Malaysian Applied Biology (2024) 53(3): 1-13
https://doi.org/10.55230/mabjournal.v53i3.2766

Review

Types of Intermittent Fasting and Their Effects on Obesity and Type 2 Diabetes Mellitus

Shu Xian Gan[1], Patricia Karissa[1], Yong Ling Sou[1], Hui Ching Low[1], Teck Yew Low[2], Timothy Simpson[3], Paulina Pei Suu Tan[1], Pey Yee Lee[2], Shamsul Mohd Zain[4], Wickneswari Ratnam[5], Yuh-Fen Pung[1]*

1. Division of Biomedical Science, Faculty of Science and Engineering, University of Nottingham Malaysia, 43500 Selangor, Malaysia
2. UKM Medical Molecular Biology Institute (UMBI), Universiti Kebangsaan Malaysia, 56000 Kuala Lumpur, Malaysia
3. Faculty of Medicine and Health Sciences, University of Nottingham, Nottingham NG7 2UH, UK
4. Department of Pharmacology, Faculty of Medicine, University Malaya, 50603 Kuala Lumpur, Malaysia
5. Department of Biological Sciences and Biotechnology, Faculty of Science and Technology, Universiti Kebangsaan Malaysia 43600 Selangor, Malaysia
*Corresponding author: yuhfen.pung@nottingham.edu.my

ABSTRACT

Obesity and type II diabetes mellitus affect millions of people both in Malaysia and worldwide due to sedentary lifestyles and unhealthy diets. Intermittent fasting reduces calorie intake by interweaving eating periods with prolonged fasting periods on a recurring basis. Therefore, it could be a potential solution to induce weight loss, leading to improved blood glucose level as observed in type II diabetes mellitus individuals. However, its feasibility remains unclear. This review aimed to compare the beneficial effects and adverse reactions from different types of intermittent fasting in obese and type II diabetes mellitus studies. The review was carried out by combing through several online databases. Keywords such as "Intermittent fasting", "Obesity", "Type II Diabetes Mellitus" were used and relevant articles were selected. The findings of this review showed that intermittent fasting is feasible and effective in reducing body weight and improving blood glucose. The beneficial effects of intermittent fasting appear to outweigh the adverse reactions. Having said that, intermittent fasting is unsuitable for individuals with packed schedules and certain health conditions such as pregnancy. This review will hopefully shed light on intermittent fasting as a potential intervention to combat obesity and type II diabetes mellitus. Further exploration of intermittent fasting could reduce both the morbidity and mortality rates from non-communicable diseases globally.

Key words: Intermittent fasting, diabetes, dietary intervention, non-communicable diseases, prolonged fasting period

Article History
Accepted: 11 June 2024
First version online: 30 September 2024

Cite This Article:
Gan, S.X., Karissa, P., Sou, Y.L., Low, H.C., Low, T.Y., Simpson, T., Tan, P.P.S., Lee, P.Y., Zain, S.M., Ratnam, W. & Pung, Y.-F. 2024. Types of intermittent fasting and their effects on obesity and type 2 diabetes mellitus. Malaysian Applied Biology, 53(3): 1-13. https://doi.org/10.55230/mabjournal.v53i3.2766

INTRODUCTION

Due to the rising levels of income and urbanization, overeating and overnutrition (coupled with unhealthy diets & sedentary lifestyles) have become a global norm (Popkin & Ng, 2022). Consequently, the global prevalence of obesity tripled between 1975 and 2016 (DeJesus *et al*., 2022). In the context of Malaysia, the prevalence of obesity among its adults is greater than in other Southeast Asian nations. Reports indicated that 19.7% of Malaysian adults are obese, 30.4% are overweight, and 1 in 7 adults who are either overweight or obese has type II diabetes mellitus (Mohd-Sidik *et al*., 2021). Meanwhile, type II diabetes mellitus has been reported to affect 6.28% (462 million) of the global population, including ~2.8 million Malaysian adults above 30, with a prevalence of 20.8% (Hussein *et al*., 2016; Khan *et al*., 2019).

Lifestyle changes such as dietary modifications and exercise have long been proposed to reduce body weight. Among the recommended changes in dietary plans, calorie restriction in the form of intermittent fasting has been gaining

popularity in the recent decade. However, the feasibility of intermittent fasting in managing obesity and type II diabetes mellitus remains unclear as there are no extensive reviews that evaluate intermittent fasting in the obese and/or type II diabetes mellitus populations. Hence, this review aimed to fill this gap by comparing the benefits and adverse reactions of intermittent fasting in obese and/or type II diabetes mellitus. Intermittent fasting may lead to weight loss, improved metabolism, and potentially lower risk factors for non-communicable diseases such as type II diabetes mellitus and cardiovascular diseases.

MATERIALS AND METHODS

First, an electronic literature search was conducted in different databases such as PubMed, Google Scholar, and Science Direct. The key words that were used for the literature search were "Intermittent fasting", "Obesity", "Type II Diabetes Mellitus", "beneficial effects", "adverse reactions" and "intervention". After removing the duplicates, the title and abstract of the journal articles were screened to exclude the irrelevant articles and include the relevant articles based on the eligibility criteria.

The exclusion criteria were as follows:

1. Studies published as a systematic review
2. Studies with small sample sizes or lacking proper control group

The inclusion criteria were as follows:

3. Studies investigated the beneficial effects of intermittent fasting
4. Studies discussed the adverse reactions of intermittent fasting
5. Studies written in English

The journal articles were reviewed to select the articles that meet the eligibility criteria. Subsequently, the quantitative or qualitative data was extracted from the included studies. A total of fifteen articles were used in this review, covering six different types of intermittent fasting. Among these, thirteen were clinical studies while the remainder focused on animal studies. The findings were compiled, analyzed, and referenced in the review. Seven articles reported beneficial effects, two studies noted adverse effects and the rest described both.

Intermittent fasting

Intermittent fasting refers to an eating pattern that restricts calorie intake by regularly interspacing one's eating period with a prolonged fasting period (Mattson *et al*., 2017; Harris *et al*., 2018). The resultant reduction in energy intake promotes the breakdown of internal glycogen and fat stores to generate energy. In comparison to absolute fasting, intermittent fasting can be practiced in several commonly adopted regimens as shown in Table 1.

Table 1. Different types of intermittent fasting

Types	Descriptions	Reference
Alternate day feeding	Alternating between consuming 25% of energy needs for 24 hour and ad libitum the following day	Bhutani *et al*.*;* Hoddy *et al,*; Razavi *et al*,.
Alternate day calorie restriction	Alternating between consuming less than 20% of energy needs for 24 hour and ad libitum the following day	Johnson *et al,*
5:2 diet/Intermittent energy restriction	2 consecutive days of fasting/low-calorie consumption followed by 5 days of ad libitum eating	Corley *et al*,; Schübel *et al,;* Carter *et al*.
Time-restricted feeding	8 to 10 hour eating period in a day	Anton *et al*.*; Chaix et al*,; Wilkinson *et al*,.
Warrior diet	Low-calorie diet during the daytime and consume carbohydrate meals for dinner	Sofer *et al*.
Ramadan fasting	Fast from dawn to sunset	Mindikoglu *et al*.

Beneficial effects of intermittent fasting

Fat loss and weight loss

Intermittent fasting has been shown to induce significant fat loss and weight loss in obese mice and humans, as demonstrated in several preclinical and clinical trials (Table 2). In a preclinical trial that

subjected 392 twelve-week-old male C57BL/6J wild-type mice to different feeding regimens, the results showed that the adiposity in mice fed a high-fat diet with time-restricted feeding decreased by 6% compared to mice fed with a normal chow diet with *ad libitum*. In hematoxylin and eosin-stained sections of the white adipose tissue, lipid droplets in time-restricted feeding mice were smaller in comparison to *ad libitum* feeding mice and large unilocular lipid droplets were absent in time-restricted feeding mice. At the same time, the mice subjected to time-restricted feeding of a high-fat plus high-sucrose diet gained less weight over 12 weeks as compared to *ad libitum* feeding of a high-fat plus high-sucrose diet. It was also shown that a longer, daily high-fat diet feeding period led to a larger increase in body weight as a 26% weight gain was observed in 9-hour time-restricted feeding whilst a 43% weight gain was observed in 15-hour time-restricted feeding. For the mice fed a high-fat diet by *ad libitum*, a 65% weight gain was observed. Moreover, time-restricted feeding decreased excessive weight gain by 20% and further weight gain was halted in older mice (Chaix *et al*., 2014).

This weight reduction was also observed in older obese individuals. In another clinical trial involving older obese and diabetic participants, significant body weight reductions from baseline were observed after 10 hour of time-restricted feeding for 12 weeks (Wilkinson *et al*., 2020).

Besides time-restricted feeding, alternate-day feeding has also been reported to decrease fat mass and body weight in obese individuals. In a study by Bhutani *et al*. (2013) conducted on 64 obese individuals (each randomized into one of the four groups), reduced fat mass was observed in the alternate-day feeding group and the combination group in which the individuals took alternate-day feeding and exercised together with the control group and the group that only practiced exercise. However, a greater decrease in fat mass, body weight, and body mass index (BMI) was observed in the combination group after 12 weeks (Bhutani *et al*., 2013). Another recent randomized clinical trial by Razavi *et al*. (2020) that consisted of 80 individuals with metabolic syndrome showed a greater and more significant decrease in body weight and BMI in the alternate-day feeding group as compared to the group with a low-calorie diet (75% energy restriction) for four months. The authors classified individuals with metabolic syndrome as those with obesity, high blood pressure, and/or high cholesterol (Razavi *et al*., 2020). The study by Hoddy *et al*. (2015) also found that the body weight and fat mass of the 59 obese subjects decreased by an average of 4.2 kg after 8 weeks of alternate-day feeding.

On a separate note, a clinical trial conducted by Johnson *et al*., (2007) showed that the body weight of obese asthmatic individuals decreased progressively by practicing alternate-day calorie restriction for 8 weeks. In addition to alternate day calorie restriction, a 5:2 diet/intermittent energy restriction reduced body weight significantly as shown in the 50 weeks of clinical trial that included 150 overweight and obese individuals (Schübel *et al*., 2018). Similarly, a clinical trial that randomized type II diabetes mellitus individuals to this diet also showed a decrease in body weight at 12 weeks (Carter *et al*., 2016). Sixteen hour of fasting per day for one month also reduced body weight with a mean weight loss of 2.6 kg in overweight and sedentary older adults aged 65 years old and above (Anton *et al*., 2019).

Next, the warrior diet reduced body fat through the consumption of low-calorie food during the daytime to decrease calorie intake instead of complete fasting. In a clinical trial conducted on obese individuals for six months, the experimental group ate a low-calorie diet during the daytime, and carbohydrates were consumed mostly at night. This intervention was like the warrior diet in which low-calorie food like fruits and vegetables were consumed during the daytime but a huge meal with high energy content was consumed at night. The results showed that the experimental diet caused a greater decrease in absolute body fat percentage compared to the control diet after 6 months. Besides, the results also showed significantly greater weight loss, greater absolute BMI reduction, and abdominal circumference reductions in the experimental diet group compared to the control group (Sofer *et al*., 2011).

In addition, Muslims practicing Ramadan fasting led to a significant decrease in body weight in a study conducted by Mindikoglu *et al*. (2020). By practicing intermittent fasting from dawn to sunset for four consecutive weeks, there was a significant reduction in body weight and BMI with both p values less than 0.0001 at the end of week 4 in the metabolic syndromes' individuals with an average age of 59 years old (Mindikoglu *et al*., 2020).

It has been well-established that cellular energy metabolism can occur via multiple pathways depending on the energy fuels consumed. In normal circumstances (when glucose is not deprived), adenosine triphosphate (ATP) is generated via the glycolytic pathway in the cytosol followed by the Krebs Cycle and oxidative phosphorylation in the mitochondria. During fasting, the reduction in glucose switches energy metabolism from glycolysis to fatty acid oxidation (which occurs in the mitochondria) utilizing fat as an alternative fuel after glycogen stores are depleted. This switch can be explained by the activation and phosphorylation of adenosine 5'-monophosphate-activated protein kinase (AMPK)

that resulted in the phosphorylation of acetyl CoA carboxylase and decrease in malonyl CoA (Figure 1) (Dyck *et al*., 2006; Kotarsky *et al*., 2021).

Typically, mitochondrial biogenesis and oxidative metabolic pathways are downregulated in acquired obesity. Heinonen *et al*. (2015) reported that overweight and obese insulin-resistant individuals manifested low levels of mitochondrial biogenesis markers and lower metabolic rates. It has been demonstrated that during intermittent fasting, mitochondrial biogenesis becomes elevated in obese individuals, and the increased number of mitochondria further promotes the metabolism of fat as fuels (Peterson *et al*., 2012; Savencu *et al*., 2021) (Figure 1).

Upregulation of mitochondrial biogenesis can be induced via increased adiponectin levels during intermittent fasting. Chaix *et al*. (2014) showed that adiponectin levels were higher in all time-restricted feeding mice. Increased adiponectin levels upregulate the protein expression of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) (Moro *et al*., 2016). Increased PGC-1α resulted in the transcription of nuclear respiratory factors (NRF), in which NRF1 and NRF2 led to increased expression of mitochondrial transcription factor A (TFAM). Translocation of TFAM directly regulated mitochondrial DNA replication and transcription to mitochondrion which stimulated the replication of mitochondrial DNA and mitochondrial gene expression (Liang & Ward, 2006; Heilbronn *et al*., 2007). Accordingly, mitochondrial biogenesis increases the number and the size of mitochondria, thus further decreasing the fat mass by promoting fat metabolism. By activating AMPK to stimulate mitochondrial biogenesis, intermittent fasting can contribute to significant fat loss and weight loss in obese mice and humans.

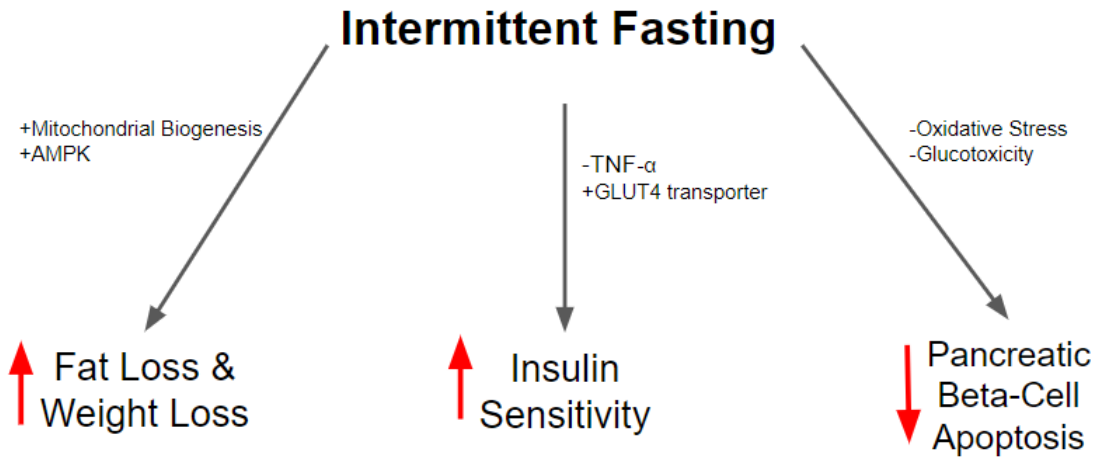

Fig. 1. Major pathways illustrating the beneficial effects of intermittent fasting in obese and type II diabetes mellitus individuals. Enhanced fatty acid oxidation in mitochondria via activation of AMPK and stimulation of mitochondrial biogenesis leads to fat loss, thus improving insulin sensitivity. Decreased tumor necrosis factor-alpha (TNF-α) levels by intermittent fasting also improve insulin sensitivity. Accordingly, pancreatic β-cell apoptosis is decreased, resulting from decreased glucotoxicity and oxidative stress.

Improved insulin sensitivity

Tumor necrosis factor alpha (TNF-α) is a proinflammatory cytokine produced by adipocytes, that is widely believed to be associated with type II diabetes mellitus (Akash *et al*., 2018). Importantly, both the expression levels and circulating levels of TNF-α are found to be particularly high in obese individuals. Different regimens of intermittent fasting have been demonstrated to decrease TNF-α levels in both healthy and obese individuals (Figure 1). In resistance-trained males for example, the levels of TNF-α decreased in the time-restricted feeding group compared to the normal diet group after 8 weeks of time-restricted feeding, i.e. 8-hour feeding period and 16-hour fasting period. After time-restricted feeding, the TNF-α level decreased significantly from 5.58 ng/L to 5.13 ng/L (Moro *et al*., 2016). In another clinical trial conducted on obese individuals for 6 months, the experimental diet group that consumed a diet like the warrior diet had a significantly lower concentration of TNF-α with a 9.2% decrease from baseline on the 180th day (Sofer *et al*., 2011).

Generally, individuals who underwent intermittent fasting had shown a decrease in TNF-α levels. TNF-α activates proinflammatory pathways that impair the insulin receptor autophosphorylation and insulin receptor substrate-1 (IRS-1) tyrosine phosphorylation (Kanety *et al*., 1995; Galicia-Garcia *et*

al., 2020). This in turn caused insulin resistance and led to an increase in lipolysis. Lipoysis released glycerol and free fatty acid; and the free fatty acid was transported in the form of triglyceride by very low-density lipoproteins (Nieto-Vazquez *et al*., 2008). Therefore, a decrease in TNF-α levels improved insulin sensitivity, lowered free fatty acid levels, and decreased hepatic triglyceride production. These findings were further supported by Iwani *et al*. (2017); in which the study reported that increased triglyceride level was positively correlated to insulin resistance. The results showed that the overweight and obese children had significantly higher triglyceride to high-density lipoprotein cholesterol ratio as compared to the control group. A high triglyceride to high-density lipoprotein-cholesterol ratio is often associated with insulin resistance. In addition to that, glucose transporter type 4 (GLUT4), a transporter responsible for insulin-regulated glucose uptake into the adipose tissue and skeletal muscle, was upregulated, further improving insulin sensitivity (Iwani *et al*., 2017). Another study also showed an improvement in mean fasting glucose with weight loss in both the 5:2 diet/intermittent energy restriction group and the continuous energy restriction group after 12 months (Carter *et al*., 2016).

Moreover, improvement in insulin sensitivity and glucose homeostasis by different types of intermittent fasting was observed in animal models (Table 2). In a preclinical trial conducted by Chaix *et al*. (2014), the homeostatic model assessment index of insulin resistance (HOMA-IR) assessment showed that mice fed with a high-fat diet had a lower insulin resistance in time-restricted feeding as compared to an *ad libitum* diet. Serum glucose level one hour after a glucose bolus was also detected to be lower in time-restricted feeding mice as compared to *ad libitum* mice. Interestingly, mice on time-restricted feeding could restore normoglycemia faster than mice on *ad libitum* after a glucose bolus and were protected against insulin resistance (Chaix *et al*., 2014).

Several clinical trials showed improved insulin sensitivity and better glucose homeostasis by practicing different types of intermittent fasting (Table 2). For instance, a study by Schübel *et al*. (2018) showed that a 5:2 diet/intermittent energy restriction reduced the fasting blood glucose levels significantly in 150 overweight and obese individuals over 50 weeks. Besides that, Carter *et al*. (2016) randomized type II diabetes mellitus individuals to the 5:2 diet/intermittent energy restriction for 12 months and the results showed reduced HbA1c levels. Identically, in another clinical trial that was conducted on obese and diabetic individuals, trends of improvement in fasting glucose, fasting insulin, and HbA1c were observed after 10 hour of time-restricted feeding for 12 weeks. It was notable that the HbA1c and fasting glucose of a type II diabetes mellitus individuals with HbA1c of 6.5% and fasting glucose of 167 mg/dL was decreased to 5.5% and 116 mg/dL respectively at the end of the trial (Wilkinson *et al*., 2020).

Moreover, a study by Sofer *et al*. (2011) found that a warrior diet improved insulin sensitivity and glucose homeostasis. It was carried out in obese individuals for 6 months and the results showed that the experimental diet group had significantly lower average daily insulin concentration than baseline (68%, $p< 0.05$) and lower insulin concentration than the control group on day 180. The experimental diet group also had a significant decrease in fasting blood glucose concentration after 6 months (Sofer *et al*., 2011).

Decreased pancreatic β-cell apoptosis and stimulated β-cell regeneration

Improved insulin sensitivity results in the lowering of both insulin concentration and fasting blood glucose level, thus preventing glucotoxicity-induced deterioration of pancreatic β-cells functions (Figure1). In addition, pancreatic β-cell apoptosis can also be induced by increased levels of oxidative stress, which is imposed on the obese and type II diabetes mellitus individuals collectively by insulin resistance, hyperglycemia, hyperinsulinemia, and dyslipidemia (Folli *et al*., 2012). Oxidative stress activates c-Jun N-terminal kinase (JNK) which stimulates the release of cytochrome c from the mitochondrial inner membrane space via a Bid-Bax dependent mechanism (Dhanasekaran & Reddy, 2008). Released cytochrome c forms apoptosomes with Apaf-1 and caspase-9, leading to the activation of the caspase-9 cascade and induction of β-cell apoptosis (Dhanasekaran & Reddy, 2008; Yung & Giacca, 2020).

The ability of intermittent fasting regimens to reduce oxidative stress in type II diabetes mellitus individuals is well supported by a few preclinical and clinical trials (Figure 1) (Table 2). In a preclinical trial carried out by Chaix *et al*., (2014), it was observed that mice treated with time-restricted feeding had significantly higher levels of serum metabolites implicated in defense against reactive oxygen species (ROS). This indicated that time-restricted feeding increased protection against ROS and oxidative stress.

Moreover, alternate-day calorie restriction also reduces oxidative stress in obese individuals. It is supported by the study carried out by Johnson *et al*. (2007). The results showed reductions in levels of oxidative stress biomarkers such as protein carbonyls, nitrotyrosine, and 8-isoprostane in the

obese asthmatic individuals' serum during the alternate day calorie restriction diet period in which the individuals ate ad libitum on the alternating days while less than 20% of their normal calorie intake was taken on the intervening days (Johnson *et al*., 2007).

Next, the reduction of oxidative stress via Ramadan fasting was proven by a clinical trial that was conducted in individuals with an average age of 59 years and who had metabolic syndromes. It was found that intermittent fasting from dawn to sunset for 4 consecutive weeks reduced oxidative stress (Mindikoglu *et al*., 2020).

In addition, Liu *et al*., (2017) showed that 6 weeks of intermittent fasting decreased β-cell apoptosis in comparison to *ad libitum* high-fat feeding and stimulated markers for β-cell regeneration. The findings from this preclinical trial demonstrated an impairment of autophagic flux and reduction in transcription levels of autophagy master regulator, transcription factor EB was linked with the loss of pancreatic β-cell in mice with diet-induced obesity. By practicing intermittent fasting, impaired autophagic flux in islets of wild-type obese mice was restored with an exception in chow-fed mice that were deficient in lysosome-associated membrane protein 2 (LAMP2), a lysosome-associated membrane glycoprotein that plays a role in the autophagy process. Intermittent fasting worsened the impairment of autophagy in chow-fed LAMP2-deficient mice. Moreover, this preclinical trial found that intermittent fasting can stimulate the markers of β-cell regeneration after high-fat diet feeding. It was achieved by inducing the expression of neurogenin 3, a marker of endocrine progenitor cells, in the nucleus and upregulating its transcriptional target, neurogenic differentiation 1 which is involved in β-cell maturation. However, β-cell regeneration relied on an intact autophagy-lysosome without LAMP2-deficient β-cell (Liu *et al*., 2017).

Adverse reactions of intermittent fasting

Apart from its beneficial effects, there are also adverse reactions associated with intermittent fasting. The adverse effects are mainly hunger, weight regain, hypoglycemia, and hyperglycemia.

Hunger and weight regain

Leptin is a hormone that is secreted by the adipose tissue and its concentration in serum is positively correlated to the amount of fat in the body. Decreased fat mass induced by intermittent fasting also reduces the serum leptin concentration (Mars *et al*., 2005). Under physiological conditions, leptin is responsible for the satiety signal, thus decreased leptin levels can trigger the feeling of hunger and may result in gorging behavior. In addition to leptin, intermittent fasting also causes hunger by increasing ghrelin levels in the blood (Figure 2).

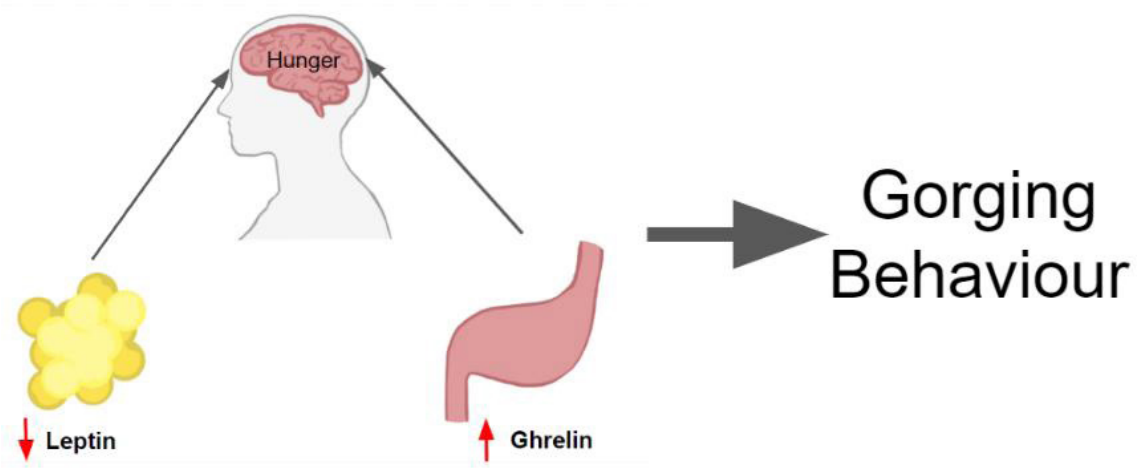

Fig. 2. Feeling of hunger induced by decreased leptin levels and increased ghrelin levels due to intermittent fasting.

Beck & Richy, (2009) showed that weight loss induced by a low-fat diet caused gorging behavior due to decreased plasma leptin levels and increased ghrelin levels. After reducing body weight, plasma ghrelin concentration of 6-month-old obese Zucker rats with marked adiposity rose by 19% in the rats fed a low-fat diet with a significant decrease in leptin levels. In rats that were fed with a low-fat diet, the gorging during the first one-hour-palatable test meal was observed, and an increased number of gorging episodes restored initial fat stores, hence resulting in weight regain (Beck & Richy, 2009). Cameron *et*

al., (2014) also proved that increased ghrelin and decreased leptin levels induced by intermittent fasting increase appetite in overweight individuals. After 24 hour of fasting, appetite scores, hedonic ratings of 'liking', and ad libitum energy intake were significantly enhanced with the increase in the feeling of wanting and liking sweet food and other food categories (Cameron *et al*., 2014).

Table 2. Preclinical and clinical trials that showed beneficial effects of different types of intermittent fasting in obese and/or type II diabetes mellitus animal models or individuals

Types of intermittent fasting	Animal models/ Clinical Trials	Key results	References
Intermittent fasting	Eight-week-old C57BL/6J mice and *Becn1+/−* mice, fed with either a chow of high-fat diet for twelve weeks followed by six-week intermittent fasting	Decreased (49%, when compared to mice with chow diet) pancreatic β-cell apoptosis, stimulated β-cell regeneration	Liu *et al*., 2017
Time-restricted feeding	Twelve-week-old male wild-type C57BL/6J mice are subjected to twelve weeks of time-restricted feeding with access to high fat and high sucrose diet during ad libitum	Induced fat loss (62%, compared to ad libitum feeding mice) and weight loss (12%), improved insulin sensitivity, protected against increased oxidative stress	Chaix *et al*., 2014
Time-restricted feeding (10 hour)	Obese individuals presented with 3 or more metabolic syndrome	Induced weight loss (3%) and percentage body fat (3%) reduced body mass index (3%) and waist circumference (4%), improved insulin sensitivity	Wilkinson *et al*., 2020
Time-restricted Feeding (16:8 method)	Overweight sedentary older adults (≥65 years)	Induced weight loss (2.6 kg)	Anton *et al*., 2019
warrior diet/ low-calorie diet and carbohydrates were consumed mostly at night	Individuals with a body mass index of over 30 kg/m^3	Induced fat loss(6.98% and weight loss (11.7%), reduced body mass index (11.7%) and abdominal circumference (10.5%), improved insulin sensitivity	Sofer *et al*., 2011
Alternate day feeding	Obese individuals undergoing alternate day feeding diet,	Induced fat loss (2 kg) and weight loss (3 kg), Reduced body mass index (1 kg/m^2)	Bhutani *et al*., 2013
Alternate day feeding	Individuals presenting metabolic syndrome	Reduced fat loss (5.88 kg) and weight loss (6.43 kg) Reduced body mass index (3.19 kg/m^2)	Razavi *et al*., 2021
Alternate day feeding	Obese Individuals	Induced weight loss (4.2 kg)	Hoddy *et al*., 2015
Alternate day calorie Restriction	Overweight asthmatic individuals with a body mass index of over 30 kg/m^2	Induced weight loss (8%), decreased oxidative stress	Johnson *et al*., 2007
Ramadan fasting	Individuals (mean age of 59 years old) presenting 3 or more metabolic syndrome	Reduced body weight (3.3 kg) Reduced body mass index (1.1 kg/m^5), decreased oxidative stress	Mindikoglu *et al*., 2020
5:2 diet/Intermittent energy restriction	Obesity and type II diabetes mellitus individuals with metformin and/or hypoglycemic medications	Induced weight loss (3.6 kg), improved insulin sensitivity	Corley *et al*., 2018
5:2 diet/Intermittent energy restriction	Overweight and obese non-smokers	Induced weight loss (5.2%), improved insulin sensitivity	Schübel *et al*., 2018
5:2 diet/Intermittent energy restriction	Type II diabetes mellitus individuals with insulin or orally administered antihyperglycemic agents	Induced weight loss (5.9%), improved insulin sensitivity	Carter, Clifton & Keogh, 2016

Several articles reported decreased leptin levels induced by different types of intermittent fasting. Johnson *et al*. (2007) found that serum leptin levels were lower in obese asthmatic individuals on alternate-day calorie restriction as compared to ad libitum days for 8 weeks (Table 3). This indicated that alternate-day calorie restriction led to hunger via decreased leptin levels. Another study by Mars *et al*. (2005) also showed a significant reduction in leptin concentration in 34 overweight and obese men after 2 days of 62% energy restriction (Table 3).

Hypoglycemia or hyperglycemia events in type II diabetes mellitus

Intermittent fasting can improve insulin sensitivity and glucose homeostasis in type II diabetes mellitus individuals who are usually prescribed hypoglycemic medication such as insulin and/or sulfonylurea. Thus, hypoglycemic, or hyperglycemic events may occur during the period of intermittent fasting and were reported in several clinical trials (Table 3).

Carter *et al*. (2018) conducted a randomized noninferiority trial in 137 individuals with type II diabetes mellitus and the individuals were assigned to an 5:2 diet/intermittent energy restriction diet which was 500 to 600 kcaL/d for two non-consecutive days per week with the usual diet for the other five days or a continuous energy restriction diet which was 1200 to 1500 kcaL/d per day for 12 months. The results reported that hypoglycemic or hyperglycemic events were observed in the first two weeks of treatment in the 5:2 diet/intermittent energy restriction group and continuous energy restriction group, affecting 35% of the participants or 16 out of 46 participants that were using insulin and/or sulfonylurea (Carter *et al*., 2018).

Another randomized controlled trial was carried out on obesity and type II diabetes mellitus individuals who were prescribed metformin and/or hypoglycemic medications and had HbA1c concentrations of 50 to 86 mmoL/moL (6.7% to 10%). In this clinical trial, the individuals were prescribed to 2092 to 2510 kJ diet 2 days per week for 12 weeks and were randomized to consecutive or non-consecutive days of fasting. The results showed that the mean hypoglycemic rate was 1.4 hypoglycemic events over 12 weeks with no significant difference between consecutive days and non-consecutive days of fasting. Nevertheless, improvements in body weight, HbA1c, and fasting glucose levels were observed in individuals in both study arms (Corley *et al*., 2018).

Moreover, a study by Carter *et al*. (2016) that randomized individuals with type II diabetes mellitus to a 5:2 diet/intermittent energy restriction reported hypoglycemic events for insulin-controlled participants and hyperglycemic events in participants who were taking orally administered antihyperglycemic agents. It was stated that a greater reduction in insulin was needed to avoid hypoglycemia while changes in orally administered anti-hyperglycemic agents were only needed on the energy restriction days to prevent hyperglycemic events on non-restricted days (Carter *et al*., 2016).

Other minor adverse effects

In addition to weight regain and hypoglycemic or hyperglycemic episodes, other minor adverse effects have been reported in several clinical trials due to different types of intermittent fasting (Table 3). The molecular pathways that caused these adverse effects were not discussed in detail.

For instance, alternate-day feeding caused minor adverse symptoms and was observed in the study conducted by Hoddy *et al*. (2015). Eight weeks of alternate-day feeding caused 2% of the obese subjects to experience water retention and less than 10% of the subjects were unable to stay asleep. There was also 29% of the subjects reported having bad breath after 8 weeks of alternate day feeding as compared to 14% of subjects at baseline (Hoddy *et al*., 2015).

Another clinical trial reported that five individuals had experienced minor adverse symptoms such as chills, tiredness, and mild headaches on energy-restricted days in the intermittent calorie restriction group which resembled the 5:2 diet/intermittent energy restriction. Two individuals were reported to have mild cognitive impairments such as lack of focus on energy-restricted days and three individuals experienced dizziness and cramps on non-restricted days (Schübel *et al*., 2018).

Besides that, Anton *et al*. (2019) assigned overweight and sedentary older adults who were equal to or more than 65 years old to 16 hour of fasting per day for 4 weeks. The results reported that two individuals had headaches during the fasting period which were overcome by drinking more water and one individual had dizziness that was resolved after eating a snack (Anton *et al*., 2019).

Overall, the reported minor adverse effects are water retention, unable to stay asleep, bad breath, chills, tiredness, headaches, lack of concentration, dizziness, and cramps.

Intermittent fasting reduces daily calorie intake and promotes the breakdown of fat mass to generate the energy needed by the body. Thus, individuals who are pregnant or breastfeeding, aged under 18 years old, and underweight (with BMI ≤25) should avoid intermittent fasting to ensure sufficient calorie

and nutrient intake for proper development and health maintenance.

Table 3. Clinical trials that showed adverse reactions to different types of intermittent fasting in obese and/or type II diabetes mellitus individuals

Types of Intermittent Fasting	Population	Key results	References
Alternate day feeding	Obese individuals (*n*=59)	Water retention (2%), unable to stay asleep (<10%), bad breath (14%)	Hoddy *et al*., 2015
Alternate day feeding	Overweight and obese men (*n*=34)	Decreased leptin levels	Mars *et al*., 2005
Alternate day calorie restriction	Obese asthmatic individuals (*n*=10)	Decreased leptin levels	Johnson *et al*., 2007
5:2 diet/intermittent energy restriction	Type II diabetes mellitus individuals with insulin and/or sulfonylurea (*n*=137)	Hypoglycemia or hyperglycemia (a total of 35%)	Carter *et al*., 2018
5:2 diet/intermittent energy restriction	Type II diabetes mellitus individuals with insulin or orally administered antihyperglycemic agents (*n*=63)	Hypoglycemia (1.4 ± 2.6 events per person over 12 weeks) and hyperglycemia	Carter *et al*., 2016
5:2 diet/intermittent energy restriction	Obese and type II diabetes mellitus individuals with metformin and/or hypoglycemic medications (*n*=37)	Hypoglycemia (1.4 ± 2.1 events)	Corley *et al*., 2018
5:2 diet/intermittent energy restriction	Overweight and obese non-smokers (*n*=150)	Chills (10%), tiredness (10%), mild headaches (10%), lack of concentration (4%), dizziness (6%), and cramps (6%)	Schübel *et al*., 2018
Time-restricted feeding	Overweight older adults (*n*=10)	Headache (20%) and dizziness (10%)	Anton *et al*., 2019

Packed working schedules, family meal schedules, and eating restrictions at social occasions are the challenges to practice intermittent fasting. Intermittent fasting, such as time-restricted feeding causes social challenges as it limits social activities in the evening, thus it is recommended to reduce time-restricted feeding to five days per week with two consecutive non-restricted days to be set on weekends. This may improve adherence to time-restricted feeding patterns (Parr *et al*., 2020).

Short-term intermittent fasting is an effective and safe intervention to reduce body weight and fat mass in obese individuals as well as decrease the risk of developing type II diabetes mellitus. These have been proven by several preclinical and clinical trials that were carried out in mice and human subjects regardless of the types of intermittent fasting. During the period of intermittent fasting, early dinner tends to cause difficulties, hence long-term adherence and compliance become hard to achieve. Due to early dinnertime, the individuals may have late evening snacking behaviors, leading to weight regain and further worsening glycemic control. However, it is important to note that adherence and compliance are vital to prevent weight regain. The types of food that are consumed during the non-restricted hour or days are also important to refrain from regaining body weight. If gorging behavior or consumption of highly palatable meals happens during the non-restricted hour or days, this may cause a two-fold or three-fold increase in their body weight as compared to the baseline. In addition to intermittent fasting, exercise also plays a crucial role in preventing muscle loss, enhancing fat loss, and exerting anti-inflammatory effects.

In type II diabetes mellitus individuals, different types of intermittent fasting can improve insulin sensitivity, decrease pancreatic β-cell apoptosis, and stimulate β-cell regeneration together with

weight loss. Several preclinical and clinical trials have proven that intermittent fasting is a safe and recommended intervention for type II diabetes mellitus individuals with or without obesity. However, type II diabetes mellitus individuals may encounter hypoglycemia or hyperglycemia as they have already been prescribed hypoglycemic medications such as sulfonylurea and insulin. Thus, consent from doctors or medical practitioners should be obtained before starting intermittent fasting.

Nevertheless, obese and/or type II diabetes mellitus individuals are usually associated with a higher risk of cardiovascular disease. *In vitro* studies and clinical trials proved that intermittent fasting lowers the risk of cardiovascular disease by decreasing systolic and diastolic blood pressure and reducing plasma triglycerides (Shaver *et al*., 2019; Ruppert *et al*., 2020; Wilkinson *et al*., 2020). Fasting increased the mRNA expression of *angiopoietin 4* and the level of angiopoietin 4 protein in human adipose tissue and plasma. Accordingly, lipoprotein lipase activity is decreased, leading to the transport of triglycerides to peripheral tissue to be used as fuel to generate energy instead of lipid storage (Ruppert *et al*., 2020).

CONCLUSION

Intermittent fasting is a feasible and effective intervention to combat obesity and type II diabetes mellitus as the beneficial effects of intermittent fasting outweigh its adverse reactions. Regardless of the type of intermittent fasting, short-term intermittent fasting can reduce weight and fat mass in obese individuals as well as improve insulin sensitivity and decrease pancreatic β-cell apoptosis in type II diabetes mellitus individuals. However, alternate-day feeding, alternate-day calorie restriction, the 16:8 method, and 5:2 diet/intermittent energy restriction caused mild adverse reactions and it could be overcome through wise management and compliance. Nevertheless, beneficial effects and adverse reactions from different types of intermittent fasting in the long term such as more than 2 years remained uncertain. Further research should also be extended to a longer duration and expanded to a larger group of participants.

ACKNOWLEDGEMENT

This work was funded by the Malaysia Ministry of Science, Technology, and Innovation Grant NMHD0002 and NMHD0003 awarded to Yuh-Fen Pung.

ETHICAL STATEMENT

Not applicable

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

Akash, M.S.H., Rehman, K. & Liaqat, A. 2018. Tumor necrosis factor-alpha: Role in development of insulin resistance and pathogenesis of type 2 diabetes mellitus. Journal of Cellular Biochemistry, 119(1): 105–110. https://doi.org/10.1002/JCB.26174

Anton, S.D., Lee, S.A., Donahoo, W.T., McLaren, C., Manini, T., Leeuwenburgh, C. & Pahor, M. 2019. The effects of time restricted feeding on overweight, older adults: A pilot study. Nutrients, 11(7): 1500. https://doi.org/10.3390/NU11071500

Beck, B. & Richy, S. 2009. Dietary modulation of ghrelin and leptin and gorging behavior after weight loss in the obese Zucker rat. Journal of Endocrinology, 202(1): 29–34. https://doi.org/10.1677/JOE-09-0080

Bhutani, S., Klempel, M.C., Kroeger, C.M., Trepanowski, J.F. & Varady, K.A. 2013. Alternate day fasting and endurance exercise combine to reduce body weight and favorably alter plasma lipids in obese humans. Obesity, 21(7): 1370–1379. https://doi.org/10.1002/OBY.20353

Cameron, J.D., Goldfield, G.S., Finlayson, G., Blundell, J.E. & Doucet, É.2014. Fasting for 24 hr heightens reward from food and food-related cues. PLOS ONE, 9(1): e85970. https://doi.org/10.1371/JOURNAL.PONE.0085970

Carter, S., Clifton, P.M. & Keogh, J.B. 2016. The effects of intermittent compared to continuous energy restriction on glycaemic control in type 2 diabetes; a pragmatic pilot trial. Diabetes Research and Clinical Practice, 122: 106–112. https://doi.org/10.1016/j.diabres.2016.10.010

Carter, S., Clifton, P.M. & Keogh, J.B. 2018. Effect of intermittent compared with continuous energy restricted diet on glycemic control in patients with type 2 diabetes: A randomized noninferiority trial. JAMA Network Open, 1(3): e180756–e180756. https://doi.org/10.1001/JAMANETWORKOPEN.2018.0756

Chaix, A., Zarrinpar, A., Miu, P. & Panda, S. 2014. Time-restricted feeding is a preventative and therapeutic intervention against diverse nutritional challenges. Cell Metabolism, 20(6): 991–1005. https://doi.org/10.1016/j.cmet.2014.11.001

Corley, B.T., Carroll, R.W., Hall, R.M., Weatherall, M., Parry-Strong, A. & Krebs, J.D. 2018. Intermittent fasting in Type 2 diabetes mellitus and the risk of hypoglycaemia: A randomized controlled trial. Diabetic Medicine, 35(5): 588–594. https://doi.org/10.1111/DME.13595

DeJesus, R.S., Croghan, I.T., Jacobson, D.J., Fan, C. & St. Sauver, J. 2022. Incidence of obesity at 1 and 3 years among community dwelling adults: A population-based study. Journal of Primary Care & Community Health, 13: 1-8. https://doi.org/10.1177/21501319211068632

Dhanasekaran, D.N. & Reddy, E.P. 2008. JNK signaling in apoptosis. Oncogene, 27(48): 6245–6251. https://doi.org/10.1038/onc.2008.301

Dyck, D.J., Heigenhauser, G.J.F. & Bruce, C.R. 2006. The role of adipokines as regulators of skeletal muscle fatty acid metabolism and insulin sensitivity. Acta Physiologica, 186(1): 5–16. https://doi.org/10.1111/J.1748-1716.2005.01502.X

Folli, F., Corradi, D., Fanti, P., Davalli, A., Paez, A., Giaccari, A., Perego, C. & Muscogiuri, G. 2012. The role of oxidative stress in the pathogenesis of type 2 diabetes mellitus micro- and macrovascular complications: Avenues for a mechanistic-based therapeutic approach. Current Diabetes Reviews, 7(5): 313–324. https://doi.org/10.2174/157339911797415585

Galicia-Garcia, U., Benito-Vicente, A., Jebari, S., Larrea-Sebal, A., Siddiqi, H., Uribe, K. B., Ostolaza, H. & Martín, C. 2020. Pathophysiology of type 2 diabetes mellitus. International Journal of Molecular Sciences, 21(17): 6275. https://doi.org/10.3390/IJMS21176275

Harris, L., Hamilton, S., Azevedo, L.B., Olajide, J., De Brún, C., Waller, G., Whittaker, V., Sharp, T., Lean, M., Hankey, C. & Ells, L. 2018. Intermittent fasting interventions for treatment of overweight and obesity in adults: A systematic review and meta-analysis. JBI Database of Systematic Reviews and Implementation Reports, 16(2): 507–547. https://doi.org/10.11124/JBISRIR-2016-003248

Heilbronn, L.K., Seng, K.G., Turner, N., Campbell, L.V. & Chisholm, D.J. 2007. Markers of mitochondrial biogenesis and metabolism are lower in overweight and obese insulin-resistant subjects. The Journal of Clinical Endocrinology & Metabolism, 92(4): 1467–1473. https://doi.org/10.1210/JC.2006-2210

Heinonen, S., Buzkova, J., Muniandy, M., Kaksonen, R., Ollikainen, M., Ismail, K., Hakkarainen, A., Lundbom, J., Lundbom, N., Vuolteenaho, K., Moilanen, E., Kaprio, J., Rissanen, A., Suomalainen, A. & Pietiläinen, K.H. 2015. Impaired mitochondrial biogenesis in adipose tissue in acquired obesity. Diabetes, 64(9): 3135–3145. https://doi.org/10.2337/DB14-1937

Hoddy, K.K., Kroeger, C.M., Trepanowski, J.F., Barnosky, A.R., Bhutani, S. & Varady, K.A. 2015. Safety of alternate day fasting and effect on disordered eating behaviors. Nutrition Journal, 14(1): 1–3. https://doi.org/10.1186/S12937-015-0029-9

Hussein, Z., Wahyu Taher, S., Kaur Gilcharan Singh, H., Chee Siew Swee Putrajaya, W., Setar, A., Jalil, B. & Lumpur, K. 2016. Diabetes care in Malaysia: Problems, new models, and solutions. Annals of Global Health, 81(6): 851–862. https://doi.org/10.1016/J.AOGH.2015.12.016

Iwani, N.A.K.Z., Jalaludin, M.Y., Zin, R.M.W.M., Fuziah, M.Z., Hong, J.Y.H., Abqariyah, Y., Mokhtar, A.H. & Wan Nazaimoon, W.M. 2017. Triglyceride to HDL-C ratio is associated with insulin resistance in overweight and obese children. Scientific Reports, 7: 40055. https://doi.org/10.1038/srep40055

Johnson, J.B., Summer, W., Cutler, R.G., Martin, B., Hyun, D.H., Dixit, V.D., Pearson, M., Nassar, M., Tellejohan, R., Maudsley, S., Carlson, O., John, S., Laub, D.R. & Mattson, M.P. 2007. Alternate day calorie restriction improves clinical findings and reduces markers of oxidative stress and inflammation in overweight adults with moderate asthma. Free Radical Biology and Medicine, 42(5): 665–674. https://doi.org/10.1016/J.FREERADBIOMED.2006.12.005

Kanety, H., Feinstein, R., Papa, M.Z., Hemi, R. & Karasik, A. 1995. Tumor necrosis factor alpha-induced phosphorylation of insulin receptor substrate-1 (IRS-1). Possible mechanism for suppression of insulin-stimulated tyrosine phosphorylation of IRS-1. The Journal of Biological Chemistry, 270(40): 23780–23784. https://doi.org/10.1074/JBC.270.40.23780

Khan, M.A.B., Hashim, M.J., King, J.K., Govender, R.D., Mustafa, H. & Kaabi, J.A. 2019. Epidemiology of type 2 diabetes – global burden of disease and forecasted trends. Journal of Epidemiology and Global Health, 10(1): 107–111. https://doi.org/10.2991/JEGH.K.191028.001

Kotarsky, C.J., Johnson, N.R., Mahoney, S.J., Mitchell, S.L., Schimek, R.L., Stastny, S.N. & Hackney, K.J. 2021. Time-restricted eating and concurrent exercise training reduces fat mass and increases lean mass in overweight and obese adults. Physiological Reports, 9(10): e14868. https://doi.org/10.14814/PHY2.14868

Liang, H. & Ward, W.F. 2006. PGC-1α: A key regulator of energy metabolism. American Journal

of Physiology - Advances in Physiology Education, 30(4): 145–151. https://doi.org/10.1152/ADVAN.00052.2006

Liu, H., Javaheri, A., Godar, R.J., Murphy, J., Ma, X., Rohatgi, N., Mahadevan, J., Hyrc, K., Saftig, P., Marshall, C., McDaniel, M.L., Remedi, M.S., Razani, B., Urano, F. & Diwan, A. 2017. Intermittent fasting preserves beta-cell mass in obesity-induced diabetes via the autophagy-lysosome pathway. Autophagy, 13(11): 1952–1968. https://doi.org/10.1080/15548627.2017.1368596

Mars, M., De Graaf, C., De Groot, L.C.P.G.M. & Kok, F.J. 2005. Decreases in fasting leptin and insulin concentrations after acute energy restriction and subsequent compensation in food intake. The American Journal of Clinical Nutrition, 81(3): 570–577. https://doi.org/10.1093/AJCN/81.3.570

Mattson, M.P., Longo, V.D. & Harvie, M. 2017. Impact of intermittent fasting on health and disease processes. Ageing Research Reviews, 39: 46–58. https://doi.org/10.1016/J.ARR.2016.10.005

Mindikoglu, A.L., Abdulsada, M.M., Jain, A., Jalal, P.K., Devaraj, S., Wilhelm, Z.R., Opekun, A.R. & Jung, S.Y. 2020. Intermittent fasting from dawn to sunset for four consecutive weeks induces anticancer serum proteome response and improves metabolic syndrome. Scientific Reports, 10: 18341. https://doi.org/10.1038/s41598-020-73767-w

Mohd-Sidik, S., Lekhraj, R. & Foo, C.N. 2021. Prevalence, Associated Factors and Psychological Determinants of Obesity among Adults in Selangor, Malaysia. International Journal of Environmental Research and Public Health, 18(3): 868. https://doi.org/10.3390/IJERPH18030868

Moro, T., Tinsley, G., Bianco, A., Marcolin, G., Pacelli, Q.F., Battaglia, G., Palma, A., Gentil, P., Neri, M. & Paoli, A. 2016. Effects of eight weeks of time-restricted feeding (16/8) on basal metabolism, maximal strength, body composition, inflammation, and cardiovascular risk factors in resistance-trained males. Journal of Translational Medicine, 14(1): 290. https://doi.org/10.1186/S12967-016-1044-0

Nieto-Vazquez, I., Fernández-Veledo, S., Krämer, D.K., Vila-Bedmar, R., Garcia-Guerra, L. & Lorenzo, M. 2008. Insulin resistance associated to obesity: The link TNF-alpha. Archives Of Physiology And Biochemistry, 114(3): 183–194. https://doi.org/10.1080/13813450802181047

Parr, E.B., Devlin, B.L., Radford, B.E. & Hawley, J.A. 2020. A delayed morning and earlier evening time-restricted feeding protocol for improving glycemic control and dietary adherence in men with overweight/obesity: A randomized controlled trial. Nutrients, 12(2): 505. https://doi.org/10.3390/NU12020505

Peterson, C.M., Johannsen, D.L. & Ravussin, E. 2012. Skeletal muscle mitochondria and aging: A review. Journal of Aging Research, 2012: 194821. https://doi.org/10.1155/2012/194821

Popkin, B.M. & Ng, S.W. 2022. The nutrition transition to a stage of high obesity and noncommunicable disease prevalence dominated by ultra-processed foods is not inevitable. Obesity Reviews, 23(1): e13366. https://doi.org/10.1111/OBR.13366

Razavi, R., Parvaresh, A., Abbasi, B., Yaghoobloo, K., Hassanzadeh, A., Mohammadifard, N., Clark, C.C.T. & Morteza Safavi, S. 2020. The alternate-day fasting diet is a more effective approach than a calorie restriction diet on weight loss and hs-CRP levels. International Journal for Vitamin and Nutrition Research, 91(3-4): 242–250. https://doi.org/10.1024/0300-9831/A000623

Ruppert, P.M.M., Michielsen, C.C.J.R., Hazebroek, E.J., Pirayesh, A., Olivecrona, G., Afman, L.A. & Kersten, S. 2020. Fasting induces ANGPTL4 and reduces LPL activity in human adipose tissue. Molecular Metabolism, 40: 101033. https://doi.org/10.1016/J.MOLMET.2020.101033

Savencu, C.E., Linţa, A., Farcaş, G., Bînă, A.M., Creţu, O.M., Maliţa, D.C., Muntean, D.M. & Sturza, A. 2021. Impact of dietary restriction regimens on mitochondria, heart, and endothelial function: A brief overview. Frontiers in Physiology, 12: 2233. https://doi.org/10.3389/FPHYS.2021.768383

Schübel, R., Nattenmüller, J., Sookthai, D., Nonnenmacher, T., Graf, M. E., Riedl, L., Schlett, C.L., Von Stackelberg, O., Johnson, T., Nabers, D., Kirsten, R., Kratz, M., Kauczor, H.U., Ulrich, C.M., Kaaks, R. & Kühn, T. 2018. Effects of intermittent and continuous calorie restriction on body weight and metabolism over 50 wk: A randomized controlled trial. The American Journal of Clinical Nutrition, 108(5): 933–945. https://doi.org/10.1093/AJCN/NQY196

Shaver, L.N., Beavers, D.P., Kiel, J., Kritchevsky, S.B. & Beavers, K.M. 2019. Effect of intentional weight loss on mortality biomarkers in older adults with obesity. The Journals of Gerontology: Series A, 74(8): 1303–1309. https://doi.org/10.1093/GERONA/GLY192

Sofer, S., Eliraz, A., Kaplan, S., Voet, H., Fink, G., Kima, T. & Madar, Z. 2011. Greater weight loss and hormonal changes after 6 months diet with carbohydrates eaten mostly at dinner. Obesity, 19(10): 2006–2014. https://doi.org/10.1038/OBY.2011.48

Wilkinson, M.J., Manoogian, E.N.C., Zadourian, A., Lo, H., Fakhri, S., Shoghi, A., Wang, X., Fleischer, J.G., Navlakha, S., Panda, S. & Taub, P.R. 2020. Ten-hour time-restricted eating reduces weight,

blood pressure, and atherogenic lipids in patients with metabolic syndrome. Cell Metabolism, 31(1): 92-104.e5. https://doi.org/10.1016/j.cmet.2019.11.004

Yung, J.H.M. & Giacca, A. 2020. Role of c-Jun N-terminal Kinase (JNK) in obesity and type 2 diabetes. Cells, 9(3): 706. https://doi.org/10.3390/CELLS9030706