Intermittent Fasting In Type 2 Diabetes Mellitus

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Abstract- *Type 2 diabetes(T2D) is a global health burden, necessitating innovative management strategies. Intermittent fasting (IF) has garnered attention for its potential benefits in glucose control, weight loss, and cardiovascular risk reduction. This systematic review synthesizes evidence from clinical trials and observational studies examining the efficacy and safety of IF in T2D management. We evaluated the effects of various IF regimens (alternate-day fasting, 5:2 diet, time-restricted feeding) on glycemic control, insulin sensitivity, body weight, and cardiovascular risk factors. Our review highlights the potential benefits of IF, including improved HbA1c, fasting glucose, and insulin sensitivity, as well as reductions in body weight and cardiovascular risk factors. We also discuss potential risks, contraindications, and clinical considerations for implementing IF in T2D management. Our findings provide insights for healthcare professionals, researchers, and patients, underscoring the need for personalized approaches and further research. Type 2 diabetes (T2DM) is a metabolic disorder characterized by insulin resistance and hyperglycemia, leading to severe complications. This review examines the hormonal mechanisms underlying T2DM development and explores intermittent fasting (IF) as a non-pharmacological treatment option. Despite IF's established benefits in obesity management, its efficacy in T2DM patients remains uncertain. We discuss the current evidence on IF's effects on glucose metabolism, insulin sensitivity, and cardiometabolic risk factors in T2DM patients, highlighting potential benefits and limitations. Our review aims to clarify IF's therapeutic potential as an adjunctive treatment for T2DM, providing insights for clinicians and researchers.*

Objective:

We conducted a systematic review to evaluate the metabolic impact of IF compared to standard diet in patients with T2DM.

Methods:

We searched PubMed, Ovid MEDLINE, and Google Scholar databases for review articles, clinical trials, and case series related to type 2 diabetes, insulin resistance, and intermittent fasting. Articles were carefully reviewed and included based on relevance to our topic.

Keywords- Diabetes, Intermittent fasting, Health, Nutrition, IF, T2DM, Type 2 diabetes mellitus.

I. INTRODUCTION

Type 2 Diabetes Mellitus (DM) is a common metabolic disorder characterized by hyperglycemia caused by various factors including impaired insulin secretion, insulin resistance, decreased glucose utilization, excessive hepatic glucose production, and systemic low-grade inflammation [1]. According to the CDC, diabetes affects 34.2 million people in the United States (10.5% of the total population) [2]. Diabetes is known to be responsible for the development of multiple long-term complications, which contribute to the disease's morbidity and mortality. For instance, diabetes is the leading cause of renal failure, new onset blindness, and nontraumatic lower extremity amputation in the United States [3]. The complications of diabetes can be either vascular or non-vascular in nature. The vascular complications include retinopathy, macular edema, mono- and polyneuropathy, autonomic dysfunction, nephropathy, coronary heart disease, peripheral vascular disease and stroke [3]. Non-vascular complications include issues with the gastrointestinal tract (gastroparesis), changes in skin color, increased risk of infections, cataracts, glaucoma, periodontal disease, and hearing loss [3]. Currently the goal of treatment for type 2 diabetes is centered around preventing or delaying complications and maintaining quality of life for the patient, as described by a consensus report for the management of hyperglycemia by the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) [4]. While it is encouraged that patients with type 2 diabetes engage in lifestyle changes including increased physical activity, weight loss, and medical nutrition therapy, a majority of patients require the use of medications to achieve control of their blood glucose levels [5]. Although it has been well described that type 2 diabetes is a disease of insulin resistance, a large amount of the medical therapies that physicians use are based around the premise of giving the patient more insulin. For instance, drugs like the sulfonylureas, GLP-1 agonists, DPP-4 inhibitors, and various insulin preparations all work by either increasing the endogenous production of insulin or increasing the amount of exogenous insulin received. While this works to reduce hyperglycemia in these patients, the idea of treating a disease of insulin resistance by increasing insulin may be counterproductive, leading to the requirement of

increasing amounts of medication over a long period of time. In fact, a study by Henry et al. [6] showed that when treating type 2 diabetics with intensive insulin therapy to achieve tight glycemic control, the patients all developed increased hyperinsulinemia and weight gain over a 6 month period.

Although the ADA and EASD describe the goal of treatment as being aimed at preventing or delaying the complications of this disease, the goal of this review is to take a closer look at the possibility of using intermittent fasting as a non-medicinal option for the treatment of type 2 diabetes through improved insulin sensitivity. When considering the therapeutic role of intermittent fasting in patients with diabetes, there are three hormones that likely play a significant role. These include insulin, as well as the adipokines leptin and adiponectin. Figures a,22 and and33 describe the effects of these hormones on various tissues. It is the purpose of this review to provide insight into the influence of these hormones on the development of insulin resistance and type 2 diabetes, as well as the beneficial effects of intermittent fasting on these metabolic markers. Moving forward, we hope this review is a summary of the current literature on the use and efficacy of intermittent fasting in the clinic. We also hope this review serves as a catalyst for physicians to publish case reports and partake in controlled studies regarding intermittent fasting and diabetes.

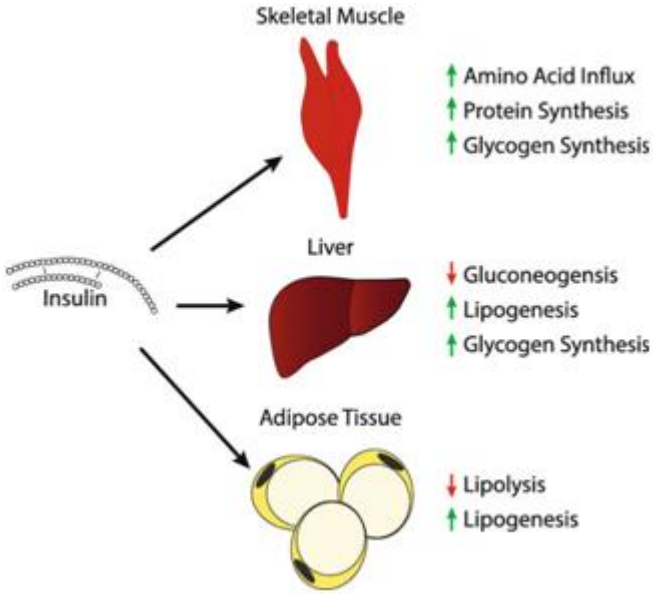

Figure b: Effects of Insulin on Various Tissues

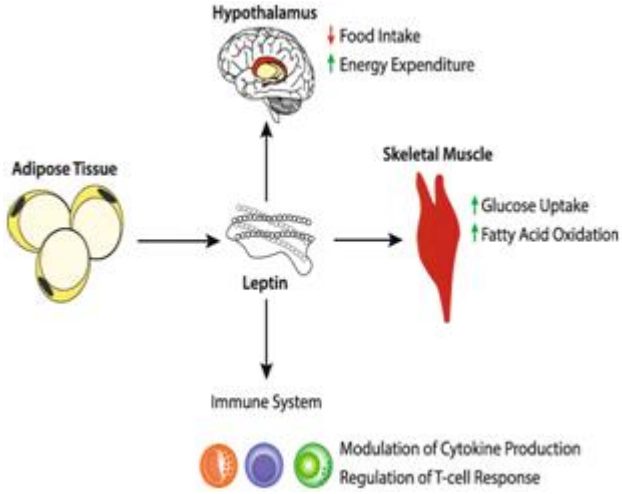

Figure a: Effects of Leptin

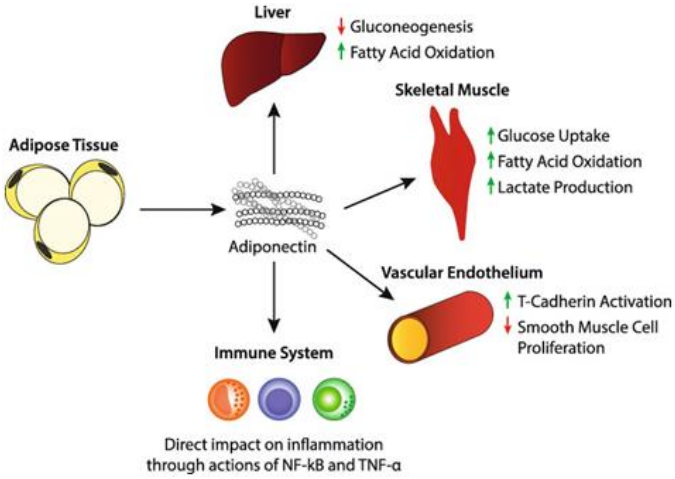

Figure c: Effects of Adiponectin

What is Type 2 Diabetes Mellitus:

Type 2 diabetes is a condition that happens because of a problem in the way the body regulates and uses sugar as a fuel. That sugar also is called glucose. This long-term condition results in too much sugar circulating in the blood. Eventually, high blood sugar levels can lead to disorders of the circulatory, nervous and immune systems.In type 2 diabetes, there are primarily two problems. The pancreas does not produce enough insulin — a hormone that regulates the movement of sugar into the cells. And cells respond poorly to insulin and take in less sugar.Type 2 diabetes used to be known as adult-onset diabetes, but both type 1 and type 2 diabetes can begin during childhood and adulthood. Type 2 is more common in older adults. But the increase in the number of children with obesity has led to more cases of type 2 diabetes in younger people.There's no cure for type 2 diabetes. Losing weight, eating well and exercising can help manage the disease. If diet and exercise aren't enough to control blood

sugar, diabetes medications or insulin therapy may be recommended.

Symptoms:

Symptoms of type 2 diabetes often develop slowly. In fact, you can be living with type 2 diabetes for years and not know it. When symptoms are present, they may include:

- Increased thirst.
- Frequent urination.
- Increased hunger.
- Unintended weight loss.
- Fatigue.
- Blurred vision.
- Slow-healing sores.
- Frequent infections.
- Numbness or tingling in the hands or feet.
- Areas of darkened skin, usually in the armpits and neck.

Causes:

Type 2 diabetes is mainly the result of two problems:

- Cells in muscle, fat and the liver become resistant to insulin As a result, the cells don't take in enough sugar.
- The pancreas can't make enough insulin to keep blood sugar levels within a healthy range.

Exactly why this happens is not known. Being overweight and inactive are key contributing factors.

How insulin works

Insulin is a hormone that comes from the pancreas — a gland located behind and below the stomach. Insulin controls how the body uses sugar in the following ways:

- Sugar in the bloodstream triggers the pancreas to release insulin.
- Insulin circulates in the bloodstream, enabling sugar to enter the cells.
- The amount of sugar in the bloodstream drops.
- In response to this drop, the pancreas releases less insulin.

The role of glucose

Glucose — a sugar — is a main source of energy for the cells that make up muscles and other tissues. The use and regulation of glucose includes the following:

- Glucose comes from two major sources: food and the liver
- Glucose is absorbed into the bloodstream, where it enters cells with the help of insulin.
- The liver stores and makes glucose.
- When glucose levels are low, the liver breaks down stored glycogen into glucose to keep the body's glucose level within a healthy range.

In type 2 diabetes, this process doesn't work well. Instead of moving into the cells, sugar builds up in the blood. As blood sugar levels rise, the pancreas releases more insulin. Eventually the cells in the pancreas that make insulin become damaged and can't make enough insulin to meet the body's needs.

Risk factors:

Factors that may increase the risk of type 2 diabetes include:

- **Weight:** Being overweight or obese is a main risk.
- **Fat distribution**: Storing fat mainly in the abdomen — rather than the hips and thighs — indicates a greater risk. The risk of type 2 diabetes is higher in men with a waist circumference above 40 inches (101.6 centimeters) and in women with a waist measurement above 35 inches (88.9 centimeters).
- **Inactivity:** The less active a person is, the greater the risk. Physical activity helps control weight, uses up **glucose** as energy and makes cells more sensitive to insulin.
- **Family history**: An individual's risk of type 2 diabetes increases if a parent or sibling has type 2 diabetes.
- **Race and ethnicity:** Although it's unclear why, people of certain races and ethnicities — including Black, Hispanic, Native American and Asian people, and Pacific Islanders — are more likely to develop type 2 diabetes than white people are.
- **Blood lipid levels:** An increased risk is associated with low levels of high-density lipoprotein (HDL) cholesterol — the "good" cholesterol — and high levels of triglycerides.
- **Age:** The risk of type 2 diabetes increases with age, especially after age 35.
- **Prediabetes**: Prediabetes is a condition in which the blood sugar level is higher than normal, but not high

enough to be classified as diabetes. Left untreated, prediabetes often progresses to type 2 diabetes.

- **Pregnancy-related risks:** The risk of developing type 2 diabetes is higher in people who had gestational diabetes when they were pregnant and in those who gave birth to a baby weighing more than 9 pounds (4 kilograms).
- **Polycystic ovary syndrome:** Having polycystic ovary syndrome — a condition characterized by irregular menstrual periods, excess hair growth and obesity — increases the risk of diabetes.

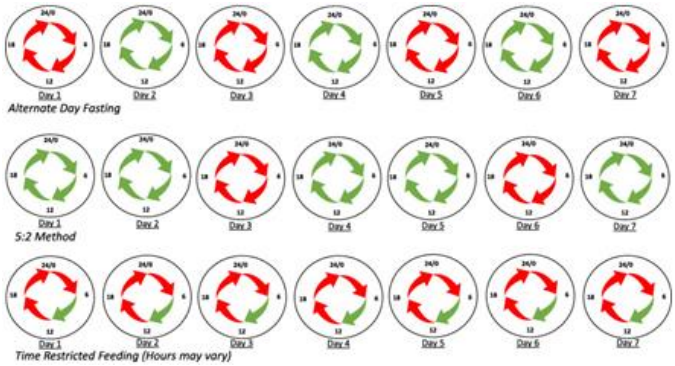

Figure d: Intermittent Fasting Regimens

What is intermittent fasting:

Intermittent fasting has recently gained popularity as a means of improving body composition and metabolic health [28, 29]. Intermittent fasting refers to eating patterns based around the principle of consuming very little to no calories for time periods ranging from 12 h to several days with a regular pattern [28]. There are several different regimens of intermittent fasting. One such regimen is alternate day fasting, in which days of fasting are separated by days of ad libitum food consumption [29]. Another method is periodic fasting, in which individuals fast for 1 or 2 days a week (also referred to as 5:2 or 6:1 fasting) [29]. Finally, the most common method is time-restricted feeding, in which food consumption is only allowed during a specified window of time each day, typically with 16–20 h daily fasts [29]. See Fig. 4 for a visual representation of the most common intermittent fasting regimens.

- Intermittent fasting may reverse type 2 diabetes: Research report by Endocrine society

After an intermittent fasting diet intervention, patients achieved complete diabetes remission, defined as an HbA1c (average blood sugar) level of less than 6.5% at least one year after stopping diabetes medication. according to a new study published in the Endocrine Society's Journal of Clinical Endocrinology & Metabolism.Intermittent fasting diets have become popular in recent years as an effective weight loss method. With intermittent fasting, you only eat during a specific window of time. Fasting for a certain number of hours each day or eating just one meal a couple of days a week can help your body burn fat. Research shows intermittent fasting can lower your risk of diabetes and heart disease.

"Type 2 diabetes is not necessarily a permanent, lifelong disease. Diabetes remission is possible if patients lose weight by changing their diet and exercise habits," said Dongbo Liu, Ph.D., of Hunan Agricultural University in Changsha, China. "Our research shows an intermittent fasting, Chinese Medical Nutrition Therapy (CMNT), can lead to diabetes remission in people with type 2 diabetes, and these findings could have a major impact on the over 537 million adults worldwide who suffer from the disease."

The researchers conducted a 3-month intermittent fasting diet intervention among 36 people with diabetes and found almost 90% of participants, including those who took blood sugar-lowering agents and insulin, reduced their diabetes medication intake after intermittent fasting. Fifty-five percent of these people experienced diabetes remission, discontinued their diabetes medication and maintained it for at least one year.

The study challenges the conventional view that diabetes remission can only be achieved in those with a shorter diabetes duration (0-6 years). Sixty-five percent of the study participants who achieved diabetes remission had a diabetes duration of more than 6 years (6-11 years)."Diabetes medications are costly and a barrier for many patients who are trying to effectively manage their diabetes. Our study saw medication costs decrease by 77% in people with diabetes after intermittent fasting," Liu said.

The other authors of this study are Xiao Yang of Hunan Agricultural University, the State Key Laboratory of Subhealth Intervention Technology and Changsha and Tourism College in Changsha, China; Jiali Zhou of Hunan Agricultural University and the Department of Shizi Mountain Primary Care in Changsha, China; Huige Shao and Bi Huang

of Changsha Central Hospital in Changsha, China; Xincong Kang of Hunan Agricultural University, the National Research Center of Engineering Technology for Utilization

Ingredients fromBotanicals and the Hunan Provincial Engineering Research Center of Medical Nutrition Intervention Technology for Metabolic Diseases in Changsha, China; Ruiyu Wu of Hunan Agricultural University and the State Key Laboratory of Subhealth Intervention Technology Achievement Application Center in Changsha, China; Fangzhou Bian of the University of California Irvine in Irvine, Calif.; and Minghai Hu of Central South University in Changsha, China.

- **Intermittent fasting, weight loss, and appetite control:**

Obesity is known to be a major risk factor for the development of type 2 DM. There are a number of mechanisms believed to contribute to the development of insulin-resistance in obese patients. These include, but are not limited to, systemic chronic inflammation and ectopic lipid deposition [7, 9, 30, 31]. Visceral adipose tissue is known to function as both a paracrine and endocrine organ through the secretion of adipokines [10]. These adipokines are either proinflammatory leading to chronic low-level inflammation, such as leptin, or anti-inflammatory such as adiponectin [10]. Leptin is known to play a role in the regulation of body weight through signaling to the hypothalamus and other brain regions to suppress food intake and increase energy expenditure [9]. The inflammatory effects of leptin are likely due to its role in the production of IL-6, which induces the synthesis of C-reactive protein in the liver as well as upregulation of the pro-inflammatory cytokine TNF-alpha [10]. Interestingly, patients with higher levels of BMI and insulin resistance were found to have increased leptin levels, possibly signifying that patients with obesity and insulin resistance are developing leptin resistance as well [10]. On the contrary, adiponectin is known to have antidiabetic and anti-inflammatory effects. Adiponectin acts on various receptors that results in an increase in skeletal muscle and hepatic fatty acid oxidation, reduced hepatic gluconeogenesis, and increased glucose uptake [10]. It also exerts anti-inflammatory effects through direct action on inflammatory cells, action of NF-kB, and interactions with TNF-alpha [10]. Adiponectin levels decrease with accumulation of visceral fat [10]. López-Jaramillo et al. performed a review with the intention of determining levels of leptin and adiponectin in patients with metabolic syndrome. They found that in patients with the metabolic syndrome, which includes obesity and insulin resistance, an imbalance in levels of leptin and adiponectin appeared to play a role in metabolic alteration that increased the risk of type 2 diabetes [10]. Interestingly, several studies have demonstrated that intermittent fasting, even in the absence of fat loss, has resulted in a reduction of leptin levels and an increase of adiponectin, which results in improvements of insulin resistance [32].

It has long been known that restricting calories can reduce body weight and increase metabolic health [33]. A study by Larson-Meyer et al. [34] showed that 25% calorie reduction either via diet alone or diet in conjunction with exercise led to improvements in insulin sensitivity and reduction in β-cell sensitivity in overweight, glucose-tolerant individuals. However, several obesity trials have demonstrated that humans have significant difficulty sustaining daily calorie restriction for extended periods of time [28]. On the other hand, intermittent fasting has higher compliance and has shown promise in the improvement of metabolic risk factors, body composition, and weight loss in obese individuals [28, 35, 36]. It has been shown that these beneficial effects are due in part to the shift during fasting from the utilization of glucose to fatty acids and ketones as the body's preferred fuel source [28]. During this transition the body begins to switch from the synthesis and storage of lipids to mobilization of fat in the form of ketone bodies and free fatty acids [28]. This transition of fuel source, or metabolic reprogramming, has been highlighted as a potential mechanism for many of the beneficial effects of intermittent fasting. Lastly, intermittent fasting has been shown to reduce adiposity, particularly visceralfat and truncal fat, largely due to mild energy deficits [12, 17]. It is through this reduction in adiposity that patients may experience improvements intheir leptin/adiponectin levels and sensitivity, leading to improved appetite control and lower levels of chronic inflammation thus improving several risk factors for type 2 diabetes.

- **Intermittent fasting and insulin sensitivity**

Insulin plays a significant role in glucose homeostasis due to its influence in promoting the storage and utilization of glucose. However, the effects of insulin are not limited to glucose homeostasis. Insulin also plays a role in the stimulation of DNA synthesis, RNA synthesis, cell growth and differentiation, amino acid influx, protein synthesis, inhibition of protein degradation, and most importantly, the stimulation of lipogenesis and inhibition of lipolysis [8].

It is the development of insulin resistance, which is defined as the necessity of higher circulating insulin levels in order to produce a glucose lowering response, that is thought to be responsible for the development of type 2 diabetes [7]. In order to promote regulation of glucose homeostasis, insulin works primarily on receptors in skeletal muscle, liver, and

white adipose tissue [7]. In short, there are several proposed mechanisms regarding the development of insulin resistance. One of the more prominent theories describes the association of increased adiposity and the subsequent chronic inflammation that leads to the development of insulin resistance in tissues [7].

Intermittent fasting, as described previously, may reduce adiposity and subsequently insulin resistance via reduction of caloric intake as well as due to metabolic reprogramming. In addition, energy/nutrient depletion (such as that achieved through reduced caloric intake) has been shown to promote healthier aging and reduction in chronic disease through increased activation of AMP activated protein kinase (AMPK) [37]. AMPK responds to both to increased AMP/ADP:ATP ratios as well as to endocrine signals of hunger and satiety [37]. The role of AMPK at a biochemical level is outside of the scope of this review, however activation of AMPK through a low energy state has been shown to initiate physiologic responses that promote healthy aging [37]. Increased levels of insulin, whether through increased energy intake or insulin resistance, leads to the activation of downstream mediators that ultimately inhibit AMPK. The role of AMPK in improved insulin sensitivity is most evident via the positive effects of the commonly prescribed biguanide, metformin. Metformin is known to promote the activation of AMPK, and has been shown to be very effective in the treatment of type 2 diabetes as well as in the mitigation of a number of chronic disease states [37]. In theory, decreased energy intake, such as that is achieved through intermittent fasting, will lead to prolonged decreased levels of insulin production and increased levels of AMPK, which likely plays a role in the improvements in insulin sensitivity and glucose homeostasis.

- **Intermittent fasting as a treatment for type 2 diabetes?**

Several studies have shown promise for the use of intermittent fasting protocols as a potential treatment for diabetes. Tables Tables11 and and22 illustrate the findings of several recent studies regarding intermittent fasting and its effect on measures including body weight, fasting glucose, fasting insulin, adiponectin, and leptin. The inclusion/exclusion criteria can be found in the supplementary file S1. In a systematic review and meta-analysis by Cho et al. [32] that included studies evaluating patients both with and without pre-diabetes (diabetic patients were excluded), it was found that of 8 studies comparing the effects of an intermittent fasting diet to a control group, BMI decreased by 0.75 kg/m2 over periods ranging from 4 to 24 weeks. Furthermore, of 8 studies comparing intermittent fasting to a control group in the evaluation of glycemic control, it was found that the intermittent fasting group had significant reductions in fasting glucose levels (-4.16 mg/dL; $p = 0.003$). Lastly, when comparing leptin and adiponectin levels between the intermittent fasting subjects and the control subjects in all studies, the reviewers found increased adiponectin levels (1008.87 ng/mL; $p = 0.023$) and decreased leptin (-0.51 ng/mL; $p < 0.001$) [32]. A case series by Furmli et al. [26] followed three patients with type 2 diabetes over several months after beginning an intermittent fasting regimen consisting of three 24 h fasts per week. Over the course of the study, all patients had significant reductions in HbA1C, weight loss, and all of the patients were able to stop their insulin therapy within 1 month [26]. Interestingly, the three patients in this case series all reported tolerating fasting very well, and no patient stopped the intervention at any point out of choice [26]. This suggests that intermittent fasting may not only be successful as a non-medicinal treatment option for patients with type 2 diabetes, but supports the notion that this intervention is tolerable as well. Carter et al. [19] performed a clinical trial in which 137 adults with type 2 diabetes were divided into two groups, one intermittent energy restriction group (500–600 kcal/day for 2 days per week and normal diet every other day) and a continuous energy restriction group (1200–1500 kcal/day). After 12 months of intervention, the two groups showed similar reductions in HbA1C levels and greater reductions in weight in the intermittent energy restriction group. Finally, a similar clinical trial by Gabel et al. [16] compared an alternate day fasting regimen (25% of energy needs on fasting days, 125% of energy needs on non-fasting days) to continuous energy restriction (75% of energy needs daily) and a control group of obese, non-diabetic patients. Over an intervention period of 12 months, there were similar reductions in body weight, BMI, and fat mass between the alternate day fasting and continuous energy restriction groups, however there were significant reductions in fasting insulin levels (-44%; $p < 0.05$) and homeostatic model assessment of insulin resistance (HOMA-IR) levels (-53%; $p < 0.05$) in the alternate day fasting group [16]. HOMA-IR is a marker used to measure levels of insulin resistance.

Challenges in Managing Type 2 Diabetes:

- **Detecting it Early:**

Type 2 diabetes (T2D) develops quietly, making early detection crucial. Screening adults aged 35-45 can help. Lifestyle changes and education are vital.

- **Screening Methods:**

Current tests include:

1. Oral Glucose Tolerance Test (OGTT) - accurate but inconvenient.

2. Fasting Plasma Glucose (FPG) and Hemoglobin A1c (HbA1c) - combining both may improve diagnosis.

- **Adopting Intermittent Fasting**

Sticking to lifestyle changes, like intermittent fasting, can be tough. Clinicians should provide motivation and support.

- **Challenges to Adherence:**

1. Losing motivation
2. Feeling hungry or sluggish
3. Social pressures
4. Difficulty self-monitoring

- **Benefits and Limitations**

Intermittent fasting can improve physical and mental health, but:

1. Long-term effects are unclear.
2. Some individuals should avoid it (e.g., those with certain health conditions).
3. Benefits may extend beyond weight loss (e.g., improving dyslipidemia, hypertension).

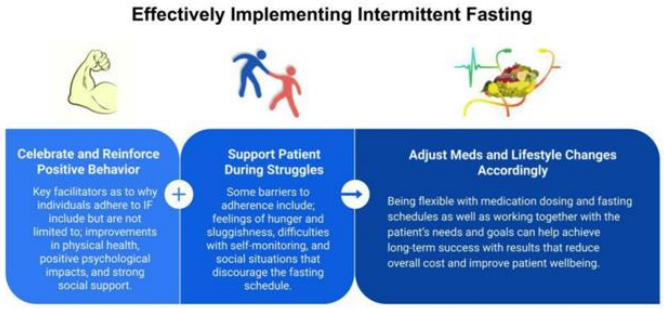

Figure e: An example of implementing IF into the lives of patients. This represents a generalized strategy that may be modified to fit the situation.

Limitations and future research:

This review is not a systematic review and as such lacks the power to summarize all trails with statistical significance. Having said that, we highlighted the research that has been done in humans and presented evidence that intermittent fasting improves insulin sensitivity, likely through a combination of weight-loss and "metabolic reprogramming". There is a significant amount of research that has been done on the effects of intermittent fasting in regards to improvements in body composition and metabolic health, however a majority of the data to date has come from animal studies, which were not included in this review. Although there are a number of case reports showing significant improvements in diabetic patients' glucose control, many of the randomized controlled trials fail to include patients with diabetes. This is an area where further research is needed, as the current trials (and case reports) included in this review that have been done on diabetic patients have shown promise in improving metabolic health with nearly no adverse effects. Most patients doing some form of intermittent fasting experience mild energy deficits and weight-loss, that may not be appropriate for all patients. As such, there needs to be more research into delineating the metabolic improvements of intermittent fasting from weight-loss.

II. CONCLUSION

Type 2 diabetes afflicts 34.2 million people in the United States, and is associated with significant morbidity and mortality [1]. Although diabetes is characterized as a disorder of insulin resistance, a majority of the pharmaceutical treatments for this disease promote increases in insulin levels to achieve better glycemic control. This leads to a number of issues including weight gain, worsened insulin resistance, increased levels of leptin, and decreased levels of adiponectin. Intermittent fasting has become an increasingly popular dietary practice for the improvement of body composition and metabolic health [28, 29]. It also has shown promise in the treatment of type 2 diabetes. This may be due to its effects on weight loss, in addition to decreasing insulin resistance and a favorable shift in the levels of leptin and adiponectin [32]. Patients may approach their physicians with questions regarding the implementation of intermittent fasting. In addition, physicians should be aware of the benefits of this dietary practice as a treatment for type 2 diabetes so that they may be able to help patients use this to combat the progression of their disease.

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