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Review article

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THE ROLE OF LOW-CALORIE DIETS AND INTERMITTENT FASTING IN THE TREATMENT OF OBESITY AND TYPE-2 DIABETES

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Obesity is a condition associated with an increased risk of metabolic disorders, and in particular of type-2 diabetes (T2D). The treatment and prevention of obesity and associated metabolic disorders present great medical challenges. A major therapeutic goal in T2D is to control blood glucose levels, which can be achieved by pharmacological and nonpharmacological measures. The latter include increased physical activity and reduction of body fat mass by limiting dietary caloric content. Low-calorie diets (LCDs) involve a reduction in daily caloric intake by 25% to 30%. LCDs should be individualized depending on the patient's energy requirements, the severity of the obesity, and any accompanying diseases and treatments. Intermittent fasting (IF) involves caloric restriction for one or several days a week, or every day as the prolongation of the overnight fast. The results of recent clinical trials have shown that LCDs and intermittent fasting in patients with obesity (including those with coexisting T2D) can lead to a reduction in body fat mass and metabolic parameter improvements. These beneficial effects arise not only from the loss of body mass, but also from the activation of metabolic pathways specific to fasting conditions. However, the paucity of large-scale randomized controlled trials makes it difficult to prescribe LCDs or IF as reliable, routine methods for successful and stable weight loss.

Key words: *obesity, type-2 diabetes, low-calorie diet, intermittent fasting,* insulin sensitivity, oxidative stress, metabolic syndrome, cardiovascular disease

INTRODUCTION

Obesity is a chronic metabolic condition which develops with the excessive accumulation of adipose tissue (AT) in the body. The World Health Organization (WHO) reported that 39% of the global population was overweight, and 13% obese, in 2016; there were three times fewer people with obesity in 1975 (1). In Poland, 62% of adult men and 46% of adult women were overweight or obese in 2014 (2). Obesity is generally considered to be caused by exogenic factors *i.e.*, overnutrition accompanied by low physical activity; however, endogenic factors in the form of particular gene variants may predispose to obesity (3, 4). Obesity increases the risk of developing multiple accompanying disorders, including cardiovascular diseases (CVDs): coronary heart disease, arterial hypertension, atherosclerosis, stroke; insulin resistance and type-2 diabetes (T2D), disorders of the digestive system, kidney disease, neurological diseases (Alzheimer's disease, dementia), obstructive sleep apnea, asthma, decreased fertility, disorders of the osteoarticular system, immune system dysregulation, as well as certain types of cancer (1, 5, 6). Importantly, meta-analysis of individual-participant data from 239 prospective studies has demonstrated that the risk of death from all-cause mortality starts to increase when the body mass index (BMI) enters the overweight range (> 25 kg/m^2) (7).

Besides age, family history, and physical inactivity, obesity is one of the major etiological risk factors for T2D (8), with 80% of diabetic patients being obese (9). Because there is a strong link between these two disorders, the term 'diabesity' has been coined to refer to their coexistence (9). Yet it should be noted that only some individuals with obesity develop T2D. *Fig. 1* presents the processes involved in the etiology of obesity-associated diabetes (8-11), as proposed by the lipid overflow, inflammation, and adipokine hypotheses (9).

Although the basic diagnosis of obesity relies on simple anthropometric measures (*Table 1*), they do not always reflect the risk of obesity-associated metabolic disorders. In particular, metabolically obese, normal weight individuals (MONW) are characterized by increased risk of CVD and T2D, despite having BMI values within the norm. These disorders can occur due to large amounts of visceral fat, which may not be reflected by BMI (12, 13). Importantly, the intra-abdominal, or visceral, adipose tissue may negatively affect the insulin responsiveness of the liver (14), promote chronic, low-grade inflammation in obesity (15), and was shown to correlate with the diagnosis of metabolic syndrome (16). There are also metabolically healthy obese (MHO) individuals who display a favorable metabolic profile and appear to be protected against obesity-related metabolic disturbances (12, 17), possibly due to the substantial secretion of the anti-inflammatory, anti-atherogenic, and insulin-sensitizing adiponectin (18). For the diagnosis of obesity, it is therefore recommended to use waist circumference (WC), as this measure reflects the amount of visceral fat well and correlates with the

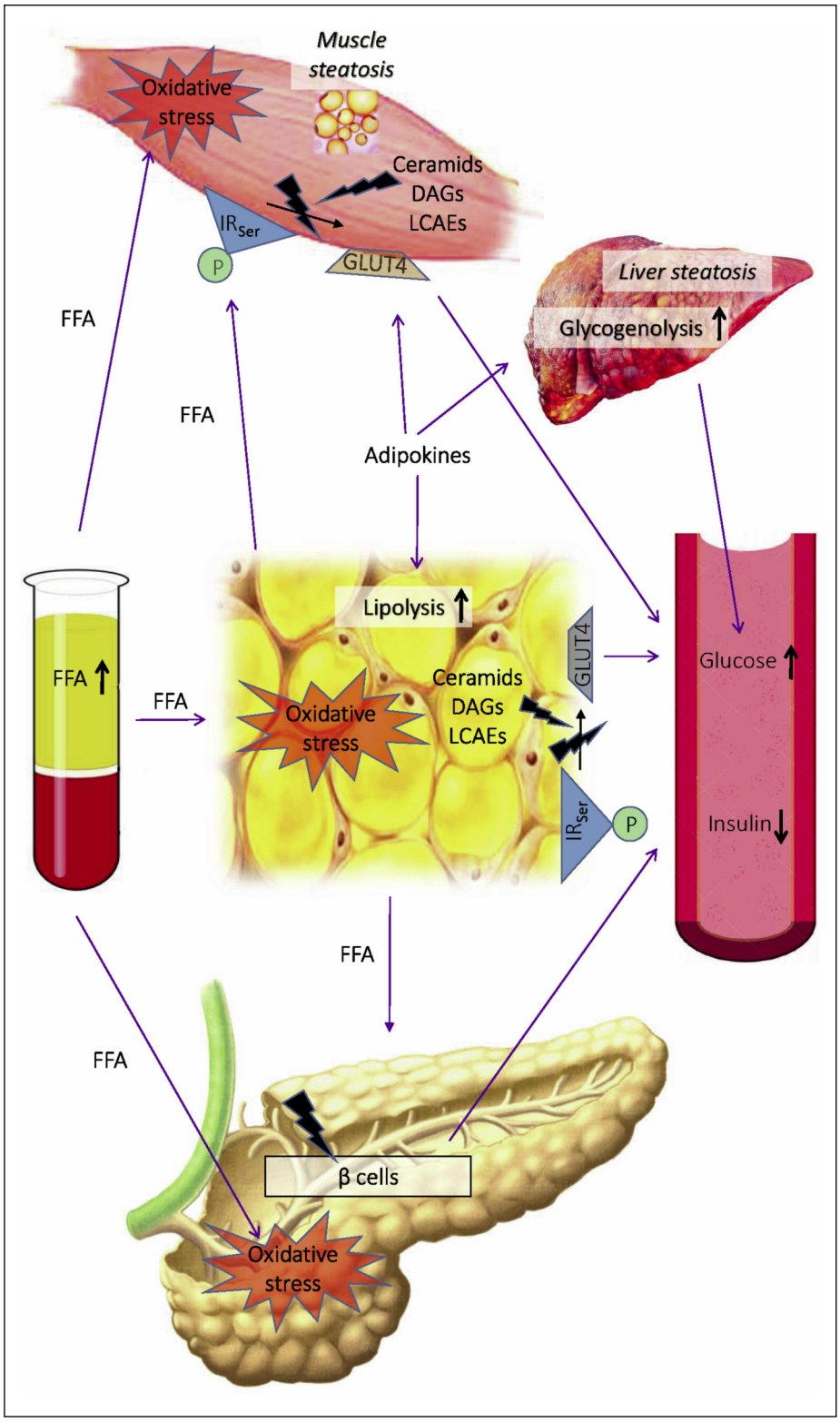

Fig. 1. The basic pathomechanisms of obesity-associated diabetes. The high serum concentration of free fatty acids (FFA) promotes oxidative stress in the cells responsible for energy homeostasis, such as adipocytes, skeletal muscle cells, pancreatic β-cells, and hepatocytes. This alters signal transduction from insulin receptors (IR), due to the phosphorylation of its serine residues (IR_{Ser}). In consequence of the developing insulin resistance, the uptake of glucose by insulin-dependent GLUT4 transporters in adipocytes and skeletal muscles declines, resulting in hyperglycemia. Moreover, the products of fatty acid metabolism, such as ceramids, diacyloglycerols (DAGs), and long-chain acyl-CoA esters (LCAEs), can directly inhibit insulin signaling pathway. Insulin resistance is associated with increased hepatic glycogenolysis and fat tissue lipolysis, mainly in visceral fat depots, due to the inhibition of insulin's antilipolytic activity by adipokines. Because adipocytes have a limited capacity to store the excess of plasma fatty acids, ectopic deposition of fat occurs in the liver, skeletal, or cardiac muscles, contributing to insulin resistance in these tissues. With the progression of diabetes, the lipotoxicity of FFA and oxidative stress affect the secretory function of the β-cells and promote their apoptosis, leading to hyperinsulinemia (8-11).

risk of metabolic disorders (16, 19, 20). Alongside fat mass (FM), another important determinant of metabolic health is the fat-free mass (FFM), which to some extent reflects lean body mass (LBM) *i.e.*, muscles, bones, internal organs, and body fluids) (8). To accurately determine body composition, techniques more reliable than anthropometric measures - such as dual-energy X-ray absorptiometry (DEXA) for fat tissue distribution or computer-assisted tomography (CT) for LBM assessment - are usually used in clinical studies (17, 21-24).

The basis for nonpharmacological treatment of obesity-associated diseases is fat mass reduction, achieved by limiting dietary caloric intake and practicing regular physical activity. As demonstrated in the Diabetes Prevention Program, which involved 3234 participants with obesity and prediabetes, body mass reduction by 7% accompanied by regular physical activity led to a 58% reduction in T2D morbidity (25). Remarkably, this outcome was better than the 31% reduction in diabetes morbidity in patients who received 1700 mg metformin on a daily basis for

Table 1. Anthropometric measures used in the diagnosis of obesity (1, 7, 8).

Measure		Reference values	
BMI		< 18.5	Underweight
		18.5 – 24.9	Normal weight
		25.0 – 29.9	Overweight
		≥ 30.0	Obesity
		30.0 – 34.9	Class 1 obesity
		35 – 39.9	Class 2 obesity
		≥ 40.0	Class 3 obesity
WHR	Women:	≤ 0.7	Normal
		≥ 0.85	Abdominal obesity
		< 0.85	Gluteal obesity
	Men:	≤ 0.8	Normal
		≥ 1.0	Abdominal obesity
		< 1.0	Gluteal obesity
WC	Women:	< 80	Normal
		≥ 80	Obesity
		≥ 88	Extensive obesity
	Men:	< 94	Normal
		≥ 94	Obesity
		≥102	Extensive obesity

WHO adult BMI classification. *Abbreviations:* BMI, the body mass index, ratio of the weight (kg) to the square of height (m); WHR, waist-to-hip ratio; WC, waist circumference (cm).

two years (25). Lifestyle interventions are therefore the key element of obesity and T2D treatment.

The purpose of our review was to examine the effects of weight-loss interventions through low-calorie diets (LCDs, also known as hypocaloric diets or calorie restriction) or intermittent fasting (IF). During various IF regimens all meals are consumed within a strictly defined window of time, followed by fasting (*e.g.*, alternate-day fasting, or fasting for one to several days a week, or eating only for several hours each day and fasting for the remainder of the day, *i.e.* time-restricted feeding (TRF). We included randomized controlled trials and some pilot studies in humans published during the last ten years, also mentioning some older studies of particular interest. The selection criteria included studies in adults with overweight or obesity, with or without T2D, on low-calorie (hypocaloric, low-energy, or calorie-restricted) diets or various intermittent fasting regimens (alternate day fasting, modified alternate day fasting, time-restricted feeding, intermittent feeding, Ramadan fasting), with optional physical activity and optional weight-loss medications, lasting for at least three weeks.

EFFECTS OF LOW-CALORIE DIETS

Low-calorie diets - also referred to as low-energy diets, hypocaloric diets, or calorie restriction (CR) - constitute weight-loss strategies for individuals with overweight or obesity that aim at improving metabolic health and diminishing the risk of obesity-associated disorders (25-28). Although the goal of weight loss in most interventions is set at a realistic 10%, in patients with BMI > 35 or in those with BMI > 30 and T2D a weight loss of 15 – 20% is recommended to achieve substantial health benefits (27). The diet is typically composed of a weight reduction phase (*e.g.* 4 – 12 weeks), followed by a weight stabilization phase. The LCD should be planned according to individual energy demands, taking into account the patient's sex, age, and physical activity level, as well as the degree of obesity, accompanying diseases, and previous treatment (26). The composition of an LCD may be based upon principles of balanced nutrition (45 – 55% carbohydrates, 15 – 25% proteins, and 25 – 30% fat) (28), but with an energy deficit of 500 – 800 kcal/day (16, 19, 29, 30). LCDs with relatively high protein contents may facilitate weight loss and prevent it being regained due to increased satiety, preservation of FFM, and sustained energy expenditure *via* diet-induced thermogenesis (31). However, it has been shown that high protein intake (such as 1.2 g protein/kg/day) during a weight-loss diet in obese postmenopausal women eliminated the improvements in insulin signaling in muscles, in contrast to a diet with lower protein content (0.8 g protein/kg/day) (32). The macronutrient composition of a diet should be therefore carefully considered. Other strategies to enhance weight loss include the use of meal replacements, alone or in combination with other nutrients, to provide better control over the calorie intake (33, 34). Indeed, it has been recently demonstrated that in obese women, three weeks of total meal replacement diet led to greater weight loss and reduced food cravings than an isocaloric diet (1120 kcal/day) (35). Moreover, it should be noted that nutritional education is a key component of weight-loss programs (16, 29). Interestingly, extended postintervention counseling does not appear to improve weight maintenance, with only one third of the patients retaining a ≥ 5% weight loss (36). As discussed later, weight regain is a common problem affecting the long-term effectiveness of dietary interventions.

Very low-calorie diets (VLCDs) that provide no more than 800 kcal/day are a strategy for obtaining quick weight loss (27, 37). Importantly, recent studies demonstrate that the rate of weight loss does not affect the extent of weight regain after completion of the dietary intervention (38, 39). However, because of an associated risk of developing hepatosteatosis, cholelithiasis, and vitamin and microelement deficiencies, VLCDs should thus be employed only at physicians' recommendations and under their supervision in a clinical setting (inpatient rather than outpatient clinics) (37).

To sum up, LCDs should be planned in order to set energy deficit at 500 – 800 kcal/day which can be obtained by using diet upon principles of balanced nutrition, with changed proportion of nutrients or meal replacements. VLCDs providing energy intake up to 800 kcal/day, lead to quick weight loss. The key issue of these dietary interventions is to maintain weight loss after returning to normal or habitual diets.

Table 2 summarizes the design of randomized controlled trials and other studies in humans, published in the last decade, on the effects of LCDs in adult individuals with overweight or obesity. Some of these effects are further discussed in the following sections.

Weight loss and body composition

Most of the health-promoting effects of low-calorie diets are associated with substantial reductions in body mass. However, LCDs may also confer benefits that are independent of weight loss (40). The degree of weight reduction is highly dependent on the design of the intervention, as well as on the patient's adherence to the dietary protocol and physical activity recommendations. In the examined studies, LCDs of various durations caused reductions in body mass ranging from 1% to 15% in selected groups of patients with diabetes after a 24-month low-intensity intervention (41), to 15% in another group of individuals with diabetes (42). The decline in body mass in patients with T2D on LCD can be hindered by the anabolic effect of hypoglycemic drugs, such as insulin (33). On the other hand, reductions in body weight in these patients improved glycemia to an extent that allowed the dose to be reduced or for pharmacotherapy to be altogether discontinued (33).

Body-weight reduction through LCD is associated with the loss of both FM and LBM to an extent dependent on the intervention design and existing comorbidities. For example, in women with overweight or obesity, a six-month diet led to a 14%

Table 2. The effects of low-calorie diets (LCD) on changes in body mass/composition, metabolic, hormonal and hemodynamic parameters in selected clinical trials.

Reference Year, Country	**Daily caloric intake, diet composition and duration**	**Patients' characteristics**	**Effects of intervention**
Larson-Meyer D., *et al*. (64) 2008, USA	LCD: until achieving 15% weight loss, then weight maintenance; Liquid diet, 5 shakes per day providing 890 kcal/day; 6 months	N = 11 (7 F, 4 M) BMI 27.8 ± 1.9 39 ± 7 years	↓ BW by 11.5 kg ↓ % body fat by 6.87% ↓ TG by 12% ↑ HDL by 12% ↓ IHL by approx. 50% ↓ ALK by 5.1 U/L ↓ hsCRP by 0.23 mg/dl (50%) ↑ insulin sensitivity by 83%
Iqbal N., *et al*. (41) 2010, USA	DCI: reduced by 500 kcal; DC: fatty acids <7% DCI, dietary cholesterol <300 mg/day (low-fat diet); 2 years	N = 74 (4 F, 70 M)[c] BMI 36.9 ± 5.3 60 ± 9.5 years Diabetic patients, only 40 completed the study	↓ BW 0.2 kg ↓ SBP by 4.5 mmHg ↓ Ch by 13.2 ↓ TG by 13.0 ↓ LDL by 6.0 mg/dl ↓ glucose by 4.3 mg/dl
Johnson W., *et al*. (29) 2011, USA	DCI: 890 kcal (12 weeks), then 1200 – 1600 kcal plus treatment with sibutramine and orlistat (4 months), followed by activities recommendations and weight loss medications; 1 year	N = 208 (178 F, 30 M) BMI 46 ± 8 49 ± 11 years* Extremely obese patients, 48 with T2D were treated with metformin	↓ BW by 8 kg (5.9%) ↓ TG by 21 mg/dl ↓ glucose by 6.2% only in T2D patients with 20% BW loss ↓ SBP by 7 and DBP by 3.5 mmHg ↓ ALT by 2 U/L, ↓ LDH by 5 U/L ↓ hsCRP by 1.6 mg/dl
Friedman A., *et al*. (68) 2012, USA	DCI: 1200 – 1500 kcal (women) and 1500 – 1800 kcal (men); DC: 55% carbohydrates, 30% fat, 15% proteins 2 years	N = 154 (105 F, 49 M) BMI 36.1 ± 3.5 44.9 ± 10.2 years Obese patients without T2D or hypertension	↓ BW by approx. 7% no significant effects on kidney function (main aim of the study)
Jensen P., *et al*. (42) 2014, Denmark	DCI: 800 – 1000 kcal for 8 weeks, then 1200 kcal for next 8 weeks	N = 30 (14 F, 16 M) BMI 34.7 ± 6 50 ± 10 years Diabetic patients with psoriasis	↓ BW by 15.8 kg ↓ BMI by 5.1 ↓ Ch by 15.5, ↓ TG by 22.4 ↓ glucose by 10.8 mg/dl ↓ glycated HbA1c by 0.7 mg% ↓ SBP by 7 and DBP by 5 mmHg ↓ heart rate by 8 bpm ↓ tPAI by 3.07 ng/ml ↓ PASI by 2.3
Kim M.K. (30) 2014, South Korea	DCI: reduced by 638 kcal 3 months	N = 18 (M) BMI 29.6 ± 0.5 44.8 ± 1.6 years	↓ BW by 10.5 kg ↓ BMI by 3.6 ↓ WC by 10.6 cm ↓ % body fat by 13.8% ↓ Ch by 22.6, ↓ TG by 57.0 ↓ glucose by 6,2 mg/dl ↓ insulin by 3.13 μU/ml ↓ SBP by 18 and DBP by 11 mmHg
Oshakbayev K., *et al*. (71) 2015, Kazahstan	DCI: reduced by 100 – 150 kcal/day; 6 months	N = 31 (16 F, 15 M) BMI 30.1 ± 1.4 47.5 ± 1.9 years	↓ BW by 11.65 kg ↓ BMI by 3.92 ↓ FM by 10.99 kg ↓ FFM by 1.99 kg ↓ Ch by 1.47 mmol/l, ↓ TG by 0.69 g/l ↓ glucose by 2.05 mmol/l ↓ SBP by 28.3 and DBP by 17.7
Razny U., *et al*. (54) 2015, Poland	LCD: 1200 kcal/d for women and 1500 kcal/d for men; 3 months	N = 24 (20 F, 4 M) BMI 35.24 ± 0.72 48 ± 2 ys	↓ BW by 7.82 kg, ↓ BMI by 2.8 ↓ % body fat by 3.25% ↓ TG by 0.23
Razny U., *et al*. (54) 2015, Poland	LCD: 1200 kcal/d for women and 1500 kcal/d for men, supplemented with 1.8 g/day n-3 PUFA; 3 months	N = 24 (18 F, 6 M) BMI 34.25 ± 0.7 45 ± 2 years	↓ BW by 6.85 kg ↓ BMI by 2.6 ↓ % body fat by 3.26% ↓ TG by 0.44 ↓ HOMA-IR by 0.76 ↓ insulin by 2.94 mIU/ml ↓ fasting GIP by 8.74 pg/ml
Weiss E., *et al*. (55) 2015, USA	DCI: reduced by 20% without changing physical activity; 14 weeks	N = 17 (13 F, 4 M) BMI 27.7 ± 0.4 57 ± 1 years	↓ BW by 7% ↓ FM by 13% ↓ FFM by 2%

Goday A., *et al*. (52) 2016, Spain	DCI: reduced by 500 – 1000 kcal; DC: < 30% of calories from fat, 10 – 20% from protein, 45 – 60% from carbohydrates; 4 months	N = 44 (28 F, 16 M) BMI 32.88 ± 1.6 54.17 ± 7.97 years	↓ BW 5.05 kg (not significant) ↓ BMI 1.9 ↓ WC by 5.4 cm ↓ HOMA value by 1.2
Kargulewicz A., *et al*. (63) 2016, Poland	60 – 70% of caloric requirements; 3 months	N = 39 (F) BMI 36.07 ± 5.62 18 – 40 years	↓ BW by 4.2 kg ↓ BMI by 1.3 ↓ WC by 8.7 cm ↓ FM by 4.9 kg, ↑ % LBM by 2.2% ↑ adiponectin by 1.9 µg/l ↓ leptin by 4.1 µg/l
McDonald V., *et al*. (44) 2016, Australia	LCD: 920 – 1200 kcal/d (up to 1200 kcal/d for patients with BMI > 40 kg/m^2); home-based resistance training; 12 weeks	N = 28 (11 F, 17 M) BMI 36.1 ± 4.5 67.6 ± 6.3 years	↓ BMI by 2.4 ↓ FM by 4.6 kg ↓ % body fat by 2.7% ↓ BODE index by 1.4 units
Smith G., *et al*. (32) 2016, USA	DCI: initially reduced by 30%, then adjusted to achieve 0.5 – 1% weight loss weekly, until 8 – 10% weight loss, then 3 – 4 weeks weight stable; DC: 0.8 g protein/kg b.w./day 27.8±2.8 weeks	N = 10 BMI 35 ± 1 58 ± 1 years	↓ BW by 10% ↑ FFM by 25% ↓ IHL by 38% ↓ FFA by 0.1 mM ↓ glucose by 3.2 mg/dl ↓ insulin by 2.4 µU/ml ↑ insulin-stimulated glucose rate of disappearance by 12 µmol/kg FFM/min
Smith G., *et al*. (32) 2016, USA	DCI: initially reduced by 30%, then adjusted to achieve 0.5 – 1% weight loss weekly, until 8 – 10% weight loss, then 3 – 4 weeks weight stable; DC: 1.2 g protein/kg b.w./day 26.4 ± 2.9 weeks	N = 10 BMI 36 ± 1 58 ± 1 years	↓ BW by 10.5% ↑ FFM by 25% ↓ FFA by 0.1 mM ↓ IHL by 50% ↓ insulin by 2.7 µU/ml
Vink R., *et al*. (38) 2016, Netherlands	LCD: 1250 kcal/day; DC: 29% energy from protein, 48% energy from carbohydrates, 23% energy from fat 12 weeks	N = 29 (15 F, 14 M) BMI 31.3 ± 0.5 51.8 ± 1.9 years	↓ BW by 8.2 kg; ↓ BMI by 2.8 ↓ WC by 7.3 cm; ↓ HC by 4.9 cm ↓ FM by 7.6 kg ↓ % body fat by 5.4% ↓ FFM by 0.6 kg ↓ SBP by 3.1 and ↓ DBP by 4.8
Einarsson S., *et al*. (74) 2017, Sweden	low calorie liquid formula diet, DCI: 880 kcal; 12 weeks	N = 152 (F) BMI 33.1 ± 1.3 31.5 ± 4.5 years women scheduled for IVF	↓ BW by 9.1 kg ↓ BMI by 3.25 ↑ live births from spontaneous pregnancies, but no effect on overall live birth rate, miscarriage rate or gonadotropin dose for IVF
Ghachem A, *et al*. (23) 2017, Canada	DCI: reduced by 500 – 800 kcal; 6 months	Group 1: N = 20, women with metabolic syndrome BMI 34.5 ± 4.7 56.9 ± 4.8 years	↓ BW by 6.9 kg ↓ BMI 2.7 ↓ WC by 5.3 cm ↓ FM by 5.5 kg ↓ LBM by 1.5 kg ↓ Ch by 0.12 ↓ TG by 0.39 ↑ LDL by 0.09 ↓ HDL by 0.13 (all lipid values in mmol/l) ↓ glucose by 0.16 mmol/l ↓ insulin by 3.6 µU/ml ↓ SBP by 4 and ↓ DBP by 2
Ghachem A., *et al*. (23) 2017, Canada	DCI: reduced by 500 – 800 kcal; 6 months	Group 2: N = 53, women without metabolic syndrome BMI 31.7 ± 4.3 58.7 ± 4.8 years	↓ BW by 5.1kg ↓ BMI by 2 ↓ WC by 5.1cm ↓ FM by 4.6 kg ↓ LBM by 0.5 kg ↓ Ch by 0.06 ↓ TG by 0.08 ↑ LDL by 0.02 ↓ HDL by 0.04 (all lipid values in mmol/l)

			↓ insulin by 1.6 µU/ml ↓ DBP by 1
Korybalska K., *et al.* (40) 2017, Poland	DCI: reduced by 300 – 500 kcal (15 – 30% energy deficit); 8 weeks	N = 41 (F) BMI 38.0 ± 6.5 34.5 ± 10 years	↓ BW by 8.3 kg ↓ BMI by 2.7 ↓ WC by 5.75cm ↓ FM ↓ SBP 13.3 mmHg ↓ Ch by 12.3, ↓ TG by 44.6 ↓ leptin by 16.6 ng/ml
Lambert E., *et al.* (117) 2017, Australia	DCI reduced by 600 kcal; 6 months	N = 10 BMI 31.9 ± 1.9 24 ± 1 years	↓ BW by 7.6 kg ↓ BMI by 2.3 ↓ WC by 5.75cm ↓ FM by 6.88 kg ↓ abdominal FM by 0.61 kg ↓ HOMA-IR by 0.46* ↓ leptin by 4.63 mg/dl ↓ SBP by 9 mmHg ↓ heart rate by 11.7 bpm ↓ MSNA by 10.5 bursts/min
Rothberg E., *et al.* (20) 2017, USA	800 kcal/d as meal replacements - first 3 months 1200 – 1500 kcal/d (women) and 1500 – 1800 kcal/d (men) - next 3 months; physical activity; follow-up until 2 years	N = 170 (88 F, 82 M) BMI 40 ± 5 51 ± 8 years	Change in the tertile with the greatest relative decrease in WC[a]: ↓ BMI by 9 BW not given ↓ Ch by 7 ↓ TG by 59 ↓ LDL by 12 ↑ HDL by 17 ↓ glucose by 9 mg/dl ↓ HbA1c by 0.8% ↓ SBP by 8 DBP by 2 mmHg
Ruggenenti P., *et al.* (50) 2017, Italy	DCI: reduced by 25%; DC: 15 – 20% energy from proteins, 45 – 50% energy from carbohydrates, 30 – 35% energy from fat; 6 months	N = 34 (5 F, 29 M) BMI 30.0 ± 3.9 59.8 ± 7.1 years	↓ BW by 4.7 kg ↓ BMI by 1.6 ↓ WC by 5.9 cm ↓TG by 13.6 ↓ LDL by 3.5 ↑HDL by 2.4 ↓ glucose by 18.1 mg/dl ↓ HbA1c by 0.8% ↓ SBP by 6.7 and DBP by 5.2 mmHg ↓ heart rate by 4.5 bpm ↓ hsCRP by 0.12 mg/dl ↓ ALT by 4.1 ↓ AST by 2.4 IU/l ↓ GFR by 7.6 ml/min
Saslow L., *et al.* (118) 2017, USA	DCI: reduced by 500 kcal; 12 months	N = 18 (16 F, 2M) BMI 36.9 (32.5 ± 39.2)[b] 55.1 ± 13.5 years	↓ BW by 1.7 kg ↓ BMI by 0.9 ↓ HbA1c by 0.2%
Vink R., *et al.* (112) 2017, Netherlands	LCD: 1250 kcal/day; 12 weeks	N = 29 (15 F, 14 M) BMI 31.3 ± 0.5 51.8 ± 1.9 years	↓ BW by 8.2 kg ↓ BMI by 2.7 ↓ WC by 7.3 cm ↓ FM by 5.4% ↓ FFM by 0.5 kg ↓Ch by 0.2 mmol/l ↓ TG by 270 µmol/l ↑ FFA by 63 µmol/l ↓ glucose by 0.2 mmol/l ↓ insulin by 4.7 µU/ml ↑ adiponectin by 0.5 µg/ml ↓ leptin by 5 ng/ml ↓ SBP by 3.1 and DBP by 4.8
Weiss E., *et al.* (47, 57)[c] 2017, USA,	DCI: reduced by 20%; 14 weeks	N = 17 (13 F, 4 M) BMI 27.7 ± 1.7 57 ± 5 years	↓ BW by 5.4 kg (7%) ↓ WC by 7.5% ↓ FM by 4.1 kg (13%) ↓ FFM by 0.9 kg (2%) ↓ leptin by 0.6 pg/ml ↓ absolute aerobic capacity by 6%
Tronieri J., *et al.* (34) 2018, USA	LCD: 1000 – 1200 kcal/day in a form of meal replacements; 14 weeks	N = 137 (118 F, 19 M) BMI 40.8 ± 5.9 46.1 ± 10.1 years	↓ BW by 10.7 kg ↓ BMI by 3.8 ↓ SBP by 13.6 DBP by 8.3 mmHg

			↓ Ch by 17.4 ↓ TG by 13.2 ↓ LDL by 7.4 ↓ HDL by 7.5 ↓ HbA1c by 0.1 ↓ HOMA-IR value by 0.5 ↓ insulin by 2.2 μU/ml
Coutinho S., *et al*. (39) 2018, Norway	LCD: 1200 kcal/day (women) 1500 kcal/day (men); 8 weeks	N = 16 BMI 33.5 ± 2.6 36.2 ± 8.7 years	↓ BW by 9.3 kg ↓ FM by 7.6 kg, ↓ FFM by 1.7 kg ↓ insulin by 50 pmol/l
Kahathudawa C., *et al*. (35) 2018, USA	LCD: 1120 kcal/day as total meal replacements; 3 weeks	N = 15 (7 F, 8 M) BMI 35.14 ± 3.75 31.27 ± 11.85	↓ BW by 4.87 kg ↓ BMI by 1.68 ↓ FM by 2.18 kg ↓ overall food cravings by 0.41 units (neurophysiological test)

Selected studies have been ordered chronologically with the name of the first author. Only statistically significant effects of the low-calorie diets are shown. BMI is expressed as mean ± standard deviation. Glucose, insulin, leptin, and adiponectin serum levels, and serum lipidogram were measured after overnight fasting. Cholesterol, TG, LDL and HDL levels are expressed in mg/dl unless otherwise stated. *Symbols:* *, as compared to the control group; [a], the study outcomes were categorized into 3 groups (tertiles) according to the relative decrease in WC - the results for only the tertile with greatest decrease in WC are presented; [b], estimated marginal mean (EMM) ± 95% CI; [c], the intervention outcomes were reported in two publications. *Abbreviations:* ALK, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate transaminase; BMI, body mass index; BODE, the body mass index, obstruction, dyspnea and exercise index; bpm, beats per minute; BW, body weight; Ch, total cholesterol; DBP, diastolic blood pressure; F, females; FFM, fat-free mass; FM, fat mass; GFR, glomerular filtration rate; HC, hip circumference; HDL, high-density-lipoprotein cholesterol; HOMA-IR, homeostatic model assessment - insulin resistance; hsCRP, high-sensitivity C-reactive protein; IHL, intrahepatic lipids; LBM, lean body mass; LDH, lactate dehydrogenase; LDL, low-density-lipoprotein cholesterol; M, men; MSNA, muscle sympathetic nerve activity; NS, not statistically significant; PASI, psoriasis area and severity index; PUFA, polyunsaturated fatty acids; RMR, resting metabolic rate; SBP, systolic blood pressure; T2D, type 2 diabetes mellitus; TG, triglycerides; tPAI, tissue plasminogen activator inhibitor; WC, waist circumference.

decrease in FM, including a 12.5% reduction in visceral fat, and a decrease in LBM ranging from 1.2% to 3.3% in patients with or without metabolic syndrome, respectively (23). Other studies showed decreases in FM by 1.7 kg and in LBM by 0.6 kg after a three-month LCD in middle-aged obese women (43), or a 10% reduction in body fat with preservation of muscle mass after weight loss in patients with obesity and COPD (44). Several studies have demonstrated that the percentage FFM loss was lower after LCD than after VLCD (38, 45). There is a general agreement that the loss of LBM (and specifically of muscle mass) should be avoided due to LBM's protective effect against insulin resistance (46). However, Myette-Cote *et al.* challenged this view by demonstrating that LCD was associated with more favorable outcomes (such as improvements in glucose disposal rate) in participants who showed postintervention decreases in LBM, in contrast to those who had the LBM preserved (24). Nevertheless, those 'positive responders' also had greater reductions in body weight (8.9% versus 3.5% in 'negative responders') and FM index (15.1% and 7.8%, respectively) (24). Moreover, a study in nonobese subjects revealed that their weight-adjusted fat mass correlated positively, while LBM correlated negatively, with the indices of metabolic abnormalities and insulin resistance, thus acting in a mirror-image fashion (8). Thus, changes in both FM and LBM influence the metabolic effects of LCDs.

It is highly recommended that weight-loss interventions include physical activity. A study in overweight sedentary women and men showed that, in comparison to CR alone, an intervention encompassing endurance exercises resulted in a similar degree (7%) of weight loss, but attenuated LBM loss and prevented the reduction in absolute aerobic capacity (47). Moreover, the weight response to purely dietary interventions is slow, especially in people with morbid obesity, while the faster effects achieved with the inclusion of physical training may better motivate the patients (48).

Excessive obesity (class III, BMI ≥ 40) is the hardest to manage, yet three independent studies (29, 48, 49) have demonstrated that significant weight loss is attainable for individuals with morbid obesity through lifestyle intervention programs in primary care practices. A seven-week intensive lifestyle intervention involving calorie restriction of 1000 kcal/day and multiple supervised aerobic physical exercise sessions resulted in 5.3% weight loss, with over 10% FM reduction (48). In another study, 10% weight loss was obtained after twelve months of LCD with physical activity recommendations (49). Lastly, participants who completed the LCD-based 24-month LOSS program lost on average 13.1% of their baseline weight (29). However, only 53% of those patients passed the one-year assessments (29), showing how difficult it is for people with severe obesity to comply with a weight-loss program.

To summarize, while weight loss is essential for achieving many of the health-promoting effects of LCDs, the interventions should promote the loss of fat mass and preservation of muscle mass, *e.g.*, through the addition of physical training.

The effects of low-calorie diets on glycemic control

The main goal of T2D treatment is the control of glycemia. Weight loss is generally recommended to improve insulin sensitivity in people with obesity; however, heterogeneous responses have been reported. Some studies demonstrated that weight loss in patients with T2D or prediabetes was associated with a lowering of blood glucose or glycated hemoglobin (HbA1c) levels. Shiau *et al.* (33) conducted a retrospective cohort study of 317 patients with diabetes and obesity, who received a full meal replacement LCD (900 kcal/day) for 6 – 12 weeks, followed by a transition period and counseling sessions for up to one year. After six months, with 16% weight loss, HbA1c levels improved by about 6.3% (33). Significant decreases in HbA1c and blood glucose levels were also observed after six months of LCD (25% calorie decrease from estimated total daily energy intake) in patients with T2D and abdominal obesity (BMI 30 ± 3.9; WC 104.1 ± 9.4; n = 34) (50). The effects

of an intensive weight-loss intervention (890 kcal/day liquid LCD up to twelve weeks, followed by a highly structured 1200 – 1600 kcal/day diet with medications, and recommended physical activity with optional pharmacological treatment for up to two years) were examined in adults with extreme obesity (BMI 40 – 60 kg/m^2, 48 out of 208 with T2D). The T2D patients showed significantly reduced plasma glucose concentrations with weight loss of at least 5%, culminating in 25% glucose reduction with ≥ 20% weight loss (29). A systematic review of pre-2004 clinical trials of lifestyle weight-loss interventions in patients with T2D revealed that there was always a trend towards improvements in glycated hemoglobin levels, although no statistical strength was found in the meta-analysis (51). In contrast to these findings, a low-intensity LCD intervention in patients with diabetes and obesity brought only minimal weight loss, associated with clinically insignificant decreases in fasting glucose (–1.8 mg/dL for a low-carbohydrate diet and –4.3 mg/dL for a low-fat LCD) and HbA1c (–0.1% and –0.2%) after 24 months (41). Likewise, a multicenter randomized control trial in patients with T2D and obesity showed no effects of a four-month LCD (with a deficit of 500 – 1000 kcal/day) on fasting glycemia, HbA1c levels, and plasma TG, in contrast to improvements through a very low-calorie ketogenic diet (VLCKD; < 50 g of carbohydrate daily) for 30 – 45 days (52). However, the VLCKD group participants were provided with their meals (vegetables with low glycemic index and high biological value protein preparations, next substituted by natural proteins), while the LCD group participants received only nutritional and lifestyle recommendations. This could have resulted in substantially greater weight loss through VLCKD than LCD (16.1% versus 5.6%, respectively), and in consequence improvements in glycemic control in the VLCKD group only (52). Nevertheless, substantial weight loss in patients with T2D and obesity can exert positive effects on hyperglycemia (29, 33, 51), rendering T2D a potentially reversible disease.

The effects of weight loss on insulin resistance were also examined in nondiabetic individuals with overweight or obesity. Blood glucose, insulin, HbA1c, and homeostatic model assessment for insulin resistance index (HOMA-IR) decreased significantly after a three-month LCD in middle-aged men with obesity (30). Fasting insulin decreased in women with overweight or obesity after an eight-week LCD, though the decrease in HOMA index did not reach statistical significance (P = 0.052) (53). In middle-aged women with class I obesity, a ninety-day LCD with a deficit of 500 kcal/day resulted in decreased serum insulin and HOMA-IR (until day 60 of the intervention) (43). In contrast, the study of Razny *et al.* (54) in a similar group of subjects showed no effects of a three-month LCD (1200 – 1500 kcal/day) on insulin concentration or HOMA-IR, unless supplemented with n-3 polyunsaturated fatty acids (PUFAs), specifically docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) in a 5:1 ratio. A three-month LCD of 1200 and 1500 kcal/day for women and men, respectively, supplemented with PUFAs significantly improved insulin resistance and positively affected the secretory ability of β cells, as estimated by the ratio of insulin to glucose areas under the curve in the oral glucose tolerance test (OGTT) (54). Moreover, incorporation of exercise into a weight-loss program improved insulin sensitivity in sedentary men and women with overweight (55) and in postmenopausal women with obesity and impaired glucose tolerance (56). The mechanisms involved may include additive effects of exercise and CR on the reductions in leptin and adiponectin serum concentrations (57), as well as the anti-inflammatory activity of the exercise-induced myokine irisin (58). However, glycemic control improvements were sustainable for at least a year in only half of the non-diabetic subjects with obesity who lost over 7% of initial body mass (59). Moreover, the positive impact of LCDs on muscle insulin sensitivity may be lost when the diet has high protein content (32).

It should be noted that LCDs had diverse effects on glucose disposal rate (GDR), which reflects peripheral insulin sensitivity (24). In this respect, Myette-Cote *et al.* (24) observed great inter-individual variability in postmenopausal women with obesity (with mean BMIs of 32 kg/m^2) after a six-month LCD aimed at reducing body weight by 10%. Some participants displayed improvements in glucose disposal after weight loss (positive responders; Δ glucose disposal ≥ 0.92 mg/kg/min, n = 19 out of 57), some showed no change, while others experienced deteriorations after LCD (negative responders; Δ glucose disposal ≤ –0.23 mg/kg/min, n = 19 out of 57). To explain these interindividual variations, the authors compared the baseline and postintervention characteristics in women from the upper and lower tertiles with regard to changes in GDR after weight loss. They found that at baseline the positive responders had lower glucose disposal values and higher levels of high-sensitivity C-reactive protein (hsCRP) and triglycerides (TG), despite similar body fat content and distribution (24). Thus, improvements in glucose disposal rate through weight-loss intervention occurred primarily in individuals with worse baseline characteristics. Likewise, insulin sensitivity determined by euglycemic–hyperinsulinemic clamp improved after six months of an LCD with a deficit of 500 – 800 kcal/day in at-risk participants (those with low insulin sensitivity at baseline; increased by 26.1%); however, insulin sensitivity decreased by 12.8% in metabolically healthy obese women, despite similar weight losses of 6 – 7% and fat mass loss of 7 – 10% in both groups (17). These results were confirmed in a more extensive study of 356 obese subjects without known diabetes who were subjected to a three-month hypocaloric low-fat, high-protein diet with 30 min/day of physical activity (60). Depending on the baseline degree of insulin sensitivity, the intervention induced positive changes in insulin sensitivity and β-cell function in insulin-resistant patients with obesity, but worsened the metabolic conditions of patients with the insulin-sensitive phenotype of obesity (60). Thus, it may be concluded that attempts to achieve weight loss in metabolically healthy obese individuals can also be harmful.

It may be generalized that majority of studies indicate that weight loss through LCDs is associated with lowering of blood glucose and HbA1c levels as well as decreasing of HOMA-IR in individuals with obesity and diabetes or impaired glucose tolerance. However, the LCDs may worsen peripheral insulin sensitivity if they are applied in metabolically healthy individuals, or when the diet has high protein content.

The effects of low-calorie diets on cardiovascular system

The excess visceral fat mass in obesity is associated with abnormal endothelial cell function, which can affect cardiovascular events (61). Besides impaired glucose tolerance and insulin resistance, other factors including elevated plasma lipid levels, hypertension, and systemic inflammation, are also risk factors for CVDs.

As shown in *Table 2*, LCD-associated weight loss can improve blood pressure and serum lipid profiles. Johnson *et al.* (29) showed that TG concentrations declined by approximately 20% with a weight loss of 5 – 20%, and 38% with more substantial weight loss. HDL cholesterol increased by 6.9% among those who lost 5 – 9.9% body weight and 18.2% in those who lost at least 20%. The changes in serum LDL cholesterol level were inconsistent across weight-loss categories, and the resting blood pressure declined independently of the degree of weight change (29). In line with these findings, Rothberg *et al.* (20) reported the greatest improvements in blood lipid profile and the greatest lowering of blood pressure in those patients who had the greatest decrease in

waist circumference after the LCD intervention. Other authors reported decreases in TG and total cholesterol levels after three months of LCD in middle-aged Koreans with obesity (30).

Since obesity is associated with increased oxidative stress and chronic low-grade inflammation, some researchers have examined the effect of weight loss on inflammation and oxidative stress. Buchowski *et al.* (62) demonstrated that in premenopausal women with overweight or obesity (BMI 32 ± 5.8 kg/m^2), a 28-day hypocaloric diet caused a rapid decline in serum F2-isoprostane levels, a validated marker of oxidative stress. Interestingly, this occurred despite there being no significant differences in body or fat mass between the LCD and control groups at the beginning or end of the intervention, or three months after it ended (62). However, the baseline elevated serum levels of F2-isoprostane were restored after three months of a habitual diet in about 80% of the women (62). The level of CRP, a marker of inflammation, did not change throughout the study (62). Thus, the weight-loss intervention resulted in only temporary improvement in oxidative stress in a vast majority of patients. However, in a group of 208 patients with extreme obesity, LCD with sibutramine and orlistat treatment caused a reduction of CRP levels (29). Moreover, adiponectin exerts a protective effect on cardiovascular function. Serum adiponectin concentration significantly increased in some (43, 63), but not all studies on LCD effects (40, 57, 62). Interestingly, despite no effect on adiponectin level, an eight-week LCD with 15 – 30% energy deficit in 41 women with obesity (BMI 38 ± 6.5 kg/m^2) decreased serum levels of tumor necrosis factor-α (TNF-α), interleukin 6 (IL-6), and leptin (40). Moreover, it improved biomarkers of endothelial cell function, such as nitric oxide (NO) and sE-selectin, in a clear relationship with the magnitude of weight reduction. Remarkably, the reduction in proinflammatory TNF-α concentration occurred equally in patients who lost more or less weight after caloric restriction, independently of weight loss (40).

However, in some studies, LCD did not affect the risk factors of CVD (*Table 2B*). No significant changes in plasma levels of total cholesterol, LDL cholesterol, or TG were found in premenopausal women with overweight or obesity after a short, four-week hypocaloric diet (61). There were also no significant changes in plasma lipid levels after interventions of longer duration, such as a three-month LCD in obese subjects (except for a 17% decrease in fasting TG) (54) or a six-month LCD in postmenopausal women with obesity (except for a significant decrease in total cholesterol) (20).

An important study by Ghachem *et al.* (23) examined the effect of LCD-induced weight loss on metabolic syndrome (MetS) markers. Inactive postmenopausal women with obesity (aged 49 – 70; BMI 32.4 ± 4.6 kg/m^2) with or without MetS were subjected to a six-month LCD aimed at reducing body weight by 10%. Despite improvements in body composition in both groups (in the form of decreased abdominal visceral fat, total fat mass, and trunk fat mass), TG levels and the TG:HDL-cholesterol ratio decreased significantly more in the MetS than the non-MetS group (23). Total, LDL, and HDL cholesterol, as well as resting blood pressure, were unaffected by the dietary intervention in either studied group. Importantly, after weight loss, metabolic syndrome was resolved in 12 out of 20 participants who had MetS at baseline, whereas 6 out of 53 without MetS at baseline developed metabolic syndrome after the intervention (23). The results of this study suggest that, in some individuals LCDs, do not always provide health benefits, despite the reduction in body mass; they can in fact cause the deterioration of some parameters characteristic of healthy metabolic status.

To conclude, even though LCDs have been advocated as improving cardiovascular health in individuals with overweight or obesity, the effects depend on the extent of weight loss, as well as the degree of obesity and the coexisting disorders. The interindividual variability suggests the involvement of some additional factors, possibly including genetic predisposition, though this remains to be tested. Moreover, results of some studies indicate that LCDs cause temporary decrease in the serum concentration of factors influencing oxidative stress as well as reduction of levels of cytokines promoting proinflammatory status which is known to be an important factor of CVD development and course.

The effects of low-calorie diets on liver, kidney and brain functions

Given the central role of the liver in energy metabolism, several researchers have examined parameters indicative of liver function in individuals with overweight or obesity undergoing LCD interventions. The serum activity of enzymes such as aspartate transaminase (AST), alanine transaminase (ALT), and gamma glutamyl transpeptidase (GGT) released from the liver under stress conditions may point to liver damage. After three months of LCD, the activities of these three enzymes were all reduced in middle-aged men with obesity (30). In an earlier study, ALT activity did not change, but liver lipid content (determined by magnetic resonance spectroscopy) and alkaline phosphatase activity decreased in overweight individuals (BMI 24.7 – 31.3 kg/m2) after LCD with a weight maintenance phase for up to six months (64). In a large study involving individuals with morbid obesity subjected to an intensive, three-phase weight-loss intervention for two years, ALT activity declined by 10.5% or more with at least modest weight loss; the same group of patients showed a reduction in serum lactate dehydrogenase activity, indicative of improved muscle integrity (29).

Interestingly, microarray analysis of hepatic gene expression following an eight-week low-fat LCD in middle-aged women with overweight or obesity (n = 12; the liver biopsies were obtained during surgery for gallstone disease) showed a global decrease in gene expression within the major functional groups, including cell signaling, cell structure, regulation of transcription, and protein and lipid metabolism (53).

Obesity may negatively affect renal function, leading to obesity-related glomerulopathy (65). A meta-analysis of thirteen interventions in adults with overweight or obesity showed that weight loss can alleviate proteinuria and microalbuminuria (66). Moreover, in patients with T2D and abdominal obesity, a reduction in dietary calorie intake by 25% for six months ameliorated glomerular hyperfiltration (50). The nephroprotective effect of a decrease in BMI in overweight males (*i.e.*, an association of weight loss with increased estimated glomerular filtration rate, eGFR) was confirmed in an observational epidemiological study in 8447 subjects followed up for three years (67). However, the study also suggested that weight loss may aggravate eGFR in males with high normal BMIs (22 kg/m^2 ≤ BMI < 25 kg/m^2) (67). Moreover, there are concerns that weight-loss diets and low-carbohydrate high-protein diets in particular, may negatively affect kidney function, causing chronic kidney disease (67). To address this problem, Friedman *et al.* (68) conducted a study of 307 obese individuals who were prescribed either a low-carbohydrate high-protein diet or a low-fat LCD for 24 months. While the study did not assess the actual caloric intake, weight loss was similar in both intervention groups. Compared with the low-fat LCD, the low-carbohydrate high-protein diet increased creatinine clearance (20.8 ml/min), 24-hour urinary volume (438 ml), calcium excretion (35.7%), and serum urea nitrogen (9.0%), most evidently after twelve months of dieting (68). The authors deemed these differences to be clinically minor. Importantly, neither intervention led to any changes in bone mineral density,

clinical presentations of new kidney stones, or altered electrolyte levels, while urinary albumin excretion tended to decrease, regardless of the type of diet (68). Thus, both types of LCD were concluded to be safe in healthy individuals with obesity.

Findings from animal studies suggest that calorie restriction can prevent or diminish aging-associated cognitive decline (69). Despite the multitude of animal studies, we have identified only one trial in humans directly pertaining to this issue. Martin *et al.* (70) conducted cognitive tests in overweight adults before and after weight-loss interventions lasting six months: 25% calorie restriction, 12.5% CR with structured exercise, or a 890 kcal/day LCD until 15% weight loss. The authors found no consistent pattern of changes in verbal memory, visual memory, or deficits in attention and concentration. Although the result might have been influenced by the small sample size (n = 12 per group), the results of statistical analysis suggested that the impact of CR on cognitive function may not be clinically meaningful (70).

In summary, LCDs appear to be beneficial or neutral for the liver and kidney functions in people with overweight or obesity, but they may have no impact on cognitive functions.

The effects of low-calorie diets on comorbidities aggravated by obesity

While obesity by itself negatively affects health, it can further aggravate certain diseases or disorders. A number of studies have thus investigated the effects of LCD-induced weight loss on particular diseases in patients with overweight or obesity.

Excess body fat has been associated with atherosclerotic diseases. Oshakbayev *et al.* (71) studied the effectiveness of LCD and exercise (*Table 2*) in patients with overweight or obesity and various manifestations of atherosclerotic disease. Indeed, this therapy resulted in a 7 – 20% reduction in initial body weight, decreasing fat mass while preserving bone mineral density and increasing lean body mass. Importantly, the weight-loss program decreased the symptoms of atherosclerosis to an extent that allowed for dose reduction or total abolition of symptomatic drugs (71).

Obesity has been linked to increased risk of colorectal cancer (CRC), possibly through chronic colonic inflammation. Pendyala *et al.* (72) examined the effects of diet (about 782 kcal/day until a weight loss of ≥ 8% was obtained) in premenopausal women with obesity (BMI 35 ± 3.5 kg/m^2) on inflammation in rectosigmoid mucosal biopsies. The weight loss led to significant reductions in the concentrations of inflammatory cytokines and down-regulation of proinflammatory cytokine and chemokine pathways, prostaglandin metabolism, and cancer-related gene pathways. The authors concluded that diet-induced weight loss improved the obesity-associated inflammatory state in the colorectal mucosa, and thereby might lower risk of CRC (72).

Increased adiposity and weight gain are established risk factors for psoriasis, a chronic inflammatory skin disease (42). Jensen *et al.* (42) investigated the effects of weight loss through LCD (800 – 1000 kcal/day for eight weeks, followed by 1200 kcal/day or normal healthy foods for eight weeks) on both the severity of psoriasis and the cardiovascular risk profile of patients with psoriasis and obesity (mean BMI 34.7 kg/m^2). A loss of about 11% body weight led to reductions in several cardiovascular risk factors (diastolic blood pressure, resting heart rate, total cholesterol, VLDL cholesterol, TG, glucose, glycated hemoglobin, and the concentration of tissue plasminogen activator inhibitor - a plasma marker associated with endothelial function). However, weight loss did not improve microvascular endothelial function as assessed by peripheral arterial tonometry, nor did it affect the levels of adhesion molecules as markers of endothelial dysfunction. With regard to the severity of psoriasis, the authors noted that the area covered by psoriasis and the severity index improved more in the intervention group than in the control patients with psoriasis, though without reaching statistical significance (P = 0.06) (42).

Obesity is becoming more common in patients with chronic obstructive pulmonary disease (COPD). McDonald *et al.* (44) investigated the effects of weight loss through a twelve-week LCD with exercise in patients with COPD and obesity (BMI 36.1 ± 4.5 kg/m^2). A modest weight loss of 6.2% was associated with improved clinical outcomes in Saint George Respiratory Questionnaire (SGRQ) results and in six-minute walk distance as a measure of exercise capacity, as well as the BMI, obstruction, dyspnea, and exercise (BODE) index (44).

Fat deposition around the pharynx, in the thorax, and in the abdomen contribute to the occurrence of obstructive sleep apnea syndrome (OSAS) (73). Besides causing sleep disorders and daytime sleepiness, OSAS is a risk factor for CVD and insulin resistance (73). Patients with OSAS and obesity (BMI 40 ± 5 kg/m^2) were subjected to an eight-week LCD with subsequent support of lifestyle changes for two years. Even though the intervention showed limited success in reducing the apnea-hypopnea index (AHI), there were significant improvements in weight, oxygen desaturation index, arousal index, and subjective symptoms (73).

Another study analyzed the effect of weight loss through LCD on live birth rates in women scheduled for *in vitro* fertilization

Table 3. Intermittent fasting (IF) schedules.

IF type	Characteristics	References
ADF (alternate day fasting)	1 day *ad libitum* feeding/1 day complete fasting	(78)
mADF (modified ADF)	1 day *ad libitum* feeding/1 day very low calorie diet (*e.g.* 25% caloric intake)	(22, 79-83, 94, 98-100)
2/5	Fasting on 2 days per week/5 days *ad libitum* feeding (*i.e.* normal)	(84, 86, 87)
1/6	Fasting 1 day per week/6 days *ad libitum* feeding	(85)
TRF (time-restricted feeding)	Each day fasting for 12 – 20 hours (as a prolongation of the overnight fast) and a "feeding window" of 4 – 12 hours	(75, 88-90)

(IVF) (74). Twelve weeks of liquid formula diet of 880 kcal/day followed by a weight stabilization period did not significantly affect the live birth rate, the miscarriage rate, or the dose of gonadotropin used for IVF stimulation. On the other hand, there were significantly more spontaneous pregnancies in the weight reduction group (16/152) than in the IVF-only group (4/153) (74).

To summarize, weight loss through LCDs causes some improvements of the indices of atherosclerotic disease and COPD, reduction of risk factors for CRC, but has limited impact on fertility in women, the manifestations of psoriasis, or OSAS.

EFFECTS OF INTERMITTENT FASTING

Although cyclic fasting was described in antiquity in the Bible and Quran (75), intermittent fasting (IF) has recently gained popularity as a means of reducing body weight and improving metabolic status. An important feature of IF schedules is that all meals are consumed during a strictly defined window of time and followed by fasting. Such fasting is achieved by ingesting little to no food or caloric drinks for periods that typically range from 16 to 24 hours, *e.g.*, as the prolongation of the physiological overnight fast (76). Thus, the IF method does not describe which nutrient types are allowed, assuming only that the person eats a balanced diet and conforms to the rules of healthy eating. Because the time span of the "feeding window" is short, the overall calorie intake is lower than if the food intake time were unlimited (77).

Different regimens of IF have been employed in daily practice and clinical trials (*Table 3*). The most popular is alternate day fasting (ADF), which involves "fast days" alternating with "feed days" (*ad libitum* food consumption), typically carried out for weeks to months (78). During modified ADF (mADF) a small number of calories (*e.g.*, 25% of energy requirements) is allowed on "fast days" (18, 79-83). There are also 1/6 and 2/5 schedules (called periodic fasting, cyclic fasting, or intermittent calorie restriction) that involve fasting for one or two days a week, respectively (84-87). Another IF regimen is time-restricted feeding (TRF), which allows food consumption only within a defined window of time (3 – 12 hours), and fasting for the remainder of the day (75, 88 – 90). Ramadan fasting is an example of TRF practiced by Muslims during the ninth month of the Islamic lunar calendar. During Ramadan, Muslims refrain from eating, drinking, smoking, and taking medication during the day, with no restriction on food or fluids from sunset until dawn (91). However, this form of religious fasting does not conform to the circadian rhythms in humans.

IF interventions induce a metabolic shift that has the potential to positively alter body composition (reviewed in (92)). This switch represents a shift from preferential lipid synthesis and fat storage to the mobilization of fat. It typically occurs in the third phase of fasting (*i.e.*, 12 – 36 hours after the last meal) when glycogen in the hepatocytes (though not in muscles) becomes depleted. Around that time, accelerated lipolysis in adipose tissue produces increased plasma levels of FFAs, which contribute to the increased synthesis of fatty acid-derived ketones in the liver, kidney, astrocytes, and enterocytes (93). IF regimens are a potential method of treatment for obesity and related metabolic conditions, including T2D and metabolic syndrome.

Table 4 presents the results of recent randomized controlled trials and other human studies on the effects of IF regimens, with the focus on patients with overweight or obesity, with or without T2D. There is great diversity of IF regimens, whose outcomes need to be considered separately. The most important results are discussed in the following sections.

Weight loss and body composition

Studies of IF vary considerably with regard to the fasting regimen employed and its duration, yet most of them show reductions in body weight and changes in body composition.

Table 4. The effects of intermittent fasting interventions in selected trials.

Reference, Year, country	Type of IF, daily caloric intake, diet composition and duration	Patients' characteristics	Effects of intervention
Alternate day fasting and modified alternate day fasting			
Varady K., *et al*. (79) 2009, USA	1 day fasting (DCI reduced by 75%; meals 12:00 – 14:00) / 1 day *ad libitum* feeding; 8 weeks	N = 16 (12 F, 4 M) BMI 33.8 ± 1 46.0 ± 2.4 years	↓ BW by 5.6 kg, ↓ % body fat by 2.9%, ↓ FM by 5.4 kg, ↓ Ch by 37, ↓ TG by 37, ↓ LDL by 30, ↓ SBP by 7 mm Hg, ↓ heart rate by 4 bpm
Bhutani S., *et al*. (80) 2010, USA	1 day fasting (25% energy needs; meals 12:00 – 14:00) / 1 day *ad libitum* feeding; 8 weeks	N = 16 (12 F, 4 M) BMI 35 ± 1 for F, BMI 34 ± 2 for M 45 ± 3 years for F, 46 ± 5 years for M	↓ BW by 5.7 kg, ↓ BMI by 2.3, ↓ WC by 4 cm, ↓ FM by 5.4 kg, ↓ Ch by 37, ↓ TG by 48, ↓ LDL by 34, ↑ adiponectin by 30%, ↓ leptin by 21%, ↓ resistin by 23%
Bhutani S., *et al*. (81) 2010, USA	1 day fasting (25% energy needs; meals 12:00 – 14:00) / 1 day *ad libitum* feeding; moderate intensity exercise program 3×week; 12 weeks	N = 18 women BMI 35 ± 1 45 ± 5 years	↓ BW by 6 kg, ↓ BMI by 2, ↓ WC by 8 cm, ↓ FM by 5 kg, ↓ LDL by 16, ↑ HDL by 9, ↑ LDL particle size by 4Å, ↓ % small HDL particles by 4%

Bhutani S., *et al.* (81) 2010, USA	1 day fasting (25% energy needs; meals 12:00 – 14:00) / 1 day *ad libitum* feeding; no exercise; 12 weeks	N = 25 (24 F, 1 M) BMI 35 ± 1 42 ± 2 years	↓ BW by 3 kg, ↓ BMI by 1, ↓ WC by 5 cm, ↓ FM by 2 kg, ↑ LDL particle size by 5Å, ↓ SBP by 4 and DBP by 2 mm Hg
Eshghinia S., *et al.* (99) 2013, Iran	fasting days (25 – 30% DCI) alternating with 1700 – 1800 kcal/day diet; 1 day per week *ad libitum* feeding; 6 weeks	N = 15 women BMI 33.2 ± 5 33.5 ± 5.9 years	↓ BW by 6 kg, ↓ BMI by 2.7, ↓ WC by 5 cm, ↓ % body fat by 2.8%, ↓ SBP by 9.7 and DBP by 8.4 mm Hg
Varady K., *et al.* (22) 2013, USA	1 day fasting (DCI reduced by 75%; meals 12:00 – 14:00) / 1 day *ad libitum* feeding; 12 weeks	N = 15 (10 F, 4 M) BMI 26.0 ± 1 47 ± 3.0 years	↓ BW by 5.2 kg, ↓ FM by 3.6 kg, ↓ Ch by 26, ↓ TG by 22, ↓ LDL by 19, ↑ LDL particle size by 4 Å, ↑ adiponectin by 0.7 µg/ml[#], ↓ leptin by 10 ng/ml, ↓ CRP by 1 mg/L[#], ↓ SBP by 7 and DBP by 6 mmHg
Klempel M., *et al.* (100) 2013, USA	ADF with a high-fat diet (45% fat); 1 day fasting (DCI reduced by 75%; meals 12:00 – 14:00) / 1 day *ad libitum* feeding; 7 weeks	N = 15 BMI 35.3 ± 0.7 42.4 ± 3.0 years	↓ BW by 5kg, ↓ WC by 7.2 cm, ↓ FM by 5.4 kg, ↑ FFM by 1.2 kg, ↓ Ch by 13%, ↓ TG by 13%, ↓ LDL by 17%, ↓ HDL by 1% (only relative values provided)
Klempel M., *et al.* (100) 2013, USA	ADF with a low-fat diet (25% fat); 1 day fasting (DCI reduced by 75%; meals 12:00–14:00) / 1 day *ad libium* feeding; 7 weeks	N = 17 BMI 35.5 ± 0.7 43.2 ± 2.3 years	↓ BW by 3 kg, ↓ WC by 7.3 cm, ↓ FM by 4.2 kg, ↑ FFM by 0.5 kg, ↓ Ch by 16%, ↓ TG by 14%, ↓ LDL by 25% (only relative values provided)
Hoddy K., *et al.* (98) 2014, USA	ADF with a meal (25% DCI) consumed at lunch (12:00 – 14:00) on fasting days, alternating with *ad libitum* feeding days; 8 weeks	N = 20 (17 F, 3 M) BMI 35 ± 1 45 ± 3 years	↓ BW by 3.5 kg, ↓ FM by 1.7 kg, ↓ visceral FM by 0.07 kg, ↓ FFM by 1.2 kg, ↑ LDL particle size by 1.3Å, ↓ heart rate by 7 bpm
Hoddy K., *et al.* (98) 2014, USA	ADF with a meal (25% DCI) consumed at dinner (18:00 – 20:00) on fasting days, alternating with *ad libitum* feeding days; 8 weeks	N = 19 (15 F, 4 M) BMI 34 ± 1 45 ± 3 years	↓ BW by 4.1 kg, ↓ FM by 2.5 kg, ↓ visceral FM by 0.13 kg, ↓ FFM by 1.3 kg, ↑ LDL particle size by 1.3Å, ↓ RMR by 198 kcal/day
Hoddy K., *et al.* (98) 2014, USA	ADF with 3 mini meals consumed at breakfast, lunch and dinner on fasting days, alternating with *ad libitum* feeding days; 8 weeks	N = 20 (18 F, 2 M) BMI 34 ± 1 46 ± 2 years	↓ BW by 4 kg, ↓ FM by 2.1 kg, ↓ visceral FM by 0.13 kg, ↓ FFM by 1.8 kg, ↑ LDL particle size by 1.3Å, ↓ SBP by 6 mmHg
Varady K., *et al.* (82) 2015, Canada	ADF with low-fat (25%) diet: 1 day fasting (25% of energy needs) / 1 day *ad libitum* feeding; 8 weeks	N = 15 BMI 34.4 ± 0.8 43.2 ± 2.3 years	↓ BW by 4.3 kg, ↓ BMI by 1.7, ↓ WC by 8 cm, ↓ FM by 1.5 kg, ↓ Ch by 0.8, ↓ TG by 0.2, ↓ LDL by 0.7 (all values in mmol/L), ↓ total FFAs by 98.62 µmol/L
Varady K., *et al.* (82) 2015, Canada	ADF with high-fat (45%) diet: 1 day fasting (25% of energy needs) / 1 day *ad libitum* feeding; 8 weeks	N = 14 BMI 34.6 ± 0.7 42.4 ± 3 years	↓ BW by 4.7 kg, ↓ BMI by 1.8, ↓ WC by 7.2 cm, ↓ FM by 2.9 kg, ↓ Ch by 0.7, ↓ TG by 0.1, ↓ LDL by 0.5 (all values in mmol/L)

			↓ total FFAs by 98.62 µmol/L
Varady K., *et al.* (82) 2015, Canada	ADF with high-fat (45%) diet: 1 day fasting (25% of energy needs) / 1 day *ad libitum* feeding; 8 weeks	N = 14 BMI 34.6 ± 0.7 42.4 ± 3 years	↓ BW by 4.7 kg, ↓ BMI by 1.8, ↓ WC by 7.2 cm, ↓ FM by 2.9 kg, ↓ Ch by 0.7, ↓ TG by 0.1, ↓ LDL by 0.5 (all values in mmol/L) ↓ total FFAs by 53.93 µmol/L
Catenacci V., *et al.* (78) 2016, USA	1 day fasting / 1 day feeding (5 – 7 pre-prepared meals, 200 kcal each); 8 weeks	N = 13 (10 F, 3 M) BMI 35.8 ± 3.7 39.6 ± 9.5 years	↓ BW by 8.2 kg, ↓ BMI by 3.2, ↓ FM by 3.7 kg, ↓ trunk FM by 2.4 kg, ↓ LBM by 3.2 kg, ↑ % LBM by 0.9%, ↓ Ch by 31.8, ↓ TG by 25, ↓ LDL by 22.6, ↓ HDL by 4.2 ↓ glucose by 6.0 mg/dl, ↓ ghrelin by 124.4 pg/ml, ↓ leptin by 13.9 ng/ml, ↓ unadjusted RMR by 100 kcal/day (no change for adjusted RMR)
Barnosky A., *et al.* (94) 2017, USA	1 day fasting (DCI reduced by 75%; meals 12:00 – 14:00) / 1 day feeding (125% DCI); 6 months	N = 21 (19 F, 2 M) BMI 34 ± 1 44 ± 2 years	↓ BW by 7.8% (7.2 kg*), ↓ FM by 17% (6.3 kg*), no changes in bone mineral content or density or markers of bone metabolism
Trepanowski J., *et al.* (83) 2017, USA	1 day fasting (25% DCI, pre-prepared meals 12:00 – 14:00) / 1 day feeding (125% DCI); 6 months	N = 34 (30 F, 4 M) BMI 34 ± 4 44 ± 10 years	↓ BW by 6.8% (6.46 kg*), ↓ FM by 4.2 kg, ↓ visceral FM by 0.4 kg, ↓ LBM by 1.5 kg, ↑ HDL by 6.2 mg/dL
1/6 & 2/5 Schedules (cyclic or periodic fasting)			
Klempel M., *et al.* (85) 2012, USA	DCI reduced by 30%, supplied as liquid-based diet combined with 1-day fasting per week; 8 weeks	N = 28 women BMI 35 ± 1 47 ± 2 years	↓ BW by 3.9 kg, ↓ FM by 2.8 kg, ↓ visceral FM by 0.7 kg, ↓ Ch by 19% (35*), ↓ TG by 17% (12*), ↓ LDL by 20% (22*), ↓ glucose by 4 mg/dl, ↓ insulin by 3 uIU/ml, ↓ adiponectin by 2.4 µg/ml, ↓ leptin by 10 ng/ml, ↓ heart rate by 3 bpm
Klempel M., *et al.* (85) 2012, USA	DCI reduced by 30%, supplied as food-based diet combined with 1-day fasting per week; 8 weeks	N = 26 women BMI 35 ± 1 48 ± 2 years	↓ BW by 2.5 kg, ↓ FM by 1.9 kg, ↓ visceral FM by 0.3 kg, ↓ FFM by 0.5 kg, ↓ Ch by 8% (15*), ↓ LDL by 7% (8*), ↓ adiponectin by 2.5 µg/ml, ↓ leptin by 9 ng/ml
Harvie M., *et al.* (86) 2013, UK	intermittent energy and carbohydrate restriction (IECR): DCI reduced by 70% on 2 consecutive days (40 g carbohydrate) + Mediterranean-type diet for 5 other days; 3 months	37 women BMI 29.6 ± 4.1 45.6 ± 8.3 years	↓ BW by 5 kg, ↓ FM by 3.7 kg, ↑ plasma β-hydroxybutyrate by 31% after fasting ↓ HOMA-IR by 0.4 ↓ insulin by 8.4 pmol/l
Harvie M., *et al.* (86) 2013, UK	IECR with *ad libitum* protein and fat: DCI reduced by 70% on 2 consecutive days + Mediterranean-type diet for 5 other days; 3 months	38 women BMI 31 ± 5.7 48.6 ± 7.3 years	↓ BW by 4.8 kg, ↓ FM by 3.8 kg, ↑ plasma β-hydroxybutyrate by 78% after fasting
Carter S., *et al.* (84) 2016, Australia	2 days fasting (DCI 400 – 600 kcal/day) / 5 days *ad libitum* feeding; DC: 45% carbohydrates, 25% fat, 30% proteins;	N = 31 (17 F, 14 M) BMI 35 ± 4.8 61 ± 7.5 years T2D patients with baseline HbA1c	↓ BW by 8 kg, ↓ FM by 3.8 kg, ↓ % body fat by 1.7%, ↓ abdominal FM by 0.6 kg, ↓ android FM by 0.6 kg,

	12 weeks	7.2 ± 1.3%	↓ FFM by 2.2 kg, ↓ android FFM by 0.5 kg, ↓ HbA1c by 0.7%
Sundfor T., *et al.* (87) 2018, Norway	2 non-consecutive days a week: 400 (F)/600 (M) kcal / 5 days of *ad libitum* feeding; 6 months	N = 54 (26 F, 28 M) BMI 35.1 ± 3.9 49.9 ± 10.1 years	↓ BW by 9.1 kg, ↓ BMI by 3.0, ↓ WC by 8 cm, ↓ HC by 6.8 cm, ↓ TG by 0.31, ↑ HDL by 0.13 mmol/l, ↓ HbA1c by 0.3%, ↓ DBP by 3 mmHg, ↓ heart rate by 2.7 bpm, ↓ RMR by 93 kcal
Time-restricted feeding			
Moro T., *et al.* (75) 2016, USA	Fasting for 16 h / 8 h feeding (meals at 8:00, 16:00 and 20:00; 2826 ± 412 kcal/day); DC: 53% carbohydrates, 25% fat, 22% proteins; with standardized resistance training program; 8 weeks	N = 34, men BW 83.9 ± 12.8 kg non-obese, resistance-trained (no BMI given), 29.94 ± 4.07 years,	no change in body mass ↓ FM 1.62 kg, ↓ TG by 8.55, ↑ HDL by 3.95, ↓ glucose by 10.72 mg/dl, ↓ insulin by 1.01 mU/ml, ↑ adiponectin by 2.1 µg/ml, ↓ leptin by 0.3 ng/ml, ↓ IL-1β by 0.12 ng/L, ↓ IL-6 by 0.25 ng/L, ↓ IGF-1 by 28 ng/ml, ↓ testosterone by 4.4 nmol/L, ↓ triiodothyronine by 8.9 ng/dL, ↓ respiratory ratio by 0.02
Byrne N., *et al.* (88) 2018, Australia	MATADOR study: intermittent energy restriction by 8 × 2-week blocks of ER (DCI 67% of requirements); 16 weeks	N = 19 men BMI 34.1 ± 4.0 39.5 ± 8.4 years	↓ BW by 13.4 kg, ↓ FM by 11.7 kg, ↓ FFM by 1.8 kg, ↓ REE adjusted for FFM and FM by 75 kcal/day
Gabel K., *et al.* (90) 2018, USA	*ad libitum* feeding 10:00 – 18:00, fasting 18:00 – 10:00; 12 weeks	N = 23 (20 F, 3 M) BMI 35 ± 1.0 50 ± 2 years	↓ BW by 3 kg, ↓ BMI by 1, ↓ SBP by 7 mm Hg
Sutton E., *et al.* (89) 2018, USA	early-TRF: pre-prepared meals (100% energy requirements) consumed within 6 h before 15:00 (control with matched food intake: 12 h feeding period); 5 weeks; washout period 7 weeks, then switch to the other schedule	N = 8, men BMI 32.2 ± 4.4 56 ± 9 years Prediabetes: fasting glucose: 10 ± 9 mg/dL; fasting insulin: 25.1 ± 14.5 mU/L; 2-h glucose tolerance: 154 ± 17 mg/dL	no change in body mass, ↑ fasting TG by 57 mg/dl, ↓ insulin by 3.4 mU/L, ↑ insulinogenic index by 14 U/mg, ↓ OGTT 3-hr incremental AUC ratio (insulin resistance measure) by 36 U/mg, ↓ plasma 8-isoprostane by 11 pg/mL (14%), ↓ SBP by 11 and DBP by 10 mm Hg
Ramadan "intermittent fasting"			
Aksungar F., *et al.* (97) 2017, Turkey	12 months of CR, one month of IF (Ramadan) and 11 months of CR again; 24 months	N = 23 women BMI 34.2 ± 2.2 36 ± 3.12 years	↓ BW by 1.25 ± 0.372 kg monthly during CR, ↓ BW by 0.47 ± 0.15 kg during Ramadan, ↓ BMI by 8.13 (24-month versus baseline) The below listed changes resulted from CR but not Ramadan: ↓ glucose by 33 mg/dl, ↓ HbA1c by 1.61%, ↓ HOMA-IR by 58.7%, ↓ insulin by 15.6 µU/ml, ↓ IGF-1 by 24 ng/ml (24-month versus baseline)

Selected studies have been ordered chronologically, with the name of the first author indicated. The presented effects refer only to the statistically significant results of weight-loss phases of the interventions based on intermittent fasting regimens. BMI is expressed as mean ± standard deviation (kg/m^2); cholesterol, LDL, and TG concentrations are expressed in mg/dl or in other indicated units. *Symbols:* $^{\#}$relative to the control group; *calculated on the basis of the reported % change. *Abbreviations* as in the legend to *Table 2*, and: ADF, alternate day fasting; AUC, area under curve; CR, calorie restriction; FFA, free fatty acids; IECR, intermittent energy and carbohydrate restriction regimens; IECR + PF, IECR regimen with *ad libitum* protein and fat; IGF-1, insulin-like growth factor 1; OGTT, oral glucose tolerance test; REE, resting energy expediture; TRF, time-restricted feeding.

However, body weight loss is not always necessary to obtain positive metabolic outcomes from IF interventions (89).

The effects of modified ADF regimens have been examined in normal-weight or mildly overweight individuals (BMI 26 ± 1 kg/m^2; twelve weeks (22)) or in subjects with obesity (BMI 33.8 ± 1 kg/m^2; eight weeks (79); BMI 34 ± 1 kg/m^2; six months (94)). The studies showed decreases in body weight (by 5.8%, 6.5%, and 7.8%, after eight-week, twelve-week, and six-month mADF, respectively) and in fat mass (by 5.4 kg, approximately 3.6 kg, and approximately 6.3 kg, respectively), generally greater with longer duration of mADF. Importantly, FFM (22, 79, 94) and bone mineral content (94) did not change after the interventions.

The 2/5 IF schedule can also result in favorable changes in body weight and composition. For example, Sundfor *et al.* (87) reported that a six-month intervention in subjects with obesity led to a weight loss of 8.0 kg and a 6.9% decrease in waist circumference. In patients with T2D and obesity, a 10% decline in body mass was associated with a 4% reduction in FFM after twelve weeks of 2/5 IF (84).

Time-restricted feeding may produce lower body-weight losses than other forms of IF. For example, twelve weeks of TRF (with an eight-hour feeding window) in people with obesity resulted in weight loss of 2.6% relative to a matched control group, with no significant change in fat mass (90). Moreover, two studies analyzing the effects of eight-week TRF in conjunction with resistance training in nonobese men showed that the intervention produced either a decrease in FM by 16.4% (with an eight-hour feeding window) (75), or no alterations in body weight and composition (with a four-hour feeding window) (95).

Some clinical trials have used dietary regimens that are combinations of LCD and IF to obtain weight loss in obese subjects. In a study of women with obesity (BMI 35 ± 1 kg/m^2), Klempel *et al.* (85) compared the effects of an eight-week liquid-based (IFCR-L) versus food-based diet (IFCR-F) involving a 30% reduction in baseline energy requirements, combined with one day of fasting per week, demonstrating that IFCR-L was superior with respect to weight loss (4.1% versus 2.6% for IFCR-F) (85). In the MATADOR study in middle-aged men with obesity (mean BMI 34.5 kg/m^2), intermittent energy restriction (ER; n = 24) realized as 8 two-week periods of energy restriction (involving a 33% reduction in the energy required for weight maintenance) alternating with two-week energy balance periods was compared with continuous ER by 33% of individual weight maintenance energy requirements (88). At the end of the intervention period, weight loss and FM loss were significantly greater for intermittent ER than for continuous ER. Importantly, these changes were accompanied by significantly smaller reduction in resting energy expenditure (adjusted for changes in body composition) in subjects undergoing intermittent ER (88). Likewise, another study, utilizing zero-calorie ADF in obese subjects, confirmed that IF did not result in reductions in resting metabolic rate (78). This can contribute to improved postintervention weight maintenance, since a decrease in resting metabolic rate has been implicated in weight regain (39).

Several comparisons of the outcomes of alternate day fasting versus low-calorie diets (78, 83, 94), or the 2/5 IF schedule versus LCD (84, 87) in participants with overweight or obesity have demonstrated that similar changes in body weight and composition are achieved with these methods. However, a comparative study on the effects of three-month IF with the 2/5 schedule (calorie intake reduced by 30% on two nonconsecutive days) with LCD (calorie intake reduced by 25% every day) showed higher reductions in fat mass in the IF group, despite similar declines in body weight (86). Likewise, a meta-analysis of trials comparing various IF and VLCD interventions suggested that IF results in higher reductions in FM and lower decline in LBM (96). On the other hand, calorie restriction resulted in substantially higher average monthly weight loss than did Ramadan fasting (1250 ± 372 g versus 473 ± 146 g, respectively) in an intervention in non-diabetic women with obesity (mean BMI 34 kg/m^2) combining twelve months of CR (recommended reduction in caloric intake by 40%) followed by a month of Ramadan fasting, and eleven months of CR again (97).

Thus, the extent of weight loss achieved through IF varies depending on the particular regimen applied. Moreover, IF regimens might promote greater reductions of fat mass and possibly smaller post-intervention weight regain than low-calorie diets.

The effects of intermittent fasting on cardiovascular system

There is general agreement that intermittent fasting reduces the risk of CVD due to improvements in plasma lipid profile, mainly through impact on the metabolism of total cholesterol, LDL, and HDL cholesterol fractions, as well as triglyceride turnover (86, 87).

A number of clinical outcome studies on fasting in humans have shown an association with a lower prevalence of coronary artery disease risk factors. Some (79, 82) though not all (98, 99)) studies have shown that eight-week ADF regimens in adults with obesity lead to reductions in total cholesterol and LDL cholesterol levels in blood serum. Moreover, twelve-week ADF in normal weight or mildly overweight subjects (BMI 26 ± 1 kg/m^2) leads to reductions in total cholesterol and LDL cholesterol concentrations by 12.9% and 15.3%, respectively (22). Furthermore, the ADF interventions resulted in decreased TG levels (by 17.5 – 20.2%) (22, 78, 79), increased LDL particle size (81, 98), and variable effects on HDL cholesterol concentrations (83). These data show that the ADF intervention may improve plasma lipid profiles in both obese and nonobese subjects, exerting cardioprotective effects. Importantly, combining ADF with endurance exercise for twelve weeks in people with obesity produced better cardioprotective results than either ADF or exercise alone (81).

Other types of IF interventions also showed positive effects with respect to plasma lipids. For instance, an intervention combining ADF with low-fat (ADF + LF) or high-fat (ADF + HF) diets in nondiabetic subjects with obesity (BMI 35.5 ± 0.7 kg/m^2), showed decreases in total cholesterol, LDL cholesterol, and TG levels, which were greater in the ADF + LF group (100). An eight-week study comparing the food-based IFCR-F and the liquid IFCR-L diet in women with obesity demonstrated that IFCR-L had a stronger effect on plasma lipid profile than IFCR-F (85).

Another risk factor of CVD is high blood pressure, which can lead to hypertension if it persists for a long time (29). Some interventions encompassing ADF for 6 – 12 weeks in people with overweight or obesity led to reductions in systolic blood pressure (BP) (79, 98) or in both systolic and diastolic BP (22, 81, 99). Likewise, in subjects with obesity (BMI 35.1 ± 3.9 kg/m^2), both intermittent ER in the 2/5 schedule and continuous ER for six months led to modest decreases in systolic BP (by 1.5% and 2.8%, respectively, for intermittent and continuous ER) and diastolic BP (by 3.4% in both groups) (87). A rigorously controlled trial on early time-restricted feeding (eTRF; all meals, providing 100% of daily energy requirements, consumed within six hours in the morning) in men with prediabetes (BMI 32.2 ± 4.4 kg/m^2) showed dramatically lowered systolic and diastolic BP after a five-week intervention, despite the lack of weight loss (89). At the same time, the resting heart rate, TG, and total cholesterol levels increased or tended to increase, while LDL and HDL cholesterol levels were unaffected (89). The IFCR-F and IFCR-L dietary regimens in women with obesity reduced systolic BP to a similar extent (by 1.7%), whereas diastolic BP decreased only after the IFCR-L diet (by 4.8%) (85).

Taking together, intermittent fasting reduces the risk of CVD due to improvements in plasma lipid profile, decreasing heart

rate and blood pressure. Results of the studies vary, giving positive or neutral effects, probably depending on the intervention design and the subjects' characteristics. In some studies, minimal effect on blood pressure was most likely due to the normotensive status of the subjects at the baseline (< 120 mm Hg systolic and < 80 mm Hg diastolic) (98).

The effects of intermittent fasting on glycemic control

Insulin is secreted in variable amounts and frequencies, depending on blood glucose levels. During fasting, pulsatile insulin release persists, but the amount of hormone released is less due to the lower glycemia levels (101). The effects of IF on glucose metabolism depend on the fasting schedule and the characteristics of the subject. As discussed below, the results of many studies suggest the effectiveness of IF in reducing risk factors for diabetes or its complications.

Most randomized control trials with various IF regimens have examined this dietary practice in nondiabetic humans. ADF for eight weeks caused a decrease in serum fasting glucose level by 6.8% and insulin concentration by 22.6% in adults with obesity (35.8 ± 3.7 kg/m^2) (79). Following six months of intermittent ER on the 2/5 schedule, glucose levels decreased by 3.4% in subjects with obesity (BMI 35.1 ± 3.9 kg/m^2), while no change occurred after continuous ER (87). A 19.4% decrease in fasting insulin concentration occurred in women with overweight or obesity (BMI 29.6 ± 4.1 kg/m^2) after a three-month intervention based on the 2/5 IF schedule, together with reduced carbohydrate intake (86). In effect, HOMA-IR values were reduced by 25% after the IF program, whereas daily ER intervention did not affect either the insulin concentration or the HOMA-IR (86). The liquid-based (but not the food-based) IFCR dietary regimen in women with obesity resulted in glucose and insulin concentrations decreasing by 3.3% and 21.4%, respectively (85). It should be noted that multiple IF trials did not produce any change in fasting glucose or insulin levels in people with normoglycaemia (86, 98).

The 2/5 IF schedule was also tested in a pilot study involving patients with T2D (mean HbA1c level 7.4%) (84), which showed modest decreases in HbA1c and insulin concentrations (by 0.6% and 0.9%, respectively) after twelve weeks of IF on the 2/5 schedule (84).

A very recent trial in men with overweight or obesity and prediabetes showed that early time-restricted feeding for five weeks significantly reduced fasting insulin concentration and improved the OGTT-derived indices of β-cell responsiveness and insulin resistance, even without weight loss (89). Interestingly, the effects of TRF on glycemic control may depend on the timing of eating, since a "feeding window" in the late afternoon or evening did not affect, or even worsened, postprandial glucose concentration and β-cell responsiveness (95, 102), whereas restricting food intake to the middle of the day exerted positive effects (89).

Ramadan fasting may be considered a type of TRF, though it does not conform to the circadian rhythms in humans. A 29-day Ramadan fasting in nonobese females (BMI 26.9 ± 0.7 kg/m^2) and males (BMI 25.4 ± 0.4 kg/m^2) resulted in decreased concentrations of glucose (by 6.3% and 3.7% in females and males, respectively), increased insulin concentrations (by 48.1% and 42.4%), and decreased HOMA-IR values (by 6.5% and 9.8%) (103). Aksungar *et al.* combined CR with Ramadan fasting in nondiabetic women with obesity (mean BMI 34 kg/m^2) and showed a decrease in HbA1c, glucose, and insulin levels by 24.9%, 26.8%, and 43.3%, respectively, resulting in a significant decrease in HOMA-IR value by 58.7% after 24 months (97). However, the Epidemiology of Diabetes and Ramadan (EPIDIAR) study showed that, during Ramadan, patients with diabetes were more likely to experience episodes of severe hypoglycemia, requiring hospitalization (104). For this reason, Islam exempts people from fasting while they are sick, or if fasting may affect their health (91).

IF regimens beneficially alter several aspects of adipocyte biology, including morphology, lipid metabolism, and adipokine release (22). In particular, various IF regimens have been shown to decrease serum leptin concentration (22, 78, 80, 84) and increase ghrelin (78). Moreover, adiponectin modulates insulin activity, reduces insulin levels, and improves beta cell functions (10). Circulating adiponectin concentrations increased by 6% after twelve weeks of ADF in people with normal weight or mildly overweight (BMI 26 ± 1 kg/m^2) (22). Moreover, some IF schedules caused decreases in serum levels of insulin-like growth factor 1 (97) and oxidative stress markers, *e.g.*, plasma levels of 8-isoprostane (89).

To summarize, there is a scarcity of data on the effects of intermittent feeding on glycemic control in patients with diabetes or prediabetes but IF seems to have positive effect on plasma glucose levels reflected by lower HbA1c concentration. In nondiabetic persons with overweight or obesity, IF may either decrease or have no effect on blood glucose and insulin concentrations. Importantly, weight loss seems to be dispensable for improvements in insulin sensitivity through time-restricted feeding. Moreover, intermittent energy restriction might be superior to a continuous diet with regard to the control of glycemia.

WEIGHT REGAIN AFTER WEIGHT-LOSS INTERVENTIONS

The efficacy of weight-loss interventions is limited by subsequent weight regain, with only approximately 15% of people with obesity succeeding in maintaining weight loss in the long-term (105). A recent study showed that in the two years following a diet-induced weight loss, individuals typically regained 70% of their lost weight (106).

Johansson *et al.* conducted a meta-analysis of 20 randomized controlled trials evaluating weight-loss maintenance strategies after VLCD/LCDs (31). Their analysis revealed that an intervention lasting an average of eight weeks (range 3 – 16 weeks) resulted in a pooled mean weight reduction by 12.3 kg. Among strategies for improving weight-loss maintenance, the most effective were antiobesity drugs such as sibutramine or orlistat (resulting in an estimated reduction in body weight of 3.5 kg for the median duration of 18 months), followed by meal replacements (3.9 kg, twelve months), and high-protein diets (1.5 kg, five months). Surprisingly, the meta-analysis did not identify exercise or dietary supplements (such as green tea, high fiber, conjugated linoleic acid, or oil supplementation) as offering significant improvements in weight-loss maintenance (31). In contrast, two randomized controlled trials addressed the issue of physical activity to enhance weight loss and prevent weight regain, showing that its intensity and frequency indeed influenced weight changes (107, 108).

Recent studies have refuted the common belief that losing weight rapidly is associated with poorer outcomes (38, 39). In one study, 33 individuals with obesity (24 women and 9 men; mean BMI 33.5 kg/m^2) underwent either rapid weight loss following four weeks of VLCD or gradual weight reduction through eight weeks of LCD, followed by a weight stabilization period of four weeks (39). Despite similar weight losses of –9% and similar changes in body composition, the two intervention groups differed at the end of the dietary regimens: the resting metabolic rate was reduced and exercise efficiency was increased only in the rapid weight-loss group, while the sensation of fasting hunger was higher in the gradual weight-loss

group. However, these differences between the groups were not visible after the weight stabilization period (39). Another study involved 57 participants (30 women and 27 men; mean BMI 31 kg/m^2) who underwent either slow weight loss (LCD, 1250 kcal/day) for twelve weeks or rapid weight loss (VLCD, 500 kcal/day) for five weeks, followed by four weeks of weight-stable period and nine months of follow-up (38). No significant differences were reported between the interventions with respect to weight loss or weight regain after follow-up (38). Also, other studies have confirmed that the rate of weight loss did not affect the proportion of weight regained (106). Thus, patients with obesity could be advised to follow a diet using the rate that is easier for them to comply with.

Continued lifestyle counseling or weight-loss medications (such as orlistat, liraglutide, or lorcaserin) may facilitate the maintenance of lost weight. However, a trial in Finland examining long-term weight maintenance after VLCD in patients with severe obesity found that the inclusion of a counseling-based maintenance program made no difference in the percentage of patients with clinically significant ≥ 5% weight loss (33% and 34% with or without maintenance program, respectively, after two years) (36). Furthermore, studies have demonstrated the mixed efficacy of drugs in aiding the maintenance of lost weight. For example, after a weight loss of ≥ 5% as a result of LCD (800 kcal/day, six weeks), the use of taranabant (a cannabinoid-1 receptor inverse agonist; 0.5, 1, or 2 mg/day) (109) or liraglitude (an analog of the incretin hormone glucagon-like peptide-1; 3 mg/day) (110) significantly improved weight maintenance at one year after the diet, as compared to the groups receiving placebo and lifestyle counseling. However, in the study by Tronieri *et al.* treatment with lorcaserin (a selective agonist of serotonin receptor and POMC activator, which reduces the feeling of hunger) did not improve long-term weight maintenance (34). Twenty-four weeks after the completion of the LCD regimen, body-weight reduction of ≥ 5% was maintained in 73.9% of patients receiving lorcaserin (10 mg twice a day) in comparison to 57.4% in the placebo-treated group. However, after another 28 weeks, the percentage of patients who preserved at least a 5% reduction in body mass amounted to about 50% in both groups (34).

Although the molecular mechanisms involved in weight regain are not well understood, researchers have suggested the role of compensatory metabolic responses. These responses may encompass reduced energy expenditure (39), changes in the concentrations of appetite-regulating hormones, like glucagon-like peptide 1 (GLP-1), ghrelin, or leptin (reviewed in 111), and relapse into old dietary habits. Because muscle mass is a key contributor to resting energy expenditure, its loss could negatively affect long-term weight maintenance. With this respect, gradual weight loss resulting from LCD might be safer than that due to VLCD regimens (38, 45). Moreover, Vink *et al.* (112, 113) investigated other potential factors involved in weight regain. They found that changes in the concentrations of FFA, retinol-binding protein 4 (RBP4, a transport protein for retinol), and angiotensin-converting enzyme activity correlated with weight regain and together explained 28% ($r = 0.532$) of weight regain variation (112). However, neither the dynamics of fatty acid uptake tested after an isotope-labeled meal nor the expression of genes important for FA uptake, storage, and release in the adipose tissue accounted for weight changes in overweight and obese participants (113).

Genetic factors contribute to the degree of weight loss from the discussed dietary interventions, as well as subsequent weight maintenance (114, 115). Based on the expression patterns of multiple genes (identified through RNA sequencing in obese patients after eight weeks of LCD and six months later) combined with clinical variables, Armenise *et al.* were able to construct models that accurately predicted the weight and glycemic outcomes (116). The study showed that a multitude of factors influence changes in body mass. We suggest that, even though predicting weight-loss outcomes could motivate some individuals to intensify their efforts to lose weight, the complexity of such predictions makes them unfeasible in clinical practice.

In summary, although weight regain is a common problem after weight-loss interventions, it can be to some extent ameliorated by the use of antiobesity drugs, meal replacements, or physical exercise. The rate of weight loss does not affect weight regain in the long-term. The mechanisms responsible for weight regain are multifactorial and involve reduced energy expenditure, changes in hormones' levels, and genetic factors.

Summary and conclusions

The increasing prevalence worldwide of obesity demands effective treatment methods that are applicable in primary-care settings. Low-calorie diets and intermittent fasting present potential methods of reducing the incidence or severity of obesity-associated disorders, and of type-2 diabetes in particular. Although morbid obesity is the most difficult to manage, weight loss through LCDs is also attainable in this group of patients when bariatric surgery is not possible. Both LCDs and IF may improve body composition (*i.e.*, reduce fat mass while mostly preserving lean body mass), reduce cardiovascular risk factors (for example by decreasing blood pressure, improving blood lipid profiles, and reducing oxidative stress), and positively affect glycemic control (such as by decreasing elevated glucose and $HbA1_c$ levels, increasing insulin sensitivity, and improving β-cell function). Moreover, LCDs have been shown to improve liver and kidney function, as well as to reduce the severity of several disorders aggravated by obesity (such as atherosclerotic disease, colorectal cancer, psoriasis, chronic obstructive pulmonary disease, and obstructive sleep apnea). The health-promoting effects of LCDs in individuals with overweight or obesity depend on the extent of weight loss, and in particular on the extent of fat mass reduction. Weight loss might not be a prerequisite for positive outcomes in the case of some IF regimens like early time-restricted feeding. However, time-restricted feeding schedules are more beneficial when meals are aligned with circadian rhythms.

Weight regain after dietary interventions is a common occurrence. Comparisons of various types of hypocaloric diets do not show any remarkable differences with regard to the effect of weight-loss rate on postintervention weight maintenance or regain. On the other hand, some evidence suggests that intermittent energy restriction might involve smaller reductions in resting energy expenditure, possibly translating into better long-term weight maintenance.

However, it is not possible to draw any clear conclusions regarding the choice of optimal low-calorie diet for people with overweight or obesity, except for the type of a weight-reducing diet that can be maintained long-term. Thus, the dietary schedule should be chosen according to the individual's preferences. Importantly, LCDs and IF regimens may be potentially harmful in nonobese or metabolically healthy obese individuals. Such schedules should thus be used with caution and under supervision of a health professional. However, the data presented in this review suggest that the paucity of controlled, large-scale research trials makes it difficult to prescribe LCDs or IF as reliable, routine methods for successful, stable weight loss.

List of abbreviations: ADF, alternate day fasting; ADF + HF, ADF combined with a high-fat diet; ADF + LF, ADF combined with a low-fat diet; AHI, apnea-hypopnea index;

ALT, alanine transaminase; AST, aspartate transaminase; AT, adipose tissue; BMI, body-mass index; BODE, body-mass index - airflow obstruction - dyspnea - and exercise capacity index; BP, blood pressure; bpm, beats per minute; BW, body weight; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; CR, calorie restriction; CRC, colorectal cancer; CRP, C-reactive protein; CT, computer-assisted tomography; CVD, cardiovascular disease; DAG, diacyloglycerol; DBP, diastolic blood pressure; DC, diet composition; DCI, daily caloric intake; DEXA, dual energy X-ray absorptiometry; DHA, docosahexaenoic acid; eGFR, estimated glomerular filtration rate; EPA, eicosapentaenoic acid; EPIDIAR, epidemiology of diabetes and Ramadan; ER, energy restriction; eTRF, early time-restricted feeding; FFA, free fatty acid; FFM, fat-free mass; FM, fat mass; GDR, glucose disposal rate; GGT, gamma-glutamyl transpeptidase; GLP-1, glucagon-like peptide 1; GLUT4, glucose transporter type 4; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment for insulin resistance index; HR, heart rate; hsCRP, high-sensitivity C-reactive protein; IF, intermittent fasting; IFCR-F, IF combined with calorie restriction - food-based diet; IFCR-L, IF combined with calorie restriction - liquid-based diet; IL, interleukin; IR, insulin receptor; IR_{Ser}, serine residue of insulin receptor; IVF, *in vitro* fertilization; LBM, lean body mass; LCAE, long-chain acyl-CoA ester; LCD, low-calorie diet; LDL, low-density lipoprotein; mADF, modified alternate day fasting; MATADOR, Minimizing Adaptive Thermogenesis and Deactivating Obesity Rebound; MetS, metabolic syndrome; MHO, metabolically healthy obese; MONW, metabolically obese - normal weight; NO, nitric oxide; OGTT, oral glucose tolerance test; OSAS, obstructive sleep apnea syndrome; POMC, pro-opiomelanocortin; PUFA, polyunsaturated fatty acids; RBP4, retinol-binding protein 4; RMR, resting metabolic rate; SBP, systolic blood pressure; SGRQ, Saint George Respiratory Questionnaire; T2D, type-2 diabetes mellitus; TG, triglycerides; TNF-α, tumor necrosis factor type α; TRF, time-restricted feeding; WC, waist circumference; WHO, World Health Organization; WHR, waist-to-hip ratio; VLCD, very low-calorie diet; VLCKD, very low-calorie ketogenic diet; VLDL, very-low-density lipoprotein.

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