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REVIEW ARTICLE

Intermittent Fasting or Ozempic: Exploring their Impact on Weight Loss and Metabolic Health

Shamreen Naaz

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ABSTRACT

Intermittent Fasting (IF) has gained widespread popularity particularly due to its remarkable effects on weight loss and regulation of metabolic homeostasis. Although it became a recent trend, its benefits have been documented in a number of studies including hepatic steatosis, cardiovascular diseases, diabetes as well as cancer. Ozempic®, the brand name of Glucagon like Peptide-1(GLP-1) receptor agonists or semaglutide, has attracted attention from celebrities and social media due to its "miraculous" effect of weight loss. Although it was originally developed as a treatment for Type–2 diabetes, as it mimics the hormone glucagon-like peptide-1 in the body, its side effect of weight loss has now become a more dominating feature. Although both these methods result in weight loss, however, IF focuses primarily on calorie restriction and metabolic regulation whereas Ozempic® works by suppression of appetite and inducing a feeling of fullness through GLP-1 receptor agonists. Studies have shown that IF provides a natural form of metabolic regulation through maintenance of circadian rhythm and increased insulin sensitivity, thereby reducing the insulin resistance and promoting liver health and detoxification. Evidences suggesting the effectiveness of GLP-1 receptor agonists in lowering glycosylated hemoglobin (HbA1c) in Type 2 diabetes along with its "off-label" use as a weight loss drug have gained attention and more research is being carried out to understand and comprehend the magnitude of its efficacy. This review presents a comparative analysis between IF and GLP-1 receptor agonist (Ozempic®) as a method of weight loss and illustrates upon it prevalent use worldwide.

KEYWORDS

• Intermittent fasting • Ozempic • Weight loss • Metabolic health

AUTHOR'S AFFILIATION:

Assistant Professor, Department of Physiology, Vidyasagar College for Women, Kolkata 700006, West Bengal, India.

CORRESPONDING AUTHOR:

Shamreen Naaz, Assistant Professor, Department of Physiology, Vidyasagar College for Women, Kolkata 700006, West Bengal, India.

E-mail: shamreennaaz89@gmail.com

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INTRODUCTION

Weight gain resulting in overweight and obese individuals has become the most prevalent form of non-communicable disease in India[1]. The obesity crisis in India is not only alarming, but also life-threatening. According to a report published by the Indian Council of Medical Research (ICMR) in April 2024, it states the fact that 56.4% of the total disease burden in India is due to unhealthy eating habits and lifestyle. The ICMR report observes that the upsurge in the consumption of highly processed foods, laden with sugars and fat, coupled with reduced physical activity and limited access to organic home cooked foods, exacerbate micronutrient deficiencies and create obese individuals. Similar to this, a concurrent rise in individuals with prediabetes and type 2 diabetes (T2D) has also been observed[2]. Additionally, there is a steep rise in other obesity-related conditions and diseases, including dyslipidemia, cardiovascular diseases, non-alcoholic fatty liver disease, and obstructive sleep apnea[1]. This was previously restricted to urban area in the sub-continent, however, in recent times this epidemic has also spread to sub-urban and rural areas too[2].

To tackle this obesity epidemic problem, recent advancements in medical treatments have highlighted the use of weight loss drugs such as Ozempic® (semiglutide) and more recently, there is a shift in interest towards improving the dietary patterns through various nutritional diets. Intermittent fasting is one such weight loss tool that has been proposed repeatedly by health experts all over the world due to its extraordinary benefits on weight management, cardiovascular health, and reduction of oxidative stress[3,4].

Intermittent Fasting and Its Types

Intermittent Fasting (IF) can be defined as periods of abstinence from calorigenic food, alternated with periods of eating. The protocols of these diet patterns may vary from a 24-hour fasting period, followed by a 24-hour non-fasting period (alternate day fasting - ADF), repeated 2-3 times per week (5:2 or 4:3 diet) to time-restricted feeding (TRF) or a daily fasting window of 16/18/20 hours a day along with a non-fasting eating interval of 8/6/4 hours in a 24 hr day (this protocol implies the reduction of daily meal frequency). This type of diet not only promotes weight loss, but also enhances overall health and life span[5]. A primary reason for the rapid rise in popularity of intermittent fasting may be its sheer simplicity and ease of following, wherein individuals simply need to restrict their eating window, while being able to eat everything in moderation. This regimen does not require individuals to extremely alter their eating patterns or stick to an unpalatable range of foods. Moreover, individuals on intermittent fasting do not necessarily have to omit various food groups from their diets or macronutrients, or diligently monitor their calorie intake per meal. These factors allow a higher acceptability and tolerability of the diet amongst overweight and obese individuals who intend to follow this regime long term to achieve their weight loss goals.

ADF involves two alternate days with one fasting day and the other being an eating day. On the days of the fast, individuals can only take water and non-calorigenic foods like black coffee, black tea, detox water or those liquids that are calorie-free[6], or, alternatively, individuals can consume 25% of their energy needs (approximately 500 kcal per day), which is called 'modified alternate day fasting[7-9]. It must be noted that the last meal before the fasting day must be eaten according to regular feeding pattern and a nocturnal pattern of fasting is usually found to be more convenient. On the eating days, individuals can eat freely, with no restrictions on types or quantities of foods consumed. The 5:2 diet is a modified version of ADF, which involves two fast days (500–1,000kcal per day), and five feast days per week[10-12]. The fast days can occur on consecutive or non-consecutive days in the week. For the time restricted pattern of intermittent fasting, usually a 16:8 division of a 24 hr day is followed with 16 hrs of fasting followed by 8 hours of feeding[12]. Depending on the convenience of the individual and fasting capacity, they are prescribed the particular regime and suggested to follow for atleast a month before visible changes can be observed.

Effects of Intermittent Fasting On Weight Loss

Nearly all IF studies have reported a certain percentage of weight loss, ranging from 2.5–9.9%[13,14], and associated fat loss. Although the literature for IF studies exhibited a variation in their IF protocol or duration, a generalized pattern of weight loss across all studies was observed owing to IF. Heilbronn *et al*. reported that 22 days of ADF (0% intake on fast days, ad

lib feast days) in 16 healthy subjects with normal BMI[13] resulted in minor weight loss (2.5%), fat loss (4%), and increased fat oxidation[13]. Another study by Eshghinia and Mohammadzadeh examined a 6 week period of ADF (very low-calorie diet (VLCD) on fast days, ad lib feast days) in women with overweight or obesity[15], led to 7.1% weight loss and visceral fat mass loss (5.7%). Klempel *et al*. evaluated the effects of 8 weeks of ADF with either a high or low-fat diet in 32 women with obesity[16], where he observed a marked reduction in weight, fat mass, and waist circumference in both groups. When comparing ADF to control group, ADF resulted in 6.5% weight loss relative to the control group.[15] All the above conducted studies showed a significant change in body fat mass after a period of IF which further corroborates its efficacy as a weight loss tool. Although the results from these studies seem promising, their long term effects are varied. In a meta-analysis of 29 long-term weight-loss studies, more than half of lost weight was regained within 2 years, and nearly 80% of lost weight was regained within 5 years[17].

Effects of Intermittent Fasting On Metabolic Health

This is perhaps the most researched area of IF that makes it a more widely accepted tool with health benefits that are not only restricted to weight loss, but also extend to the reduction and amelioration of metabolic health diseases such as non-alcoholic fatty liver diseases (NAFLD), non-alcoholic steatohepatitis (NASH) and liver cirrhosis[18].

Reports suggesting that the pathophysiological changes resulting from overweight and obesity conditions could lead to metabolic dysfunction, chronic inflammation, and impaired immune system regulation have been widely circulated[18]. It was observed that obesity and insulin resistance are the key factors controlling the onset of NAFLD[19]. Globally, it is estimated that NAFLD cases may shoot up by 56% between 2019 and 2030[20]. Researchers have concluded that perhaps, before medical intervention, lifestyle management and modification, including weight reduction and increased physical activity, may be a primary approach for the treatment of NAFLD[21]. It has been previously documented that a significant weight-loss of ≥10% can decrease the occurrence of hepatic steatosis and result in fibrosis regression[22]. In many cases, researchers have also observed a complete reversal of Grade 1 fatty liver in individuals undergoing a routine of intermittent fasting. IF has demonstrated health benefits without weight loss in cancer[23,24], cardiovascular disease[24], and cognitive and brain function.[25]

Intermittent Fasting has also benefitted individuals with insulin resistance or pre-diabetes and they lost equal amount of weight in comparison to their non-diabetic counterparts.[26] Only two clinical trials have examined whether fasting is effective for weight loss in patients with type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM).[12,27] A study reported that after 52 weeks of following the IF regime of 5:2 diet, patients with T1DM and obesity lost nearly 7% of their total body weight[27]. In contrast to these findings, individuals with T2DM and obesity showed 7% weight loss after 52 weeks of fasting 2 days per week[12]. Overall, these findings suggest that intermittent fasting might be beneficial to pre-diabetic and diabetic individuals with a significant reduction observed in their weight, insulin resistance, as well conditions of pre-diabetes, T1DM and T2DM.

Other benefits of IF reported are the metabolic benefits of IF, including weight loss[28], improved glycosylated hemoglobin[28], decreased atherogenic risk,[29,30] improved circulating cytokines,[29,30] and immune cell proliferation.[31] Wang *et al*. reported in a systematic review and meta-analysis of five randomized controlled trials (RCTs) comparing IF to energy restriction in patients with type 2 diabetes mellitus and metabolic syndrome, changes observed in glycosylated hemoglobin and fasting plasma glucose were found to be similar between groups; however, IF appeared to have a greater weight-loss benefit (−1.70 kg, 95% confidence interval [CI]: −3.28 to −0.11 kg)[31].

Apart from weight loss, IF related studies document its role in the improvement in insulin resistance,[32] reduction in oxidative stress,[32,33] improvements in serum cholesterol and triglycerides,[33] and decreased levels of systemic inflammatory markers, including tumor necrosis factors (TNF)-α and brain-derived neurotrophic factors[33] have been carried out. An umbrella review of 11 meta-analyses, including a total of 130 RCTs with different comparator groups assigned either

continuous energy restriction or regular diet, reported that IF was associated with weight loss; reduced fat mass and improvements in blood lipids, fasting plasma glucose, fasting insulin, blood pressure, and C-reactive protein[34]. IF group had greater improvement in insulin sensitivity and marked reduction in waist circumference[35,36].

Effects of Intermittent Fasting on Cognitive Health and Aging

Emerging evidences suggests that intermittent fasting can support brain health and enhance cognitive function. Mayor *et al*. have shown that intermittent fasting can stimulate the production of brain-derived neurotrophic factor, a protein that supports neuronal growth and protects against neurodegenerative diseases[37]. Human studies, although limited, suggests potential cognitive benefits of IF included reduction of brain fog and reduced oxidative stress, which might slow brain aging and could reduce the risk of neurodegenerative conditions like Alzheimer's[38]. Time restricted eating patterns have been observed to reset the circadian rhythms in patients with Alzheimer's who may benefit from improved synchronization of circadian rhythms[39]. Furthermore, studies carried out on lower mammals have shown that IF offers numerous health benefits against aging related detrimental changes in the body[40]. IF activates metabolic pathways that stimulate cellular repair, reduce oxidative damage and all processes that lead to degeneration of cells, and promote autophagy, all potentially contributing to increased longevity[40]. In humans, long-term studies are still needed to conclusively determine the impact of intermittent fasting on lifespan. However, preliminary data is promising such as a review article in the *New England Journal of Medicine* describes the numerous benefits of intermittent fasting beyond weight loss, including improved cellular function and resistance to stress and reduced inflammation[41].

Mechanisms of Intermittent Fasting

To understand the physiological mechanisms that are involved in the beneficial effect of IF, it has been postulated that the temporary calorie deficit in IF, produces a moderate oxidative stress that activates genes responsible for mechanisms of cell repairing and protection[42]. In a paper published by Mattson et al., it is stated that IF has a positive effect on health since it mimics the feeding patterns of human being in the ancient and medieval era where there could have been temporary scarcity of food for long periods followed by over abundance of food which in turn could potentially alter the feeding habits of our ancient ancestors[43]. Current patterns of insulin resistance observed in modern day primates could be the reason for the development of type 2 diabetes[44]. During periods of food scarcity experienced by humans in the past, adaptation to calorie restriction represented a survival advantage. Such an adaptation involved dependency on the utilization of hepatic and muscle glycogen and mobilization of free-fatty acids from adipose tissues and subsequently their conversion to ketones, as a source of alternative energy.[45,46] Autophagic processes are required to preserve muscle mass[47]. Intermittent fasting also produces adaptive responses that improve the physical qualities required to obtain food such as endurance capacity and muscle force, but also enhance cognitive functions and stress resistance[48-51]. Studies by Mattson, Longo and Harvie supported the idea that calorie restriction initiates the stem cell regeneration and has long-term metabolic effects, but more studies are needed to verify the magnitude of these effects in the case of an intermittent exposure, as well as their potential to prolong life span in humans[52].

Ozempic'R' / Semiglutide Glucagon-Like-Peptide 1 (GLP-1) receptor agonist

Ozempic, the brand name for Semaglutide, acts as a Glucagon-Like Peptide-1 (GLP-1) receptor agonist was approved by the U.S. Food and Drug Administration (FDA) in 2017 and it was first prescribed to patients with type 2 diabetes to keep blood sugar levels under control along with some suggested lifestyle changes and moderate exercise pattern. Since semiglutide acts as a GLP-1 RA (GLP-1 receptor agonist), its mechanism of action involves: stimulation of pancreatic beta (β) cells, in response to glucose, to release insulin, inhibition of glucagon release and slowing down the process of gastric emptying[53]. Semaglutide targets the main concern of type 2 diabetes mellitus, i.e. insulin resistance or insufficient insulin production, by stabilizing blood sugar levels through improved insulin secretion after a meal and simply lowering the hepatic glucose outflux. This benefits not only fasting but postprandial glucose levels as well, which was found to

reduce glycosylated hemoglobin (HbA1c) levels, a key regulator of glycemic index. Another unwarranted effect of Ozempic that has received considerable attention nowadays is its effectiveness in weight loss, although, it might just be a side effect of the drug. This has found wide acceptance and noteworthy results in individuals who have type 2 diabetes and are overweight or obese. Semiglutide, being a GLP-1 receptor agonist, mimics its action and perhaps, promotes weight loss by suppressing appetite and slowing down gastric emptying, thereby giving a feeling of fullness for a longer time which reduces the need for frequent re-feeding[54]. Semaglutide is usually administered as subcutaneous dose though sometimes may be taken orally. It has been proved to be safe for adults and even in subjects with renal or hepatic disturbances.

Effects of Ozempic'R' on Weight Loss

GLP-1, an incretin-peptide hormone, secreted after a meal from the small intestine, initiates downstream signalling through GLP-1 Receptor present in various organs, including the brain, pancreas, and gastrointestinal tract[55,56]. These group of GLP-1 RA drugs imitate the naturally occurring GLP-1 hormone and stimulate the pancreas to initiate insulin secretion and inhibit glucagon release[57]. This mechanism regulates blood glucose levels in type 2 diabetic individuals[58] and also has anti-obesity benefits resulting from GLP-1 RA actions in the brain which include reduction in body weight, reduced food cravings and loss of appetite, along with increased satiety and enhanced eating control which function as effective weight loss strategies[59]. The stimulation of the central nervous system by semiglutide has been documented to modulate neuronal activity involved in appetite regulation and significant trimming down of food intake[60]. Studies depicting the role of GLP-1 agonists in augmenting adipose tissue catabolism specially of the face, are few but significant. Rapid weight loss due to semiglutide has resulted in face volume loss and the appearance of "Ozempic face" has been documented in cases of extreme weight loss with features similar to the face of an aged individual.[61]

Evidence suggests that an approved dose of 1 mg semaglutide once-weekly (s.c.) by the US Food and Drug Administration in 2017 was documented for the treatment of type 2 diabetes. Orally, a maximum dose of 14 mg per day, was approved for treating type 2 diabetes in the US in 2019[62]. For weight loss, the ideal dose of semaglutide was found to be 2.4 mg when administered (s.c.) once weekly, based on a phase 2 clinical trial in which a higher weight loss was observed with once-daily semaglutide, 0.4 mg (equal to 2.8 mg weekly), than with placebo or liraglutide 3.0 mg/day[63]. Recently, development of single-use, prefilled pens have been made available which is user friendly. The initial dose is 0.25 mg, administered by (s.c.) injecting in the abdomen, thigh, or upper arm once weekly for 4 weeks. The dose is increased over a period of 4-week intervals (over a total of 16 weeks) until a maximum dose of 2.4 mg per week was attained.

Interestingly, a STEP programme was designed to comprehensively evaluate the efficacy of once-a week 2.4 mg dose of semaglutide (s.c.) in overweight or obese people with each trial evaluating and addressing a particular aspect. Six trials were completed in this study and they can be categorized as follows: STEP 1 (large pivotal study), aiming at weight loss[64]; STEP 2, to evaluate weight loss in type 2 diabetes[65]; STEP 3, to study weight loss along with intensive behavioural therapy[66]; STEP 4, effect of continuing versus withdrawing of semaglutide on weight-loss maintenance[67]; STEP 5, observing weight maintenance over 2 years[68]. In addition to these STEP trials, STEP 6, an additional region trail was carried out to assess the effect of semaglutide versus placebo for weight management in 401 adults from east Asia (Japan and South Korea) with obesity, with or without type 2 diabetes[69,70]. The future of Ozempic in healthcare appears promising, as its role extends beyond just diabetes management and is being considered as a drug for obesity and weight management related issues.

Effects of Ozempic'R' on Metabolic Health

Studies have reported a significant decrease in HbA1c of 1–1.5%, as well as profound changes in body weight, blood pressure and lipid profile[71]. The extensive distribution of GLP-1 receptors throughout the body has also been reported to be associated with several adverse effects such as pancreatitis, pancreatic cancer and thyroid cancer[72]. Additionally, the development of semaglutide related hypoglycemia[73], gastrointestinal disturbances,

such as nausea, vomiting and diarrhea, reduced kidney function,[74] increased risk of gallbladder stones,[75] diabetic retinopathy[76] was observed. It was also noted that the prevalence of metabolic syndrome, a strong predictor of NAFLD/NASH[77] was found to be significantly decreased over 52 weeks of semaglutide treatment in the weight management trial conducted by Newsome *et al*.[78] In patients with type 2 diabetes who received semiglutide treatment and were at high cardiovascular risk, was found to be significantly protected from cardiac injury than among those receiving placebo.[79]

Mechanisms of Action of Ozempic'R'

Semaglutide is a long-acting GLP-1 receptor agonist with 94 percent homology with native human GLP-1. Its structural conformational changes enable it to bind reversibly to albumin leading to reduced renal clearance. This results in slower degradation and an impressive half-life of 155 to 184 hours, allowing for once-weekly subcutaneous dosing without compromising weight loss efficacy. Unlike the native GLP-1 that is degraded by DPP-4 (dipeptidylpeptidase 4), its counterpart GLP-1 agonist is more resilient to DPP-4 degradation and thus is able to have a longer lasting effect on GLP-1 receptor. This unique property of GLP-1 agonist, including appetite suppression, delayed gastric emptying along with reduced blood glucose levels, enhanced insulin secretion collectively contribute to its efficacy and prowness[80]. Their effective binding and activation of GLP-1R stimulates pancreatic β-cells for a glucose-dependent insulin secretion, suppresses glucagon secretion, delays gastric emptying and a marked reduction in appetite is observed[54]. The regulation of appetite is dependent on the interaction with the hormone leptin[81]. GLP-1 is secreted in response to nutrients released from a meal that passes through the gut from the enteroendocrine L cells, which increase in the distal gut, with maximum cells found in the intestinal ileum and colon[82]. These enteroendocrine L cell also function in sensing of inflammatory response[83].

Comparing the Benefits of Intermittent Fasting and Ozempic'R'

1. Regulation of Hunger and Appetite Suppression

Perhaps, the regulation of hunger and suppression of appetite are the two most studied benefits of Ozempic, which can be exceedingly helpful for individuals who are on IF. Suppression of hunger by Ozempic during fasting window, signals the feeling of satiety and reduces appetite.[54,59,60] A combination may help control hunger during fasting periods, making it easier to adhere to the fasting window without feeling deprived.

2. Effective Blood Sugar Management

Improved insulin sensitivity and reduced insulin resistance are related to Ozempic in managing blood sugar. This benefit coincides with IF, which has also shown to be the same.[32] Both of these may be beneficial specially in individuals who are obese with type 2 diabetes. However, IF may be considered unsuitable for people with low blood pressure or heart disease or people who take certain medications. Hypoglycemic obese individuals, pregnant or breastfeeding women, and those with a history of eating disorders are not recommended Ozempic and may be suggested lifestyle modifications considering their low glucose levels. Although controlled IF appears safe for people with type 2 diabetes[12,27], it may become dangerous if done along with medication. Proper medical guidance and surveillance is needed for such individuals.

3. Management of Metabolic Health and Weight Loss

Both Ozempic and IF promote weight loss in different ways. Ozempic reduces appetite, leading to a reduction in calorie intake, while IF increases fat oxidation by prolonging periods without food. Ozempic's effects on hunger suppression may make it easier to stick to the restricted calorie intake that often becomes difficult during fasting window in IF. With Ozempic, quick weight changes are observed in people without making any significant lifestyle changes, however, IF on the other hand is a no cost natural alternative that encourages healthy eating habits and physical activity along with the benefits of a boosted metabolic health status[35,36].

4. Enhanced Fat Burning

IF can increase the body's ability to burn fat for fuel, especially during fasting periods when glycogen stores are depleted. Ozempic however aids fat loss by reducing appetite. Both can lead to a healthier body composition by promoting the burning of stored fat. The

goal of weight loss should be to burn as much fat as possible. Some studies have shown that semaglutide may be associated with bone loss and lean mass loss, which can reduce core strength and slow the metabolism. "Ozempic rebound," has been observed in people who tend to regain weight after they stop their semaglutide medication without making any lifestyle modification.

5. Potential Side Effects

Semaglutide can cause mild nausea, indigestion, and diarrhea. In more severe cases, side effects can include stomach paralysis, pancreatitis, thyroid problems including cancer, and gall bladder problems. During IF, due to less food, hunger and fatigue may be experienced, which can lead to irritability and reduced concentration. Some more side effects of IF include reduced energy levels, headache, presyncope, decreased concentration, mood swings or bad temper, feeling cold, constipation, bad breath, and preoccupation with food. Some may even develop acid reflux that adds discomfort to everyday activities.

CONCLUSION

Although both Intermittent fasting and Ozempic work alike in promoting fat loss and aiding in effective weight management, scientific evidence supports that Intermittent Fasting has an edge over Ozempic usage relating to its benefits in boosting metabolic health, regulating body composition, reducing inflammatory markers, improving cardiovascular health, brain function, and potential longevity along with the primary benefit of being a no cost, non-medicated and absolutely natural process that has benefitted humans through centuries. Additionally, IF also increases cellular resistance against oxidative stress and promotes insulin sensitivity. Regarding safety, preliminary data indicate that Intermittent Fasting leads to lesser gastrointestinal, neurological, hormonal or metabolic adverse effects. However, studies vary greatly on their definition of IF, protocols, and the duration of IF. The capacity of existing intermittent fasting protocols to help manage weight long-term is still poorly understood, as the majority of studies have only been done for short durations. Personalized customizable diet plans best suited to the needs of the individual must be followed for optimum benefits. Although, both Ozempic (semaglutide) and intermittent fasting have the potential to promote weight management, however, Intermittent Fasting is a lifestyle choice, and semaglutide is a medication. The data on the effect of Ozempic and intermittent fasting on long term usage is limited and needs further research so that their efficacy in management of lifestyle disorders and metabolic health can be assessed and they can be used as a sustainable method for the treatment of obesity.

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