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The effect of intermittent fasting regimens as a feasible approach on Metabolic Syndrome: A literature review

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Metabolic syndrome (MetS) is a growing problem worldwide. Gulf countries, being part of the Middle East, have shown a high prevalence of metabolic syndrome. MetS typically reflect the clustering of individual cardiometabolic risk factors including central obesity, elevated fasting plasma glucose, dyslipidemia, and elevated blood pressure. Intermittent fasting (IF) has gained prominence as a promising approach for weight loss and mitigation of metabolic syndrome. This review investigates the effect of current evidence of intermittent fasting on metabolic syndrome. Three databases were used to identify studies between 2010 and 2021 using relevant selected keywords to explore the evidence of intermittent fasting's impact on metabolic syndrome. The article selection was made based on the inclusion and exclusion criteria concerning the participants' characteristics, study design, intervention protocols, and targeted dependent variables. We assessed 834 studies for eligibility and Twenty-one articles were identified and reviewed in our narrative synthesis. Overall, the available evidence suggests that IF is considered effective for losing weight, normalizing blood glucose, reducing lipids, and lowering blood pressure, particularly among obese subjects. Studies are urgently needed especially, randomized controlled trials with a long-term follow-up period of the abovementioned four variables.

Keywords: intermittent fasting; metabolic syndrome; hyperglycemia; abdominal obesity; dyslipidaemia; blood pressure

INTRODUCTION

With the successful conquest of many of the old infectious diseases globally, non-communicable diseases (NCD) have emerged as the foremost cause of mortality and morbidity in both developed and developing countries. Among many of these NCDs, metabolic syndrome (MetS) has become a worldwide scourge (Saklayen, 2018). The concept of metabolic syndrome has now been in existence for several decades; since Gerald M. Raevan was first described in the 1980s, numerous definitions and diagnostic criteria have been devised for Syndrome X (also known as Metabolic Syndrome) (Sarafidis & Nilsson, 2006). MetS concepts are mainly composed of one or more clinical variables or biomarkers that indicate the critical characteristics of the MetS concept [central adiposity, hypertension, high triglycerides, low high-density lipoprotein cholesterol, and hyperglycemia] (Alberti et al. 2006). The selection of the variables and their thresholds has been a complex task because the main MetS traits could be measured by several indicators that provide complementary information [for instance, fasting plasma glucose, HbA1c, or even the 2-hour glucose concentration after an oral glucose load for the "hyperglycemia" trait] (Aguilar-Salinas & Viveros-Ruiz, 2019).

The incidence of MetS typically coincides with the incidence of obesity and type II diabetes

mellitus (DM). According to a 2015 global obesity study conducted in 195 countries, 604 million adults and 108 million children were obese. Obesity prevalence has doubled in 73 countries since 1980 and has risen in other countries (Saklayen, 2018).

According to CDC reports from 2017, 30.2 million people aged 18 and over, or 12.2% of all adults in the United States, have type II DM (T2DM). One-quarter of these individuals (23.8%) were unaware that they had DM. T2DM prevalence rose with age, peaking at 25.2% among US seniors (65 years or older). Prediabetes or metabolic syndrome (MetS) were found to be three times more common. As a consequence, MetS affects almost one-third of Americans (Saklayen, 2018). The Middle East has a high incidence of metabolic syndrome, with 45.5% being reported. According to the ATP III and IDF guidelines, the prevalence of MetS in the Arabian Gulf countries ranges from 17% in Oman to 40.5 % in the United Arab Emirates. A recent nationwide study to assess the prevalence of MetS in Saudi Arabia was estimated to be 39.8 % among men and 31.6 % among women (Al-Rubeaan et al. 2018). MetS diagnosis was based on the International Federation of Diabetes definition: waist circumference (WC) ≥ 80 for women or ≥ 94 cm for men when two or more of the following components are present: fasting plasma glucose ≥ 100 mg/dL; systolic (or diastolic) blood pressure ≥ 130 (or ≥ 85) mm Hg; HDL cholesterol < 50 mg/dL for women or < 40 mg/dL for men; triglyceride ≥ 150 mg/dL (Grundy et al. 2005). There are four most widely used definitions of MetS, including the World Health Organization (WHO), the European Insulin Resistance Study Group, the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III), and the International Diabetes Foundation (IDF). The components of these definitions are relatively the same. They include impaired fasting glucose (IFG), impaired glucose tolerance (IGT), homeostatic model assessment for insulin resistance (HOMA-IR) (explain this term), obesity, dyslipidaemia, hypertension (WHO criteria), waist circumference, blood pressure, fasting triglyceride levels, fasting high-density lipoprotein (HDL), and fasting blood glucose (FBS) (NCEP ATP III criteria) (Huang, 2009; O'Neill & O'Driscoll, 2015).

Intermittent fasting (IF) has risen in popularity as one of the most straightforward regimens to implement in recent years (Pilon, 2013). In general, IF involves abstaining from food for a while, followed by intervals of daily consumption ad libitum. Fasting times can vary from a few hours to a few days (Patterson & Sears, 2017). There are three main regimens of IF for health benefits: alternate-day fasting (ADF), modified weekly fasting regimens (MIF), and time-restricted feeding (TRF) are among the most common forms of IF (Patterson & Sears, 2017). While in alternate-day fasting, one consumes not more than 500 kcal every alternate day, the rest of the days eating consciously. As the name suggests, alternating days of fasting cause a person to alternate between days of eating and days of fasting**.** In the modified fasting regime or the 5:2 plan, eating takes place five days a week, and fasting generally takes place two days a week (typically nonconsecutive). It usually allows 20-25% of the energy to be consumed regularly scheduled 'fast' days 400/600 kcal (female/male). Ultimately, Time-Restricted Feeding refers to a regular eating schedule where food intake occurs within a fixed time window in the day and fasting beyond that period. This entails fasting for 16 hours a day (24 hours) and willfully feeding for the next eight hours (Patterson et al. 2015). Fasting has been suggested as a viable method for reducing MetS risk factors such as lipid profile, blood pressure, and waist circumference (de Azevedo et al., 2013). In short-term trials, fasting appears to benefit insulin resistance, blood sugar, blood cholesterol, inflammation, short-term weight loss, and brain health in both humans and animals (de Cabo & Mattson, 2019; Mattson et al., 2017). However, long-term studies on the effectiveness of fasting on long-term weight loss and other health effects, on the other hand, are also required (Mattson et al., 2017; Patterson et al., 2015). The purpose of the present literature review is to provide a comprehensive overview of the benefits of IF on metabolic syndromes that would enable an understanding of its clinical results associated with it.

MATERIALS AND METHODS

An initial scoping search was conducted using Google Scholar. Further in-depth searches have been performed using PubMed and Web of Science. Trials/observational studies included in which the design of the study concerned one of three IF regimens most often reported: alternate-day fasting, modified fasting regimens, or time-restricted feeding. All databases were confined to trials with human participants aged 18 years and above, published in English, and full-text articles. While studies excluded if they are performed on

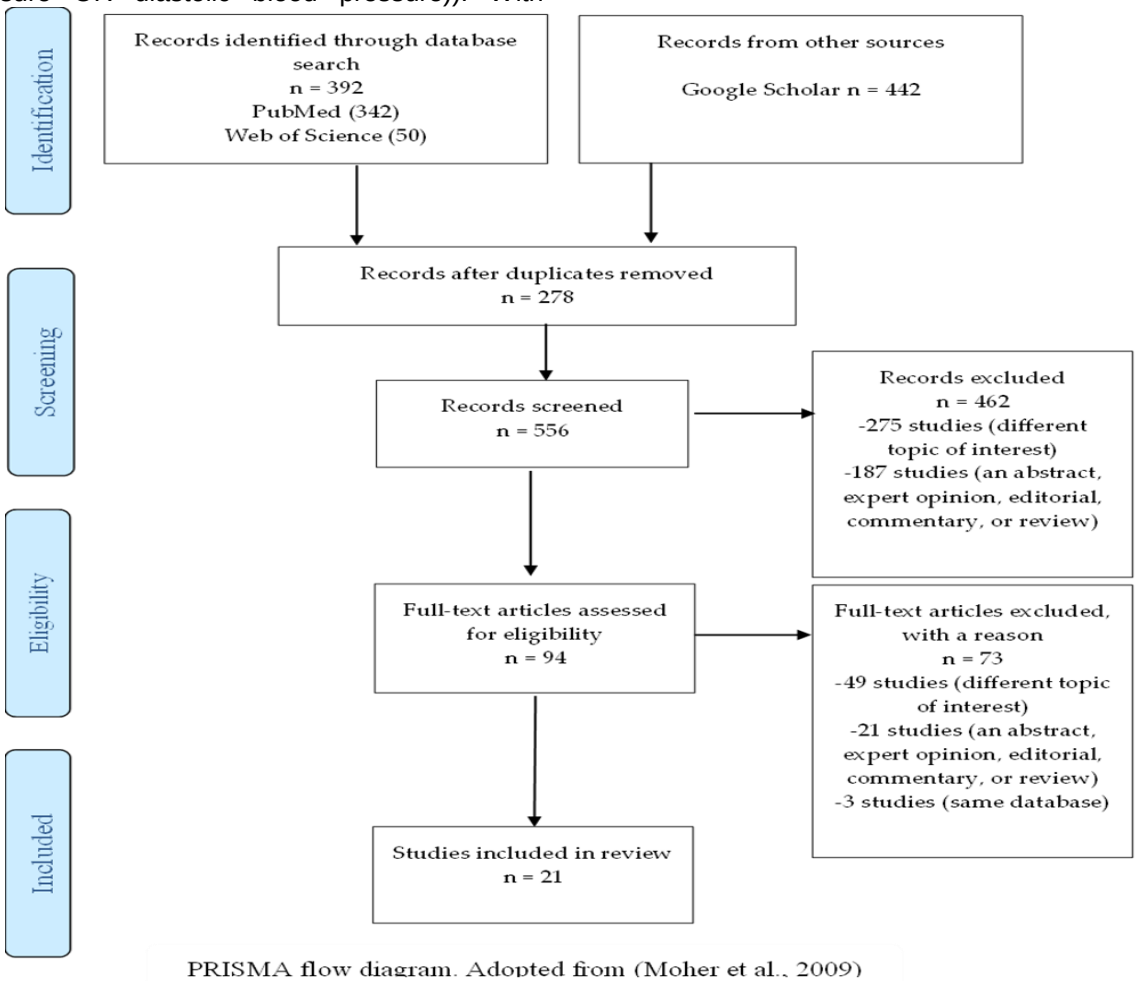
pregnant females, and studies with individuals <18 years old, animals, abstracts, or studies with insufficient information on IF regimens. The literature's timeframe was imposed on the database searches from January 1st, 2010, to February 28th, 2021.

Search Strategy

The complete set of keywords was ((intermittent fasting OR time-restricted feeding OR alternate day fasting OR modified fasting regimens) AND (insulin resistance OR blood glucose OR diabetes OR hyperglycemia OR hypoglycemia) AND (lipid profile OR cholesterol OR triglycerides OR low-density lipoprotein OR high-density lipoprotein) AND (bodyweight OR waist circumference OR overweight OR obesity OR weight loss OR body mass index) AND (blood pressure OR hypertension OR systolic blood pressure OR diastolic blood pressure)). With these keywords, each string was built using AND and OR operators. Combinations of intermittent fasting AND blood glucose, intermittent fasting AND bodyweight, intermittent fasting AND lipid profile, intermittent fasting AND blood pressure, and all four dimensions were searched for relevant results. The search string was input into the databases, and the results were restricted to articles published after January 1st, 2010, until the last date of search, i.e., February 28th, 2021.

Selection Process

Results from all database searches were exported to the reference management program Mendeley Desktop (Version 1.19.8). Duplicates across databases were detected and eliminated. The title, year of publication, and abstract of each publication were screened for relevance based on inclusion and exclusion criteria by one author.



PRISMA flow diagram. Adopted from (Moher et al., 2009)

Figure 1: A flow chart showing the screening process of the literature search. The flow chart was adopted from Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2009 version (Moher et al., 2009).

After applying the eligibility criteria, the full-text articles were reviewed. Regarding the roles, one author searched all the databases using search queries discussed and agreed upon by all authors. Then the other author also assessed the articles to see if they met the criteria for inclusion or exclusion.

All authors reached a consensus on papers for a full review. In total, 21 papers met the inclusion criteria for this narrative synthesis review. A detailed description of the search process can be found in Figure 1.

RESULTS

3.1. Search Results and Study Characteristics

The articles identified through the PRISMA template were 392 (342 from PubMed and 50 from Web of Science). Another 442 articles were selected from Google Scholar, making it a total of 834. after 278 duplicates were removed, the remaining 556 articles were taken for screening. Four hundred sixty-two of the articles did not meet the inclusion criteria and hence were removed, leaving 94 full-text articles that were then assessed for eligibility. Upon the assessment, 73 articles were removed, making the number of articles that qualified for the review to be 21 included in the qualitative synthesis. IF regimens ranged through studies, with some involving alternate day feeding, others incorporating a modified fasting regime or the 5:2 strategy, while others concerning time-restricted feeding. The duration of the IF regimens varied from one to twelve weeks. These studies were conducted in the United States, Australia, Canada, New Zealand, Germany, Norway, Poland, China, Turkey, Iran, and Pakistan between 2013 and 2021. The included trials' sample sizes ranged from 3 (Furmli et al. 2018) to 1422 (De Toledo et al., 2019) participants. Subjects included those with type II DM, overweight or obese, and individuals who had comorbidities such as NAFLD (Cai et al., 2019).

3.2. The Impact of IF on Diabetes and Insulin Resistance

Although the widespread popularity of IF in the lay media, few studies have been conducted in patients with T2DM (Horne et al., 2020). Insulin resistance, the most prominent feature of T2DM, has long been considered to improve with caloric restriction. After a fasting period, insulin sensitivity increases, and insulin levels decrease (Grajower & Horne, 2019). This improves fasting and postprandial glucose levels. Additionally, since insulin stimulates adipose tissue growth, there is less tendency to gain weight and possibly even weight loss (Grajower & Horne, 2019). Grajower & Horne, (2019) investigated that IF, when performed for health missions in diabetes, both types I and II, has been stated in a small number of human studies to stimulate weight reduction and decrease insulin needs. The findings of Arnason et al. (2017) showed that daily short-term IF may be a safe and satisfactory dietary intervention in T2DM that may enhance significant impacts, including reducing the fasting glucose, body weight, and postprandial variability. Besides, according to an investigation by Hutchison, Regmi, et al. (2019) on the effectiveness of (TRF) time-restricted feeding in fifteen men at risk of T2DM, where the trial shows that there was a substantial reduction in glucose level after one week by 36% and a slight decrease in triglycerides with TRF, in addition to a favorable impact on fasting and postprandial insulin. These results should be considered exploratory, and a more prolonged and more extensive study is necessary to confirm these findings.

Moreover, A. R. Cho et al. (2019) indicate that IF has a significant impact on reducing the fasting glucose level and a homeostatic model evaluation of insulin resistance. The IF diet enhanced insulin sensitivity even when the calories saved were comparable to those in the control group, without much modification in body weight. It shows that IF, itself, can be beneficial to glucose metabolism regardless of body weight changes. In a recent study, Gabel et al. (2019) compared an alternating day fasting regimen (25% of energy needs on fasting days, 125% of energy needs on non-fasting days) to a constant energy restriction (75% of energy needs daily) and a placebo group of obese, non-diabetic patients in a clinical trial.

Throughout a 12-month intervention phase, all dietary intervention groups observed similar reductions in body weight, BMI, and fat mass; however, the alternate-day fasting group reported more significant reductions in fasting insulin levels (-44 %; $p < 0.05$) and homeostatic model measurement of insulin resistance (HOMA-IR) levels (-53 %; $p < 0.05$). HOMA-IR is a marker used to assess insulin resistance. However, contrary to other results, IF did not improve glucose and lipid metabolism in some controlled, randomized crossover trials.

As well, there have also been conflicting findings on the weight-loss effect. Although some researchers specified a substantial weight loss in the IFD group Eshghinia & Mohammadzadeh, (2013), many other studies did not investigate clinically significant weight loss (Tinsley et al., 2017).

Furthermore, IF decreases obesity and thus insulin resistance by reducing caloric intake and metabolic reprogramming. Additionally, it has been shown that energy/nutrient depletion (which is accomplished by reducing caloric intake) promotes healthy ageing and reduces chronic disease by increasing activated protein kinase (AMPK) activation (Burkewitz et al., 2016). The biochemical role of AMPK is outside the scope of this review; however, it has been demonstrated that activating AMPK through a low energy state initiates physiological responses that promote healthy ageing (Burkewitz et al., 2016). Increased levels of insulin, either by increased caloric intake or through increased insulin resistance, cause downstream activation of mediators, which ultimately inhibit AMPK. The AMPK's role in improving insulin sensitivity is demonstrated by the positive influences of the commonly prescribed metformin, biguanide. Reduced caloric intake, such as that accomplished through IF, will result in increased levels of AMPK and prolonged lower levels of insulin production, which will likely demonstrate a major role in improving insulin sensitivity and glucose homeostasis (Albosta & Bakke, 2021).

Furmli et al. (2018) observed three subjects with type II DM over several months after initiating an IF protocol of three 24-hour fasts per week. All patients had a significant HbA1C decrease and weight reduction during the study period, and the three subjects could cease insulin treatment within one month. The limited sample sizes, however, weaken this review's external validity. S. Carter et al. (2019) conducted a clinical trial among adults with T2DM divided into two main groups, an intermittent caloric restriction group, and a continuous caloric restriction group. After a year of intervention, both groups show a comparable decline in HbA1C levels and a greater decrease in weight in the intermittent dietary restriction group. However, the high dropout rate among participants from the study's intervention groups may have inflated the sample size affecting the representativeness and generalizations of findings (S. Carter et al., 2019). Few trials have been conducted to assess intermittent fasting's long-term safety (Liu et al., 2020). This is supported by Corley et al. (2018)'s investigation, which reveals that both 5:2 diet regimens raised the rate of hypoglycemic events regardless of a decrease in anti-diabetic medications.

3.3. The Impact of IF on Body Weight and Waist Circumference

IF has greater adherence and has approved promising results in improving body composition, metabolic risk factors, and weight reduction in obese people (Anton et al., 2018). These positive outcomes have been linked to the body's transition from carbohydrates to fatty acids and ketones as a good energy source during fasting (Anton et al., 2018). During this transformation, the body shifts from fat synthesis and storage to mobilizing fats in ketone bodies and free fatty acids. This transformation of the fuel source, or metabolic reprogramming, has been approved as a possible mechanism for many positive outcomes of IF.

Additionally, IF has been approved to decrease obesity, especially visceral and stem fats, mainly because of moderate energy deficiency. Through this decrease in obesity, patients may feel improvements in levels and sensitivity of leptin/adiponectin, resulting in improved control over appetite and reduced levels of chronic inflammation and, therefore, improvement in many risk factors for T2DM (Catenacci et al. 2016). A systematic review of 40 trials revealed that IF was efficient and effective for losing weight, with an average loss of 7-11 pounds over ten weeks (Seimon et al. 2015). On the other side, A randomized controlled trial that examined 100 obese individuals for one year did not find IF to be more effective than daily calorie restriction (Trepanowski et al. 2017). Stephanie Welton et al. (2020) revealed that IF found a weight loss of 0.8% to 13.0% of basal weight with no dangerous adverse events. The majority of weight loss with IF is fat loss (Sharayah Carter et al. 2018; Catenacci et al. 2016; Cho et al. 2019; Coutinho et al. 2018).

A study by M. N. Harvie et al. (2011) estimated that 79% of weight loss was primarily due to fat loss. Furthermore, patients for 6 months or longer after undergoing IF programs ranged from 8 weeks to 1 year, and most research showed a 1% to 2% rise in body weight (S. Carter et al. 2019; Catenacci et al. 2016). Five experiments involved maintenance and/or follow-up periods, with comparatively minimal communication with subjects for 4–26 weeks (Catenacci et al. 2016; M. Harvie et al. 2013;

Schübel et al. 2018; Sundfør et al. 2018; Trepanowski et al. 2017). Over these follow-up years, there was no disparity between the IMF and CER groups regarding weight regain (Rynders et al. 2019). The study was done by S. Carter et al. (2019), showed that most participants demonstrated a maintained weight loss. After 12 weeks of IF, Zuo et al. (2016) observed a BMI rise of less than 1% over a year. The amount of weight regained after IF, and calorie restriction was comparable in trials comparing the two approaches (Schübel et al. 2018; Sundfør et al. 2018; Trepanowski et al. 2017). This was confined to lean body mass in the 11 IF patients who completed follow-up, while the 10 calorie-restricted patients who completed follow-up recovered all fat and lean body mass (Catenacci et al. 2016).

Previous studies in the same context have had consistent results. After a few weeks of alternate-day fasting, one of the trials observed a decrease in body weight compared to the baseline Cai et al. (2019) and found similar results to those obtained by Bhutani, Klempel, Kroeger, Trepanowski, Phillips, et al. (2013), which is indeed a factor contributing to the short duration of the trial and implementation.

Fasting has been revealed to counteract the MetS, which may have a heart-protective effect on women as they age. While broad, well-designed trials on women and fasting are needed, fasting can be recommended as a healthy medical approach as well as a lifestyle regimen that can boost women's health in many ways Nair & Khawale, (2016), while weight reduction by 5–10% has been displayed to boost metabolic parameters such as blood glucose, lipid profile, and blood pressure (Schroder et al. 2021). This is supported by the Domaszewski et al. (2020) trial; overweight women aged 60 and up were placed on a fasting schedule that included fasting from 8 p.m. to noon the next day. When their feeding window opened up, the women's food options were not restricted. Despite this, they lost an average of 4.4 pounds (2 kg) over six weeks, with no substantial loss of muscle mass.

On the other hand, IF studies typically demonstrate that hunger levels remain constant Coutinho et al. (2018) or decrease during IF (Kroeger et al. 2018). A study of 30 participants over 12 weeks by Krista A. Varady et al. (2013) stated reports of hunger during IF were no higher than with unrestricted consumption. Kroeger et al. (2018) noticed that hunger reduced, and fullness increased for those who lost the most weight after 12 months of IF. In contrast, the Sundfør et al. (2018) trial reported higher hunger in the IF group than the calorie-restricted group.

3.4. The Impact of IF on Lipid Profile and Dyslipidaemia

IF tends to have a beneficial effect on lipid values. Several scientific types of research have been conducted to ascertain the function of different IF approaches involving caloric restriction and IF. It also decreases the weight by 3-7% over two to three months and enhances lipids and blood pressure (Ahmed et al. 2021). Keogh et al. (2014) demonstrated that IF is almost as effective for weight loss as 8 weeks of continuous calorie restriction. The impact of IF on the lipid profile, which could lead to changes in cardiometabolic fitness, may be explained by decreased caloric consumption and weight loss (Stockman et al. 2018).

Moreover, Bhutani, Klempel, Kroeger, Trepanowski, & Varady, (2013) measured the combination of IF with performing an exercise that was revealed to be superior rather than fasting or exercise alone in terms of lipid levels and modification in body mass composition. The study's results revealed that both the exercise and compound groups lost weight. Furthermore, the combined group had a 5% decrease in LDL, a decrease in HDL small particles, a decrease in waist circumference, and a decrease in fat mass while preserving lean mass. Furthermore, Krista A. Varady et al. (2013) performed a randomized controlled trial to evaluate the effect of IF in weight loss in overweight and normal-weight subjects. People had a rotating feeding day with a fast day with 25% of total energy intake. The group of IF had an increased low-density lipoprotein (LDL particle size (4 ± 1)), fall in fat mass of 3.6 kg, leptin, and triglyceride (TG) concentrations (20 ± 8%), and plasma adiponectin (6 ± 10%)). While leptin was fallen by (40 ± 7%) when compared to the control group.

Additionally, for 12 weeks, a randomized study compared ADF (altering 24 h fast with a 25% daily energy supply and 24 h feeding ad libitum) and TRF (8 h feeding and 16 h fasting) to a placebo group (diet supplying 80% of energy needs). The findings revealed that both fasting approaches resulted in a substantial change in lipid profile and an improvement in dyslipidaemia in a short period when compared to the control group (Cai et al. 2019). The above finding is consistent with Maroofi & Nasrollahzadeh, (2020), which compared the efficacy of an 8-week

intermittent caloric restriction regimen to continuous caloric restriction in subjects with hypertriglyceridemia. The authors noticed that these approaches reduced body weight and fat mass similarly and improved plasma triglycerides among eighty-eight participants but had no impact on HDL-C levels. These results are in line with studies were done by (Hutchison, Liu, et al. 2019; Meng et al. 2020), which displayed advantageous effects on the lipid profile by substantially reducing TC, LDL-C, and TG concentrations comparative to control groups. However, no significant effects were identified for HDL-C after IF subsequently, as this can be explained because HDL cholesterol can take more than 16 weeks to be altered. Despite prior evidence, Santos & Macedo, (2018) gathered data from various trials and concluded that different forms of IF could increase HDL by 1–14 mg/dl, decrease LDL by 1–47 mg/ dl, decrease TC by 5–88 mg/dl and decrease TG by 3–64 mg/dl. However, interestingly, this is contrary to a study conducted by Conley et al. (2018) among 24 participants over six months, there was no statistically significant difference in total, LDL, and HDL cholesterol or triglycerides in either intermittent or continuous energy restriction groups. It may, however, be explained by a possible gender bias that was restricted to obese males, raising the inquiry as to how applicable these results would be to other demographics.

Previous research has demonstrated that IF for 12–36 hours causes a metabolic switch Anton et al. (2018), resulting in the breakdown of triglycerides into fatty acids and glycerol and the conversion of fatty acids to ketone bodies in the liver de Cabo & Mattson, (2019), throughout fasting, fatty acids and ketone bodies deliver energy to cells and tissues (Malinowski et al. 2019). Recently, in Ahmed et al. (2021) trial, the IF group fasted for ∼12 h during day time, three times per week for 6 weeks had a substantial reduction in total cholesterol, HDL, and LDL cholesterol, with no significant improvements in either of the control group's markers.

3.5. The Impact of IF on Blood Pressure and Hypertension

If diet utilization has a significant influence on decreasing blood pressure. This was demonstrated in animal studies, after which the diet's effectiveness in humans was confirmed. Studies on male Sprague Dawley rats at the University of Buffalo, USA, reported the IF diet's beneficial effect on the cardiovascular system. Telemetry transmitters were implanted to overcome cardiac function. After a few weeks of close attention and examination, a drop in systolic and diastolic blood pressure, as well as a decrease in heart rate, was noticed (Malinowski et al. 2019). The diet's effectiveness in humans has also been documented in studies undertaken at the Buchinger Wilhelmi Clinic in Germany. The study consisted of 1,422 participants who were followed for a year and on the IF diet. The study demonstrated that participants who fasted for an extended time had lower systolic and diastolic blood pressure (De Toledo et al. 2019).

Furthermore, A randomized cross-over trial was carried out by Sutton et al. (2018) observed early time-restricted feeding (eTRF) as an effective approach to enhance certain features as the study explored insulin sensitivity, oxidative stress, and blood pressure. After 5 weeks of fasting for 18 hours, eight overweight men with pre-diabetes had an average systolic blood pressure reduction of 11±4 mm Hg and a diastolic blood pressure reduction of 10±4mmHg. Similarly, in a single-arm pilot study performed by Wilkinson et al. (2020), the substantial reduction in blood pressure was revealed to be consistent over a comparatively short time, by 5.12 ± 9.51 mmHg and 6.47 ± 7.94 mmHg in systolic and diastolic blood pressure, respectively. However, smaller sampling sizes were used in experiments, affecting the representativeness and generalizability of results under TRF protocols. The mechanism of hypotension can be associated with parasympathetic nervous system activation due to brain-derived neurotrophic factor (BDNF), increased norepinephrine excretion through the kidneys, and increased sensitivity to insulin and natriuretic peptides (De Toledo et al. 2019). It has been noted that the health benefits of cardiovascular do not last longer than the IF diet. Post completion, the values of pressure return to their initial values (Malinowski et al. 2019). The impacts of IF on blood pressure have been demonstrated in other different studies. A research finding by Erdem et al. (2018) similarly points towards that IF produces a significant improvement in office and ambulatory patients' blood pressure values; this may be owing to different lifestyles and various dietary intakes in addition to the interval of fasting. Accordingly, Kord-Varkaneh et al. (2020) insisted on the energy restriction through IF and incorporating diets that would create better health outcomes for subjects. Even though the systematic study and meta-analysis included 23 trials, the results revealed that energy-restricting diets lowered

blood pressure and induced weight loss in 1397 participants. However, the efficacy of IF in lowering SBP and DBP is dependent on the intervention period of no more than 12 months and fasting regimens.

DISCUSSION

Although, there have been limited studies on IF for patients with MetS, and the plurality of it has focused on obese or overweight people. However, based on the established themes, we confirmed that IF improved fasting blood glucose, insulin resistance, weight loss, lowering blood pressure, and lowering lipid profile as compared to a non-fasting control group. According to the findings of a four-week study that evaluated the impact of these various diets on cardiometabolic pathways, changes in metabolic parameters included insulin resistance, blood pressure, and lipids were observed in both groups, independent of weekly energy distribution (Pinto et al. 2019).

In individuals suffering from MetS, 5–10% weight loss is recommended for blood glucose regulation, improvement of dyslipidaemia, and lowering blood pressure (Wing et al. 2011). The constrained use of glycogen and fatty acids for fuel is due to the constant availability of glucose (Mattson et al. 2017). Therefore, the primary aim of the clinical approach to treating obesity is to reduce this accumulation of adipose tissue (Schroder et al. 2021). Fasting is an effective and vital strategy that enables the body to rely on fat for energy rather than just sugars, even while maintaining hormones for proper metabolism and resulting in less water retention and fat weight (Patterson & Sears, 2017). These processes turn white fatty tissues into brown fat. Brown fats are more metabolically active fat that produces more fuel. Fasting considerably lowers the risk of fatty liver disease and ameliorates insulin resistance (K. A. Varady, 2011).

Therapeutic fasting can reverse insulin resistance and the discontinuation of insulin treatment for controlling blood sugar fluctuations. The patients were able to significantly reduce their fat weight and waist measurement. Improved HbA1c regulation is another advantageous consequence of therapeutic fasting (Furmli et al. 2018). Clinical trials showed that comparing intermittent energy restriction to continuous energy restriction, as in Sharayah Carter et al. (2018), body weight and A1C decreases are comparable. This indicates that either IF regimens may be a realistic choice for weight loss and blood sugar control. Interestingly, there were no variations in findings between the consecutive and non-consecutive 2-day a week fasts in the Corley et al. (2018) study. It implies that, based on desire, a patient could fast every day or every other day and produce the same outcomes.

Furthermore, Triglycerides, total, and LDL cholesterol concentrations following an IF period were decreased in clinical trials, particularly among subjects with dyslipidaemia (Bhutani, Klempel, Kroeger, Trepanowski, Phillips, et al. 2013; Cai et al. 2019), these reductions may be related to weight loss and may not be direct consequences of an IF diet. However, whether from the immediate effects of the IF diet or the decline of body fat, these improvements can be anticipated to lower the risk of cardiovascular disease and stroke. Studies on the effectiveness of IF in healthy people are needed to demonstrate changes in lipid profile as a significant benefit of IF.

Interestingly, adults diagnosed with MetS had substantial reductions in systolic and diastolic blood pressure for 10 h over 12 weeks without any special effort to change physical exercise or dietary composition (Wilkinson et al. 2020). However, according to the European Society of Hypertension, the first line of elevated blood pressure management in people with MetS is improved physical exercise (30 minutes of moderate to intense physical activity each day) and reduced body weight (Redon et al. 2008). Therefore, the greater impact of IF on blood pressure decrease could be correlated with further reductions in body weight. Previous research found that the overall weight loss with both IF and calorie restriction was comparable between the two groups. Evidence is limited concerning the tolerability, consistency, and safety of IF in the general population as used as an intervention for weight loss mission and the other variables examined in this review. According to Krista A. Varady et al. (2013), two subjects experienced minimal side effects such as constipation and a mild headache, while participants of the intermittent calorie restriction study group experienced more pronounced feelings of hunger (Sundfør et al. 2018).

People can easily integrate IF into their daily routines without making any additional attempts to prepare low-calorie meals. The 12-hour fast can be sustained by eating a light breakfast and dinner conveniently, which works on both weekdays and weekends. People who work late nights or have an active social life with daily dining out habits may find it challenging (Ahmed et al.

2021).

Strengths and Limitations

To the best of our knowledge, this is the first review of its kind that focuses on the effect of IF approaches on MetS. However, most of the participants in this study are obese, which is a target of the deleterious effects of excess adipose tissue, which might induce MetS at any time. In future studies, selecting subjects based on BMI during randomization would be more useful in evaluating the losing weight of subjects using different types of IF. This review, on the other hand, may have some limitations. Although this study followed an extensive procedure review, there are several limitations. Because of the recent popularity of IF, few studies are definitive on the health effects of this diet regimen. Longer trials (more than one year) in human subjects are required to validate the benefits of IF. This review did not discuss or investigate the risks and negative impacts of IF. Due to the study's length and the rigid dietary schedule in terms of both calorie allotment and the time window in which subjects are permitted to consume, it could be difficult to recruit subjects. Because of these considerations, there is also the possibility of a strong attrition rate as well as an unwillingness to fully stick to the treatment for the duration of the research. Furthermore, there is the possibility of reporting bias because participants would be asked to self-report their mealtimes, exercise, regular calorie consumption, and self-adherence to the diet. As a result, reporting can be variable and unmanageable. This bias could be eliminated by conducting phone interviews with participants throughout the trial

CONCLUSION

The present review of the previous studies mentioned above revealed that IF was effective for losing weight, normalizing blood glucose, reducing lipids, and lowering blood pressure among obese people. More studies are urgently needed especially randomized controlled trials with a long-term follow-up period to follow diet commitment and long-term maintenance of the four variables mentioned above. Future studies should include population subgroups, such as those with risk factors for cardiovascular disease and T2DM since these patients benefit greatly from weight loss, which can modify the disease process.

CONFLICT OF INTEREST

The authors declared that the present study was performed in absence of any conflict of interest.

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AUTHOR CONTRIBUTIONS

All authors were responsible for all parts of the work. All authors have read and agreed to the published version of the manuscript.

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