES

La dr.ssa Marina Caputo dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Novo Nordisk
- Astra Zeneca

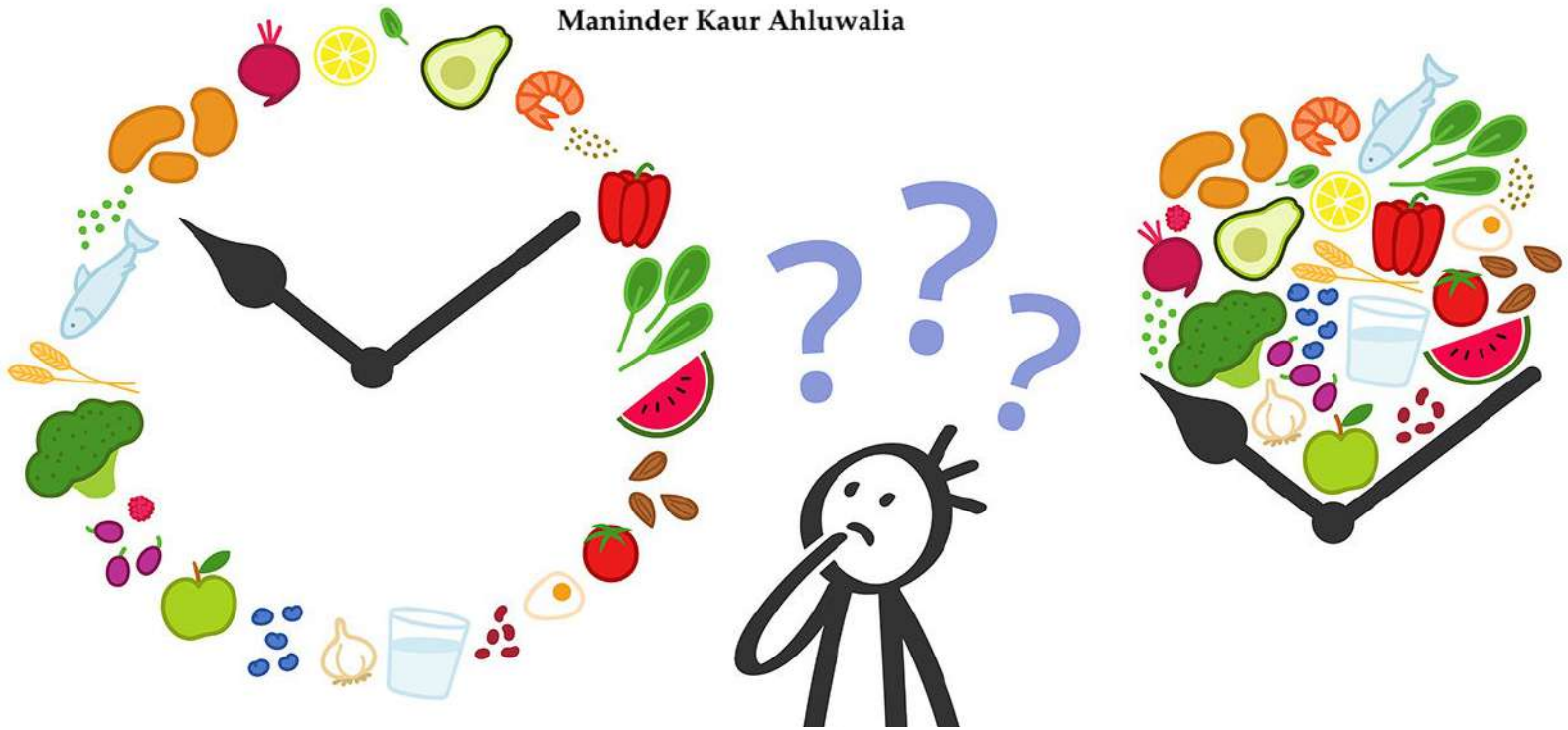
Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

nutrients

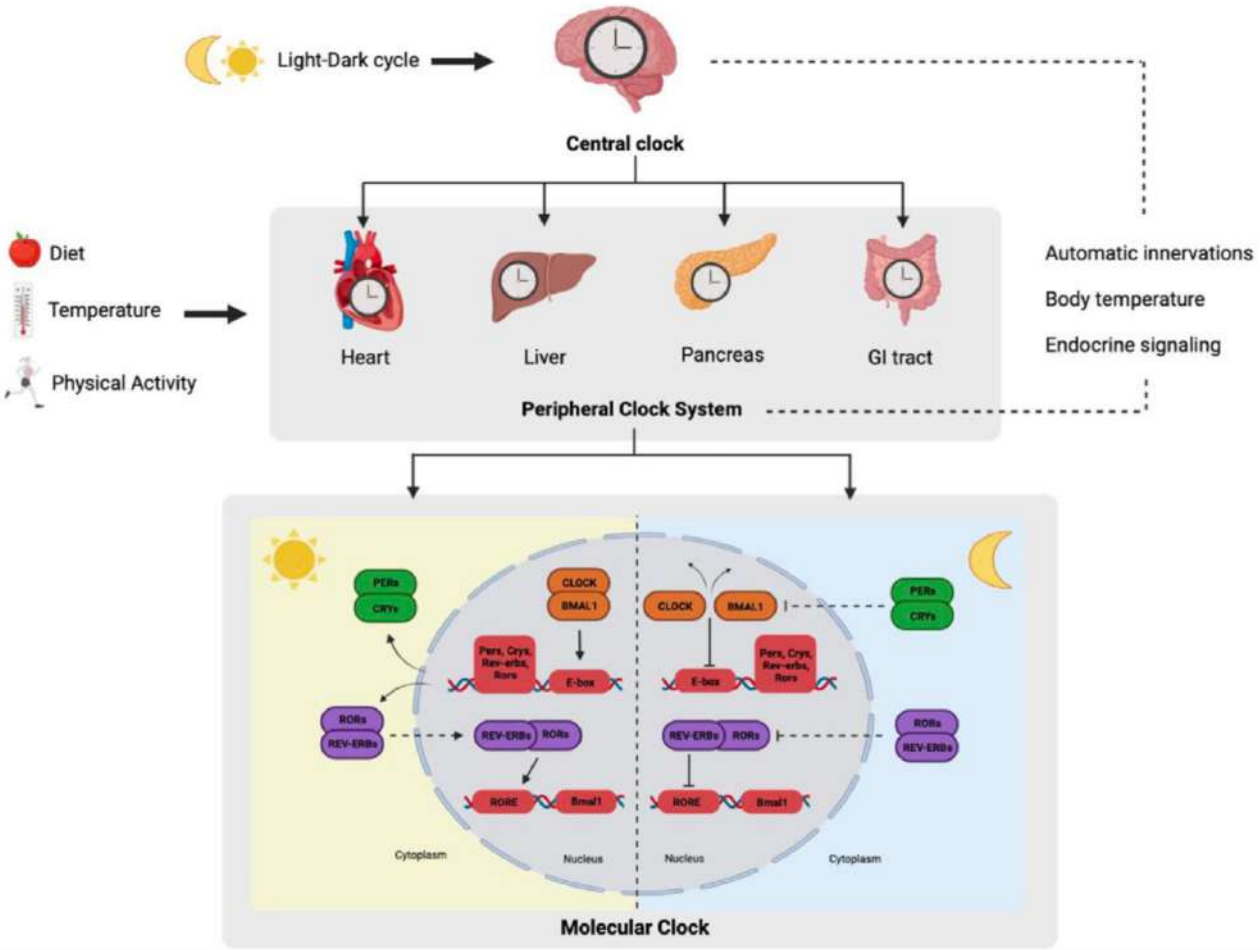
Review

Chrononutrition—When We Eat Is of the Essence in Tackling Obesity

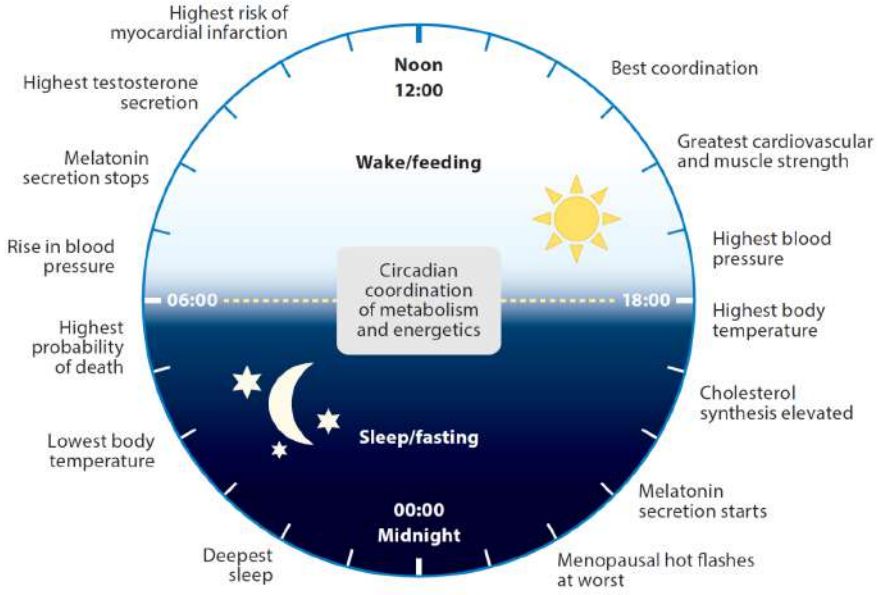
Maninder Kaur Ahluwalia



CIRCADIAN BIOLOGY



Wake/feeding	
Liver	Glycogen, cholesterol, and bile acid synthesis
Pancreas	Insulin secretion
Fat	Lipogenesis, adiponectin production
Muscle	Glycolytic metabolism



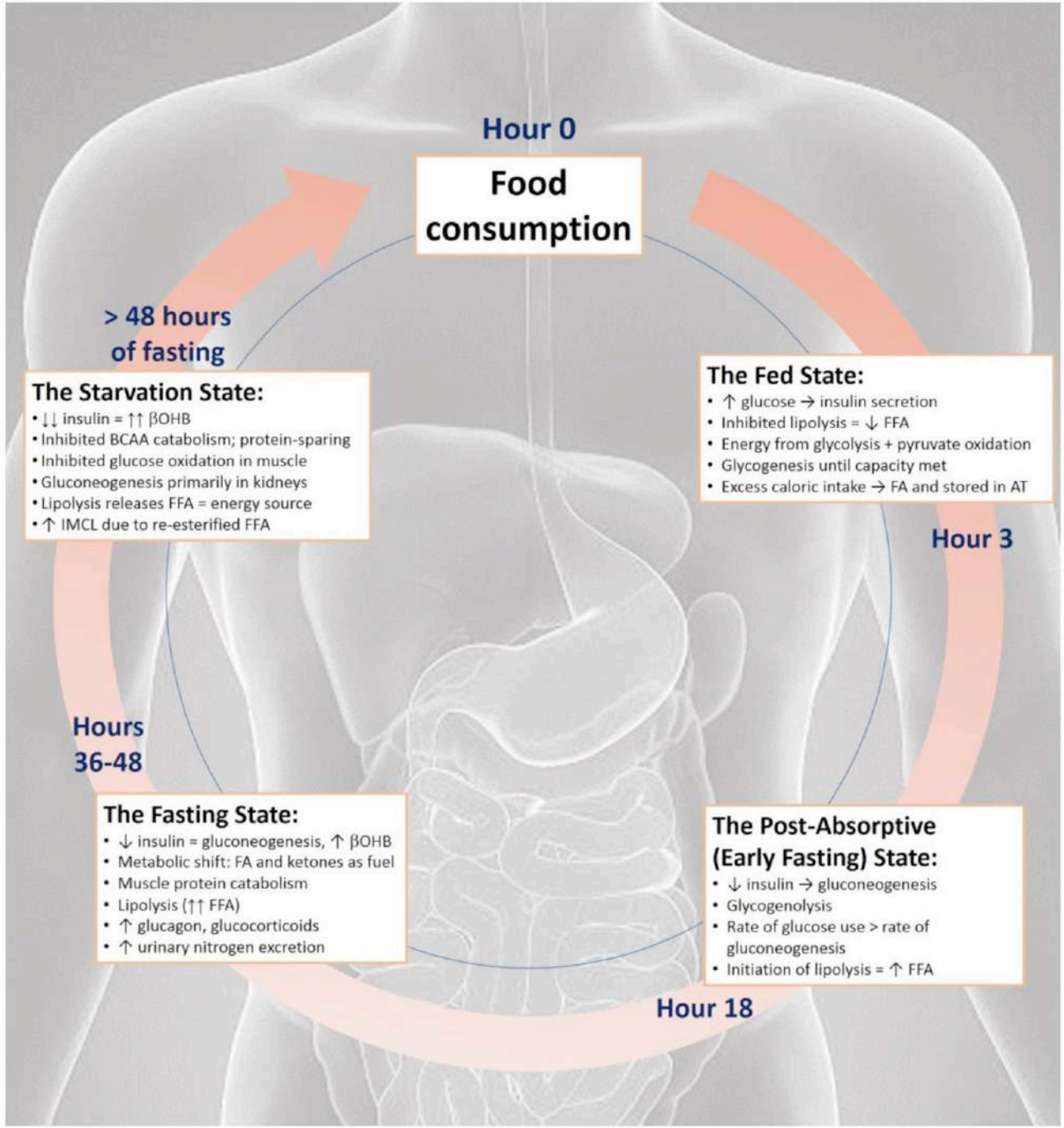
Sleep/fasting	
Liver	Gluconeogenesis, glycogenolysis, mitochondrial biogenesis
Pancreas	Glucagon secretion
Fat	Lipid catabolism, leptin secretion
Muscle	Oxidative metabolism

Di Francesco A et al. Science 2018
Lotti S et al, Nutrition, Metabolism & Cardiovascular Diseases 2023

FOOD and FASTING are the most important modifiable environmental factors for human health.
They affect lifespan and susceptibility to diseases.

METABOLIC PROGRAMMING

CHRONO-NUTRITION



Stockman MC et al. Curr Obes Rep 2018

Table 1. Hormones and growth factors that are specifically affected by the nutritional status.

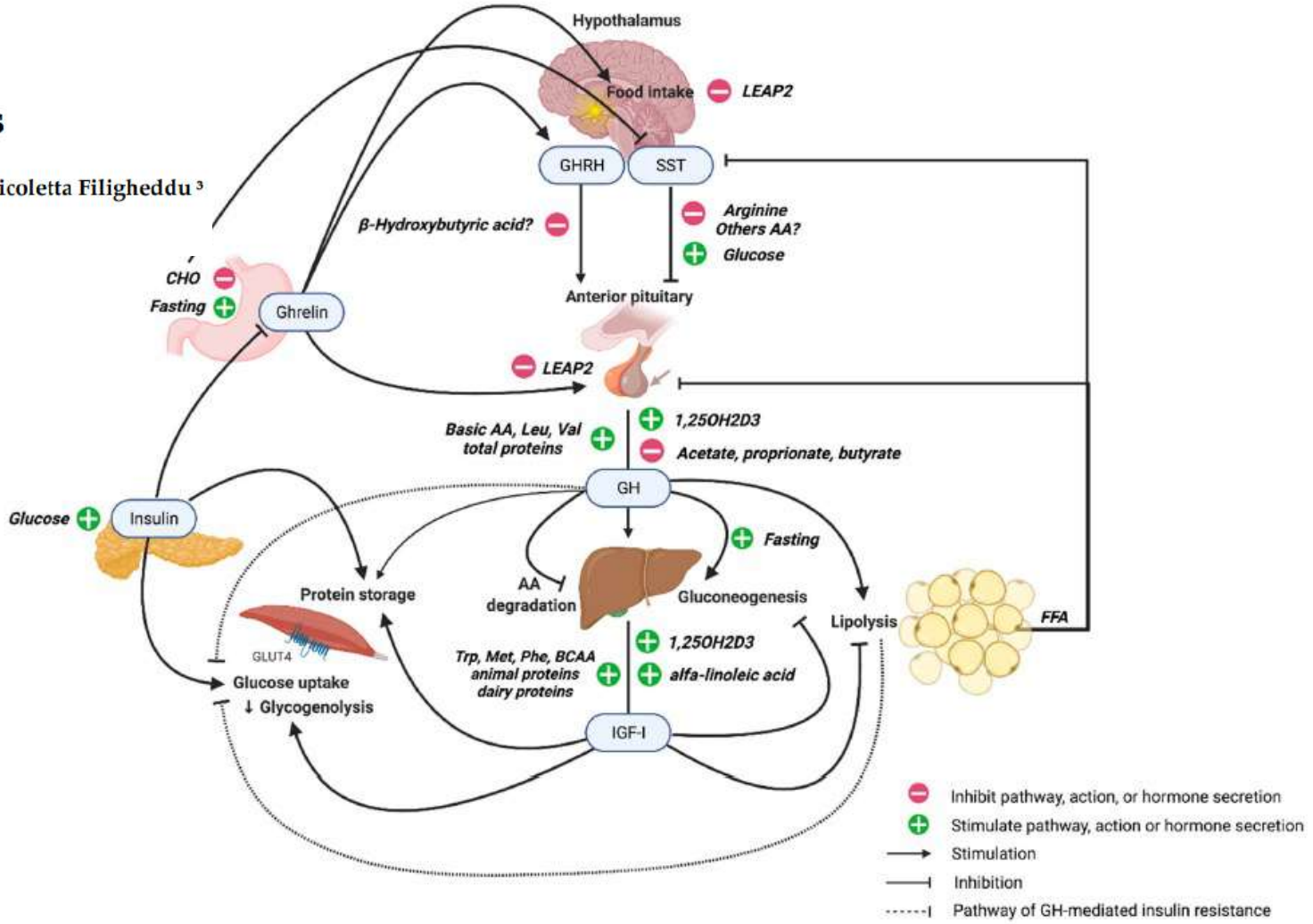
Hormone	Affected by food restriction	Effect on growth
Insulin	Reduced	Stimulates growth
Growth Hormone	Reduced (rats and mice)/increased (humans, rabbits, sheep, cows and pigs)	Stimulates growth
Insulin like growth factor 1	Reduced	Stimulates growth
IGFBP-1	Increased	Inhibits growth
Leptin	Reduced	Stimulates growth
Glucocorticoids	Increased	Inhibits growth
Thyroid hormones	Reduced	Stimulates growth
FGF21	Reduced/increased	Inhibits growth
Vitamin D	Reduced	Required for proper growth, inhibits chondrocyte proliferation at high concentrations
Sex hormones *	Reduced	Stimulates growth (testosterone), hastens EGP closure (estrogen) *

Gat-Yablonski G et al. Nutrients 2015

Review

Regulation of GH and GH Signaling by Nutrients

Marina Caputo [1,2], Stella Pigni [1], Emanuela Agosti [2], Tommaso Daffara [1], Alice Ferrero [1], Nicoletta Filigheddu [3] and Flavia Prodam [1,2,*]



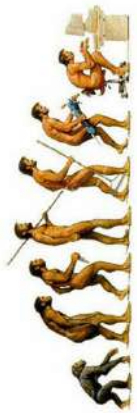


Table 1 Intermittent fasting regimens hypothesized to impact health outcomes

Type of fast	Description
Complete alternate-day fasting	Involves alternating fasting days (no energy-containing foods or beverages consumed) with eating days (foods and beverages consumed ad libitum)
Modified fasting regimens	Allows consumption of 20–25% of energy needs on scheduled fasting days; the basis for the popular 5:2 diet, which involves severe energy restriction for 2 nonconsecutive days per week and ad libitum eating for the other 5 days
Time-restricted feeding	Allows ad libitum energy intake within specific time frames, inducing regular, extended fasting intervals; studies of <3 meals per day are indirect examinations of a prolonged daily or nightly fasting period
Religious fasting	Variety of fasting regimens undertaken for religious or spiritual purposes
Ramadan fasting	A fast from sunrise to sunset during the holy month of Ramadan; the most common dietary practice is to consume one large meal after sunset and one lighter meal before dawn. Thus, the feast and fast periods of Ramadan are approximately 12 hours in length
Other religious fasts	Members of the Church of Jesus Christ of Latter-Day Saints routinely abstain from food and drink for extended periods of time. Some Seventh-day Adventists consume their last of two daily meals in the afternoon, resulting in an extended nighttime fasting interval that may be biologically important

Patterson RE et al. Ann Rev Nutr 2017

ALTERNATE-DAY FASTING

Alternate-day fasting allows you to eat normally on non-fast days, but you then restrict the number of calories consumed on fast days to around 25% of your usual intake. Normal caloric intake ranges anywhere from 1,600 to 2,400 for women and from 2,000 to 3,000 for men depending on age and level of physical activity.

THE 5:2 PLAN

The 5:2 plan is similar to alternate-day fasting. On five days of the week, you eat normally. On the other two days of the week, you restrict the number of calories consumed to around 500–600. Fast days should not be consecutive days.

WEEKLY 24-HOUR FAST

With this style, you eat normally six days out of the week but fast completely during a 24-hour period. This style can be very difficult to maintain since it requires consuming only liquids for 24 hours straight

FAST FOR A SET NUMBER OF HOURS EACH DAY (16: 8) (TIME-RESTRICTED FEEDING)

You have a window of time during which you eat, and you then fast for the remainder of the day. The number of hours fasted is unique to each individual.

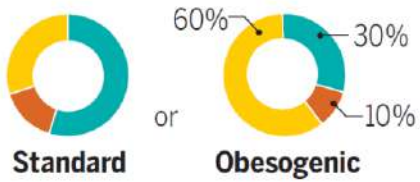
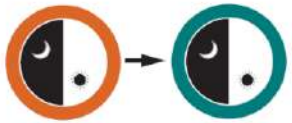
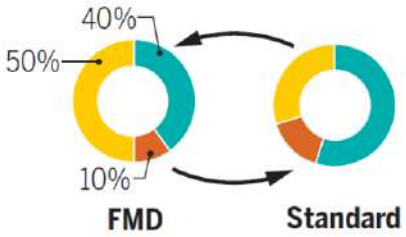
FASTING MIMICK DIET

Reduced caloric intake (~30% of energy needs) for **five** consecutive days before returning to normal eating cycles of FMD once a month or every 3 to 4 months per year.

FOR ALL?

- You have a healthy relationship with food
- You can control your eating once you break your fast
- You feel sharper and more productive during the fast
- You are in good health
- You have little stress or it is well managed

- You have a history of eating disorders
- You overeat once you break your fast
- You are preoccupied with food during the fast
- You are experienced hormonal issue
- You are in a stressful period of your life

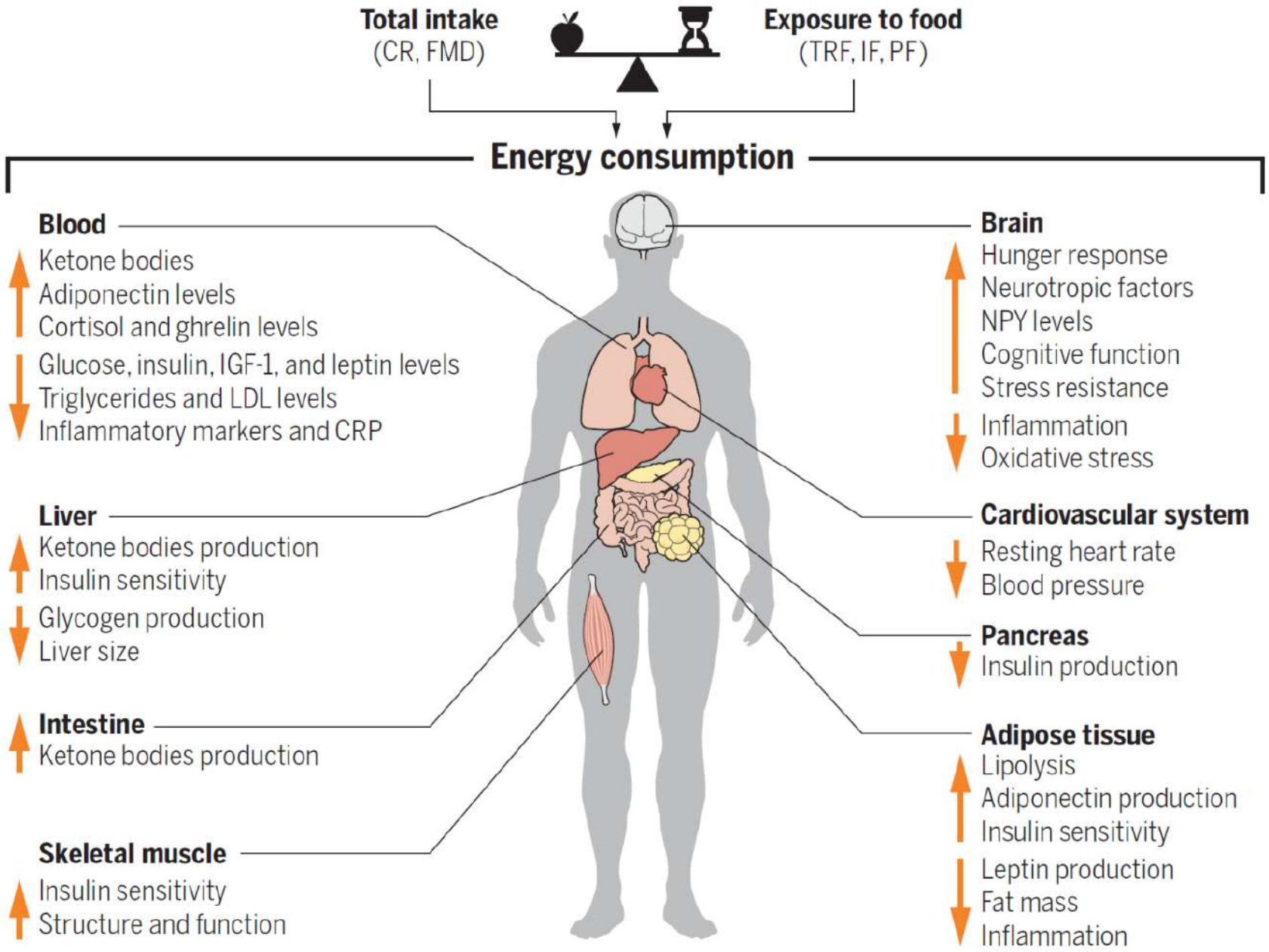
Feeding regimen	Description	Macronutrient balance ● Fat ● Protein ● Carbohydrate	Feeding time ● Fasting ● Feeding	Median life-span increase	Effects on health
Caloric restriction (CR)	Daily reduction by 15 to 40% of caloric intake without malnutrition			Yes 	Prevention of obesity, diabetes, oxidative stress, hypertension, cancer, cardiovascular disease
Time-restricted feeding (TRF)	Daily food consumption restriced to 4- to 12-hour window			No data	Defense against type II diabetes, hepatic steatosis, hypercholesterolemia
Intermittent or periodic fasting (IF or PF)	**IF:** Alternation of 24-hour fasting or very low calories (25% of energy needs) with a 24-hour ad libitum eating period **PF:** 1 to 2 days fasting or very low calories followed by a 5-day ad libitum eating period (5:2)			Yes 	Protection against obesity, oxidative stress, cardiovascular disease, hypertension, neurodegeneration, diabetes
Fasting-mimicking diet (FMD)	Reduced caloric intake (~30% of energy needs) for five consecutive days before returning to normal eating cycles of FMD once a month or every 3 to 4 months per year			Yes 	Protection from cancer and diabetes, improved risk factors associated with multiple age-related diseases

Di Francesco A et al. Science 2018

Table 1. The Influence of Dietary Timing Patterns on the Host Immune System and the Gut Microbiome in Different Mouse Disease Models[a]

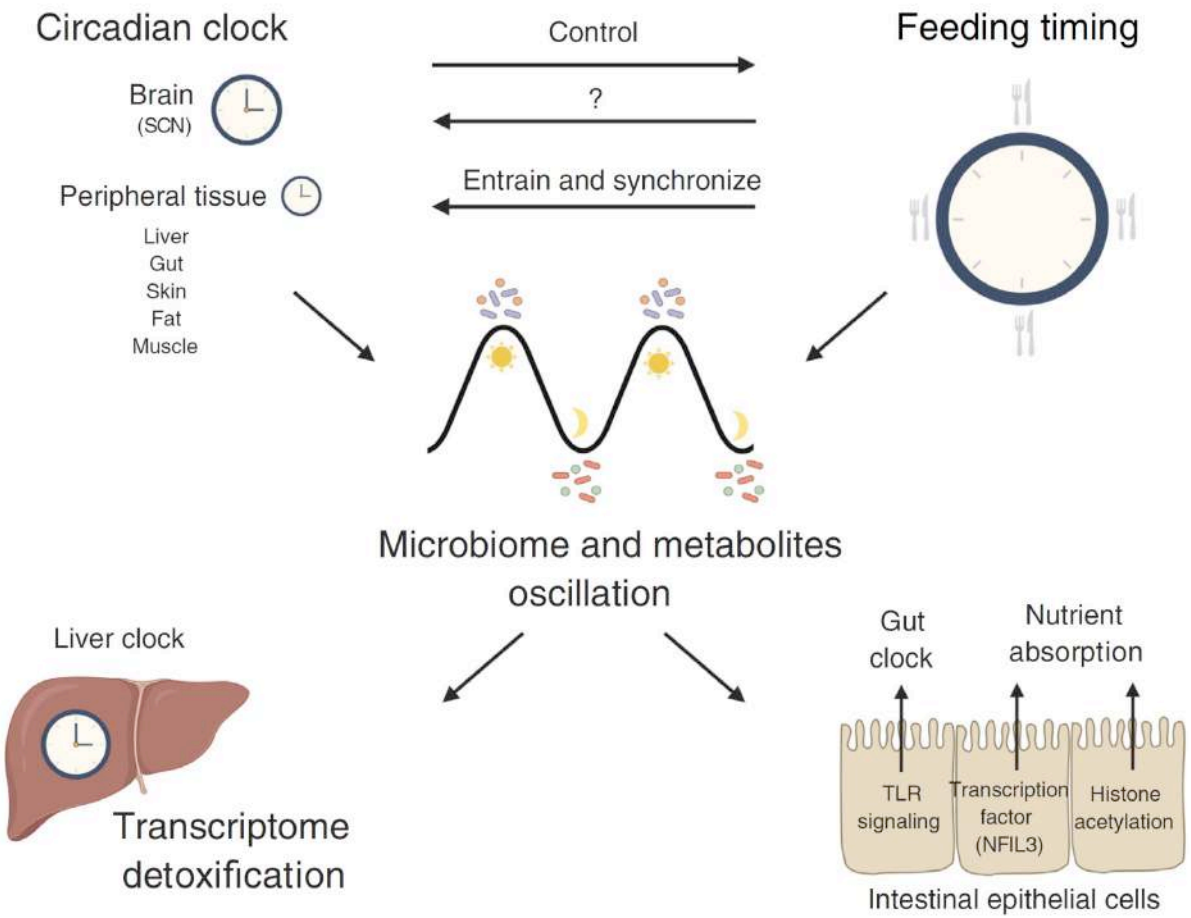
Mouse disease models	Dietary timing	Impact of dietary timing on the immune system	Impact of dietary timing on gut microbiota	Impact of dietary timing on disease outcomes	Refs
Multiple sclerosis: EAE	ADF or FMD	T_{reg} ↑ T_H1, T_H17, and APC↓ IFN-γ, IL-17, and TNF-α ↓ Demyelination ↓	*Bacteria richness*↑ *Lactobacillaceae*↑ *Bacteroidaceae*↑ *Prevotellaceae* ↑ Ketone metabolism↑ Glutathione metabolism↑ FMT from fasting-treated mice ameliorates the course of EAE	Clinical severity ↓ Pathology improved	[140,121]
Parkinson: MTPT-induced PD	FMD	Number of glial cells ↓ TNF-α and IL-1β ↓	*Firmicutes*↑ *Tenericutes*↑ *Opisthokonta*↑ *Proteobacteria* ↓ Butyric acid and valeric acid↑ FMT from FMD-treated mice confers neuroprotection for PD	Motor function↑ Dopaminergic neurons↑	[143]
IBD: chronic dextran sulfate sodium colitis	FMD	Serum lymphocytes ↓ Serum granulocytes and neutrophils↑	*Lactobacillaceae* ↑ *Bifidobacteriacea*↑ FMT from FMD-treated mice improves DSS induced clinical severity	Intestinal inflammation ↓ Intestinal regeneration↑ Intestinal pathology improved	[131]
Colon cancer: alcohol-induced polyposis in genetic susceptible mice	Eating at rest phase ('wrong'-time eating)	Hyperpermeability protumorigenic mucosal inflammation CD3↓ T_{reg}/T_H17 ratio↓	Dysbiosis Alpha diversity ↓ Butyrate↓ *Turcibacteraceae* ↑ *Turicibacter* ↑ *Lachnospiraceae* ↓	Colon carcinogenesis↑	[168]

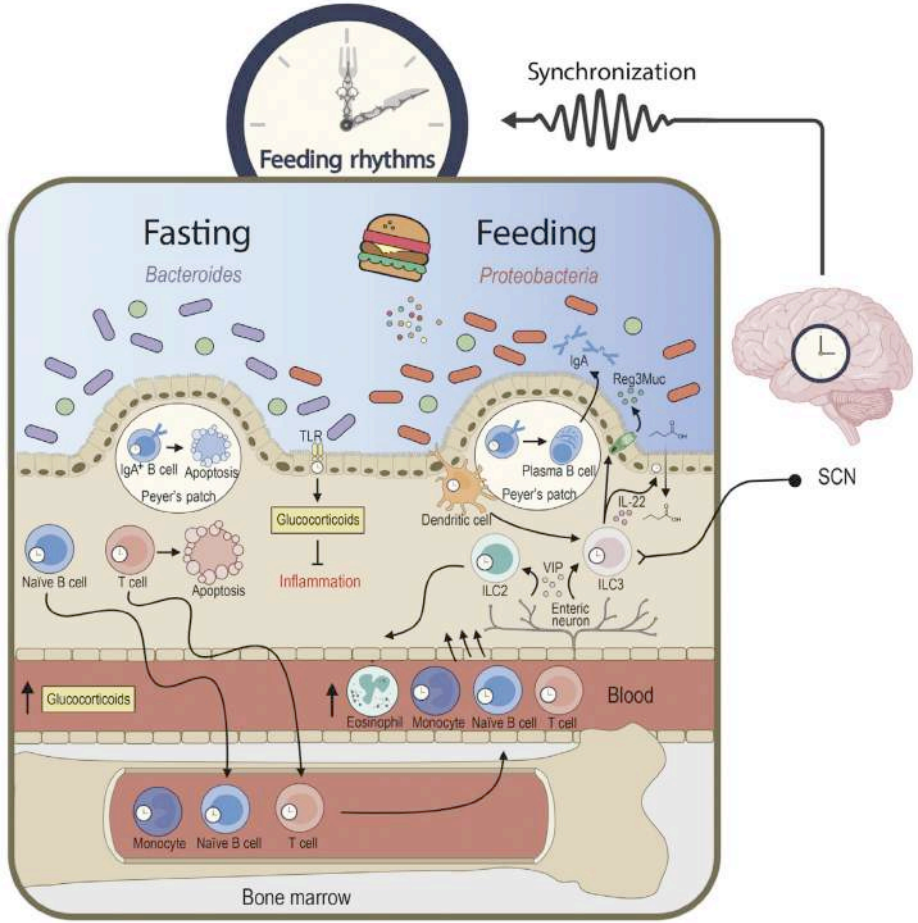
Zheng D et al. Trends Immunol 2020



Di Francesco A et al. Science 2018

MICROBIOTA





Zheng D et al. Trends Immunol 2020

5. Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes: *Standards of Care in Diabetes—2023*

Diabetes Care 2023;46(Suppl. 1):S68–S96 | https://doi.org/10.2337/dc23-S005

MEDICAL NUTRITION THERAPY

Please refer to the ADA consensus report "Nutrition Therapy for Adults With Diabetes or Prediabetes: A Consensus Report" for more information on nutrition therapy (70). Despite agreement in nutrition recommendations from large scientific bodies, including the American Heart Association, American College of Lifestyle Medicine, and the U.S. Dietary Guidelines (87–93), confusion and controversy remain. For many individuals with diabetes, the most challenging part of the treatment plan is determining what to eat. There is not a "one-size-fits-all" eating pattern for individuals with diabetes, and meal planning should be individualized. Nutrition therapy plays an integral role in overall diabetes management, and each person with diabetes should be actively engaged in education, self-management, and treatment planning with the health care team, including the collaborative development of an individualized eating plan (70,94). All health care professionals should refer people with diabetes for individualized MNT provided by an RDN who is knowledgeable and skilled in providing diabetes-specific MNT (21,95,96) at diagnosis and as needed throughout

There has been an increased interest in time-restricted eating and intermittent fasting as strategies for weight management. Intermittent fasting is an umbrella term which includes three main forms of restricted eating: alternate-day fasting (energy restriction of 500–600 calories on alternate days), the 5:2 diet (energy restriction of 500–600 calories on consecutive or nonconsecutive days) with usual intake the other five, and time-restricted eating (daily calorie restriction based on window of time of 8–15 h). Each produces mild to moderate weight loss (3–8% loss from baseline) over short durations (8–12 weeks) with no significant differences in weight loss when compared with continuous calorie restriction (148–151). A few studies have extended up to 52 weeks and show similar findings (152–155). Time-restricted eating (shortening the eating window) is generally easier to follow compared with alternative-day fasting or the 5:2 plan, largely due to ease, no need to count calories, sustainability, and feasibility. This may have implications as people with diabetes are looking for practical eating management tools.

METABOLIC SYNDROME AND RELATED DISORDERS
Volume XX, Number XX, 2020

Pp. 1–12
DOI: 10.1089/met.2020.0048

The Effects of Intermittent Fasting on Glycemic Control and Body Composition in Adults with Obesity and Type 2 Diabetes: A Systematic Review

Abstract

The purpose of this study was to evaluate the effects of intermittent fasting on glycemic control and body composition in adults with obesity and type 2 diabetes. Although intermittent fasting has shown some promise in improving glucoregulatory indicators and body composition in adults with obesity, there is currently no systematic review evaluating these effects in adults with obesity and type 2 diabetes. A database search of PubMed, CINHAL, and MEDLINE identified five studies that met inclusion criterion. All studies were randomized controlled trials in adult subjects ($n=46–137$) with type 2 diabetes and a body mass index of $\geq 30\,kg/m^2$. Four different intermittent fasting regimens were reviewed. All fasting regimens revealed strong evidence to support intermittent fasting as a feasible diet to improve glycemia and body composition measures within 12–24 weeks. Follow-up 12–18 months after intermittent fasting did not show promising results for continued weight loss and improved glycemic control. The majority of the studies demonstrated insignificant differences between intermittent fasting and continuous energy restriction for measures of glycated hemoglobin a1c and body composition. More data on intermittent fasting in adults with obesity and type 2 diabetes are needed to determine its benefits within this patient population. Future research should include consistent fasting regimens and larger sample sizes to improve the reliability and generalizability of the data. Also, consistent follow-up after a fasting intervention may enhance long-term benefits and should be considered in future research.

The Journal of Clinical Endocrinology & Metabolism, 2021, Vol. 106, No. 3, 902–911
doi:10.1210/clinem/dgaa926
Meta-Analysis

Meta-Analysis

Metabolic Impact of Intermittent Fasting in Patients With Type 2 Diabetes Mellitus: A Systematic Review and Meta-analysis of Interventional Studies

Emily Borgundvaag,[1] Jessica Mak,[1,4] and Caroline K. Kramer[1,2,3]

Abstract

Context: Intermittent fasting (IF) has been proposed as a weight-loss strategy with additional cardiometabolic benefits in individuals with obesity. Despite its growing popularity, the effect of IF in patients with type 2 diabetes (T2DM) remains unclear.

Objective: We conducted a systematic review and meta-analysis to evaluate the metabolic impact of IF compared to standard diet in patients with T2DM.

Methods: Embase, PubMed, and clinicaltrials.gov between 1950 and August 12, 2020 were searched for randomized, diet-controlled studies evaluating any IF intervention in adults with T2DM. We examined the impact of IF on weight loss and glucose-lowering by calculating pooled estimates of the absolute differences in body weight and glycated hemoglobin A_{1c} (HbA_{1c}) compared to a control group using a random-effects model.

Results: Seven studies (n = 338 participants; mean body mass index [BMI] 35.65, mean baseline HbA_{1c} 8.8%) met our inclusion criteria. IF induced a greater decrease in body weight by −1.89 kg (95% CI, −2.91 to −0.86 kg) compared to a regular diet, with no significant between-study heterogeneity (I^2 21.0%, $P = .28$). The additional weight loss induced by IF was greater in studies with a heavier population (BMI > 36) (−3.43 kg [95% CI, −5.72 to −1.15 kg]) and in studies of shorter duration (≤ 4 months) (−3.73 kg [95% CI, −7.11 to −0.36 kg]). IF was not associated with further reduction in HbA_{1c} compared to a standard diet (HbA_{1c} −0.11% [95% CI, −0.38% to 0.17%]).

BIAS:

- Inclusion of studies of **very low-calorie diets**
- **Control group**: a standard diet consisting of either a healthy pattern dietary recommendation with caloric deficit or normal caloric intake

The Journal of Clinical Endocrinology & Metabolism, 2023, **108**, 1415–1424
https://doi.org/10.1210/clinem/dgac661
Advance access publication 14 December 2022
Clinical Research Article

Effect of an Intermittent Calorie-restricted Diet on Type 2 Diabetes Remission: A Randomized Controlled Trial

Xiao Yang,[1,2,3] Jiali Zhou,[1,4] Huige Shao,[5] Bi Huang,[5] Xincong Kang,[1,6,7] Ruiyu Wu,[1,8] Fangzhou Bian,[9] Minghai Hu,[10] and Dongbo Liu[1,2,11]

Abstract

Context: The 2021 consensus report on the definition and interpretation of remission of type 2 diabetes (T2D) has been released. Although intermittent fasting diets (IF) are becoming very popular, no studies have investigated their benefit in diabetes remission.

Objective: The present study examined the effectiveness of IF in diabetes remission and potential remission durability.

Methods: Participants between ages 38 and 72 years with a duration of T2D of 1 to 11 years, a body mass index (BMI) of 19.1 to 30.4, 66.7% male, and antidiabetic agent use and/or insulin injection were randomly allocated at a ratio of 1:1 to the Chinese Medical Nutrition Therapy (CMNT) or control group. The primary outcome was diabetes remission, defined as a stable glycated hemoglobin A_{1c} (HbA_{1c}) level of less than 48 mmol/mol (< 6.5%) for at least 3 months after discontinuing all antidiabetic medications. The secondary outcomes included HbA_{1c} level, fasting blood glucose level, blood pressure, weight, quality of life, and medication costs. We conducted a 12-month follow-up to assess the continuation of remission.

Results: On completing the 3-month intervention plus 3-month follow-up, 47.2% (17/36) of participants achieved diabetes remission in the CMNT group, whereas only 2.8% (1/36) of individuals achieved remission in the control group (odds ratio 31.32; 95% CI, 2.39-121.07; $P < 0.0001$). The mean body weight of participants in the CMNT group was reduced by 5.93 kg (SD 2.47) compared to 0.27 kg (1.43) in the control group. After the 12-month follow-up, 44.4% (16/36) of the participants achieved sustained remission, with an HbA_{1c} level of 6.33% (SD 0.87). The medication costs of the CMNT group were 77.22% lower than those of the control group (60.4/month vs 265.1/month).

Conclusion: This study demonstrated the clinical efficacy of CMNT in achieving diabetes remission for at least 1 year.

Diabetologia (2022) 65:1710–1720
https://doi.org/10.1007/s00125-022-05752-z

ARTICLE

Three weeks of time-restricted eating improves glucose homeostasis in adults with type 2 diabetes but does not improve insulin sensitivity: a randomised crossover trial

Charlotte Andriessen[1] · Ciarán E. Fealy[1] · Anna Veelen[1] · Sten M. M. van Beek[1] · Kay H. M. Roumans[1] · Niels J. Connell[1] · Julian Mevenkamp[1,2] · Esther Moonen-Kornips[1] · Bas Havekes[3] · Vera B. Schrauwen-Hinderling[1,2] · Joris Hoeks[1] · Patrick Schrauwen[1]

Intervention During the TRE intervention, volunteers were instructed to consume their habitual diet within a 10 h window during the daytime, with the last meal completed no later than 18:00 hours. Outside this time window, volunteers were only allowed to drink water, plain tea and black coffee. To increase compliance, volunteers were also allowed to drink zero-energy soft drinks in the evening hours if consumed in moderation. During the control (CON) intervention, volunteers were instructed to spread their habitual diet over at least 14 h per day without additional restraints on the time window of food intake. For both intervention periods, volunteers were instructed to maintain their normal physical activity and sleep patterns and to remain weight stable. Food intake and sleep times were recorded daily using a food and sleep diary. Volunteers based the food intake of their second intervention period on the food and sleep diary filled out during the first period to promote similar dietary quantity and quality in both intervention arms. To optimise compliance, a weekly phone call was scheduled to monitor the volunteers and to provide additional instructions if necessary.

Table 1 Baseline characteristics of participants

Characteristic	Measurement/value
N	14
Sex, *n* female/*n* male	7/7
Age, years	67.5±5.2
BMI, kg/m^2	30.5±3.7
Diabetes medication, *n* yes/*n* no	10/4
Metformin only, *n*	7
Metformin + gliclazide, *n*	3
Fasting plasma glucose, mmol/l	7.9±1.3
HbA_{1c}, mmol/mol	46.1±7.2
HbA_{1c}, %	6.4±0.7
AST, μkat/l	0.4±0.1
ALT, μkat/l	0.4±0.2
GGT, μkat/l	0.4±0.2
eGFR, ml min^{-1} 1.73 m^{-2}	79.9±14.5

What are the new findings?

- The 3 week 10 h TRE regimen did not result in alterations in hepatic glycogen and insulin sensitivity as compared with spreading food intake over at least 14 h
- TRE decreased both 24 h and fasting glucose levels and resulted in an increased time spent in normoglycaemia but did not alter energy expenditure or substrate oxidation
- The TRE regimen was safe and feasible to adhere to for adults with type 2 diabetes and, additionally, resulted in weight loss

How might this impact on clinical practice in the foreseeable future?

- Our findings support the use of TRE as an additional strategy for the treatment of type 2 diabetes and provides a foundation to study the long-term effects of TRE in adults with type 2 diabetes

A Systematic Review of the Association of Skipping Breakfast with Weight and Cardiometabolic Risk Factors in Children and Adolescents. What Should We Better Investigate in the Future?

Alice Monzani [1,†], Roberta Ricotti [1,†], Marina Caputo [2], Arianna Solito [1], Francesca Archero [1], Simonetta Bellone [1,3] and Flavia Prodam [1,2,3,*]

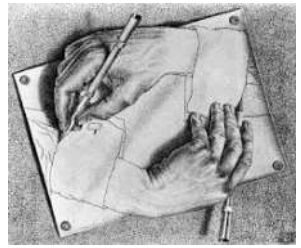
Abstract: The incidence of skipping breakfast in pediatric subjects is rising, and a relationship with overweight (OW) and obesity (OB) has been shown. Associations with cardiovascular outcomes and skipping breakfast in adults have been reported. The purpose of this systematic review was to summarize the association of skipping breakfast with body weight and metabolic outcomes in the pediatric population. We searched relevant databases (2008–2018) and identified 56 articles, of which 39 were suitable to be included, basing on inclusion criteria (observational; defined breakfast skipping; weight and/or metabolic outcomes). Overall, 286,804 children and adolescents living in 33 countries were included. The definitions of OW/OB, skipping breakfast, and the nutrient assessment were highly heterogeneous. Confounding factors were reported infrequently. The prevalence of skipping breakfast ranged 10–30%, with an increasing trend in adolescents, mainly in girls. Skipping breakfast was associated with OW/OB in the 94.7% of the subjects. The lack of association was shown mainly in infants. Moreover, 16,130 subjects were investigated for cardiometabolic outcomes. Skipping breakfast was associated with a worse lipid profile, blood pressure levels, insulin-resistance, and metabolic syndrome. Five studies reported a lower quality dietary intake in breakfast skippers. This review supports skipping breakfast as an easy marker of the risk of OW/OB and metabolic diseases, whether or not it is directly involved in causality. We encourage intervention studies using standardized and generalizable indicators. Data on confounders, time of fasting, chronotypes, and nutrition quality are needed to establish the best practice for using it as a tool for assessing obesity risk.

Nutrients 2019

“FOOD” FOR THOUGHT

- Few and short clinical trials
- Discrepancies among some studies
- Potential differences among fasting regimens
- Age-related and genetic effects (children, older individuals)
- Acute diseases (infections)

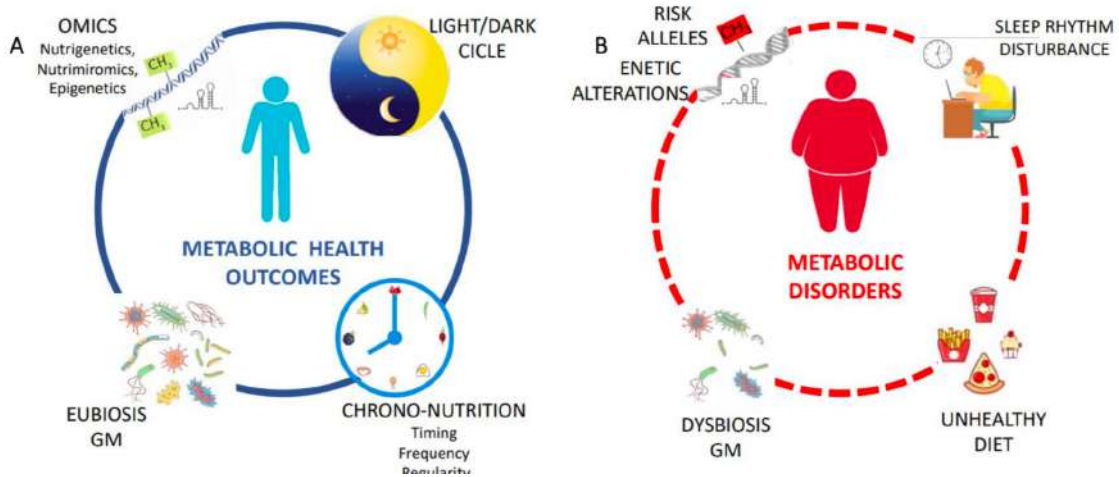
DRUG EFFECTS



DIET COMPOSITION IN REFEEDING

TAKE HOME MESSAGES

- ✓ Dietary interventions that are accompanied by long fasting periods have emerged as **promising strategies** to target **a myriad of clinical parameters** that constitute triggers for metabolic syndrome, cardiovascular disease, cancer, and even neurodegenerative diseases.
- ✓ Although the specific mechanisms are far from being fully understood, the periodic absence of energy intake appears **to improve multiple risk factors** and, in some cases, reverse disease progression in mice and humans.
- ✓ **More studies** on circadian genomics, transcriptomics, and metabolomics of the host and microbiota are needed to shade more light on this new topic and allow a safe **personalized chrono-nutrition**.
- ✓ Although promising, these approaches are still experimental and should not be initiated without **medical supervision**.



UNIVERSITÀ DEL PIEMONTE ORIENTALE

RINGRAZIAMENTI

Endocrinologia,
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Gianluca Aimaretti

Paolo Marzullo
Flavia Prodam
Simonetta Bellone
Grazia Mauri
Maria Teresa Samà
Valentina Bullara
Marco Zavattaro
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Alice Ferrero
Beatrice Cavigiolo
Samuele Costelli
Martina Romanisio
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Rosa Pitino
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Davide Vimercati