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The effectiveness of fasting in combating insulin resistance among type 2 diabetic individuals

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THE EFFECTIVENESS OF FASTING IN COMBATING INSULIN RESISTANCE AMONG TYPE 2 DIABETIC INDIVIDUALS

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ABSTRACT

For over 50 years, Americans were led to believe that diets high in carbohydrates but low in dietary fat was healthy and normal. Now, over 34 million Americans are diagnosed with diabetes, 95% of that population having Type 2 Diabetes Mellitus (T2DM). Insulin resistance is a known marker for pre-diabetes and other health related issues. An individual can develop insulin resistance by chronic intake of high carbohydrate and high fat foods. Researchers are constantly finding methods to improve an individual's insulin sensitivity and hopefully cure T2DM. There is now a general agreement amongst the literature that a diet lower in refined carbohydrates together with exercise can aid in the prevention of insulin resistance and therefore T2DM. A newer, more drastic method that is still being researched and evaluated is known as fasting. Various forms of fasting exist such as intermittent fasting, alternate day fasting (ADF), brief fasting (BF), and prolonged fasting (PF). Fasting itself is not new and has had religious roots in Catholicism and Islam.

Across the current literature, studies have suggested that fasting results in marked weight loss, and in some cases, fat mass loss. It should be noted that some cases report no significant difference in weight loss between caloric restriction and fasting. Fasting may

have other health benefits that could be advantageous to an individual over solely caloric restriction. Many cases also claim improvement in insulin sensitivity, decreased insulin resistance, as well as positive changes to blood pressure, glucose levels and cholesterol levels. A few studies reported other benefits such as decreased appetite, increased cognition, autophagy, and reduced inflammation. Individuals who suffer from insulin resistance and T2DM may also suffer from hypertension, obesity, high cholesterol, and other negative health issues. Compared to caloric restriction, patients may find it beneficial to practice fasting alongside caloric restriction and exercise to improve insulin sensitivity.

Given the current literature, negative health issues or side effects associated with fasting have not been reported. The biggest issue amongst trials was adherence of the fasting practice. One study had noted after a one-year follow up; subjects regained most of their lost weight. Further research, specifically long term randomized controlled trials on human subjects, is needed to reach a more significant conclusion. The longest study was one year in duration. Some studies also have used mice as subjects but not all theories have been tested on humans. Because of to the lack of long-term trials, certain health benefits or negative health issues associated with fasting are still unknown.

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LIST OF ABBREVIATIONS

ACA	Acetoacetate
ADF	Alternate day fasting
ATP	Adenosine triphosphate
BBB	Blood-brain barrier
BF	Brief fasting
BHB	Beta-hydroxybutyrate
cAMP	Cyclic-AMP
CAT	Carnitine-acylcarnitine translocase
CDC	Center for Disease Control and Prevention
CPT-1	Carnitine palmitoyl transferase
CR	Caloric restriction
eTRF	Early time-restricted feeding
FA	Fatty acids
FAO	Fatty acid oxidation
G1P	Glucose-1-Phosphate
G6P	Glucose-6-Phosphate
GLUT-1	Glucose Transporter-1
HSL	Hormone-sensitive lipase
IR	Insulin resistance
IF	Intermittent fasting
MCT-1	Monocarboxylate Transporter-1

MRC	Mitochondrial Respiratory Complex
PF	Prolonged fasting
T2DM	Type 2 Diabetes Mellitus
UCP-2	Uncoupling Protein-2

INTRODUCTION

There are over 34 million Americans who suffer from diabetes and 88 million adults are prediabetic. The overwhelming majority of those individuals, 90-95%, are diagnosed with Type 2 Diabetes Mellitus (T2DM) (Center for Disease Control and Prevention [CDC], 2019). In the United States alone, the presence of obesity has increased from 30.5% in 1999-2000 to 42.4% in 2017-2018 (CDC, 2021). Along with obesity and T2DM, there has also been an increase in other related conditions including cardiovascular disease, stroke, and death from these diseases. The obesity epidemic could be attributed to an event that occurred over 50 years ago. It has been reported that the sugar industry had quietly paid money to scientists and researchers to draw attention to dietary fat as the culprit of poor health (National Public Radio, 2016). The belief that nutritional fat causes obesity has led to the increase of supposedly healthier "fat free" foot products in grocery stores shaping the development of the Western Diet - a diet marked by overconsumption of sugar and processed food (Kopp, 2019).

Food high in carbohydrates but low in dietary fat and protein do not offer much satiety and therefore are easier to consume in excess (Tremblay & Bellisle 2015). Chronic intake of both high carbohydrate and high fat foods will eventually lead to the development of insulin resistance (IR) and T2DM (Khathi et al., 2018). IR can be clinically noted as the inability of insulin, endogenous or exogenous, to be utilized within the body to increase uptake of glucose (Lebovitz, 2001). T2DM is related to IR and can be defined as cellular dysfunction of beta cells, resulting in hyperglycemia (Goyal and Jialal, 2020).

Metabolically, the consequences of IR are many. IR can affect glucose disposal rates, hypertension, hyperglycemia, inflammation, visceral adiposity, and endothelial dysfunction (Freeman and Pennings, 2020). The development of IR can be both genetic and acquired. Genetic factors can include ataxia-telangiectasia, Werner's syndrome, myotonic dystrophy, Alstom syndrome, Rabson-Mendenhall syndrome, and lipodystrophy. Acquired factors include aging, nutritional deficits and imbalance, excess adipose tissue, glucose toxicity, and lipotoxicity. Medications such as protease inhibitors, glucocorticoids, and atypical antipsychotics have also been linked to IR as acquired factors (Freeman and Pennings, 2020). IR has the possibility if untreated to lead to T2DM.

Individuals with T2DM usually suffer from symptoms such as frequent urination, nausea, dizziness, tiredness, and extreme thirst (CDC, 2021). There are many risk factors for developing T2DM. The most common risk factors are genetic factors, medications affecting carbohydrate metabolism, especially sugar, smoking, high carbohydrate and high sugar diet, lack of physical activity, and being overweight. Individuals with T2DM also can develop other health problems such as diabetic foot that could lead to amputation, cardiovascular disease, ketoacidosis, and damage to the kidneys, eyes, and nerves (CDC, 2021).

Within the last decade, several low carbohydrate style diets have become popular - ketogenic diet and Paleo diet etc. – as the negative health consequences of high

carbohydrate consumption was realized. Along with these lower carbohydrate diets, the practice of fasting became more popular. Fasting is rooted in history and religious practices. During the month of Ramadan, Islamic individuals fast every day from dawn to sunset. Catholic individuals practice fasting during Lent, eating only one meal on Fridays. It has been reported that lower carbohydrate diets and fasting reverse IR caused by dietary overconsumption of high fat and high carbohydrate foods (Freeman et al., 2018). Current experimental and clinical data indicate that fasting can lower body weight, improve insulin sensitivity, and lead to beneficial effects on blood pressure (Li et al., 2017).

Figure 1 illustrates the effects of IF and demonstrates glucose and ketone level fluctuation in typical American diets as well as time restricted feeding and one day fasting (Figure 1) (Mattson et al., 2017). Fasting also decreased levels of insulin and leptin while improving sensitivity to both; lower body fat, decreased blood pressure, and reduced inflammation were other results from fasting (Mattson et al., 2017).

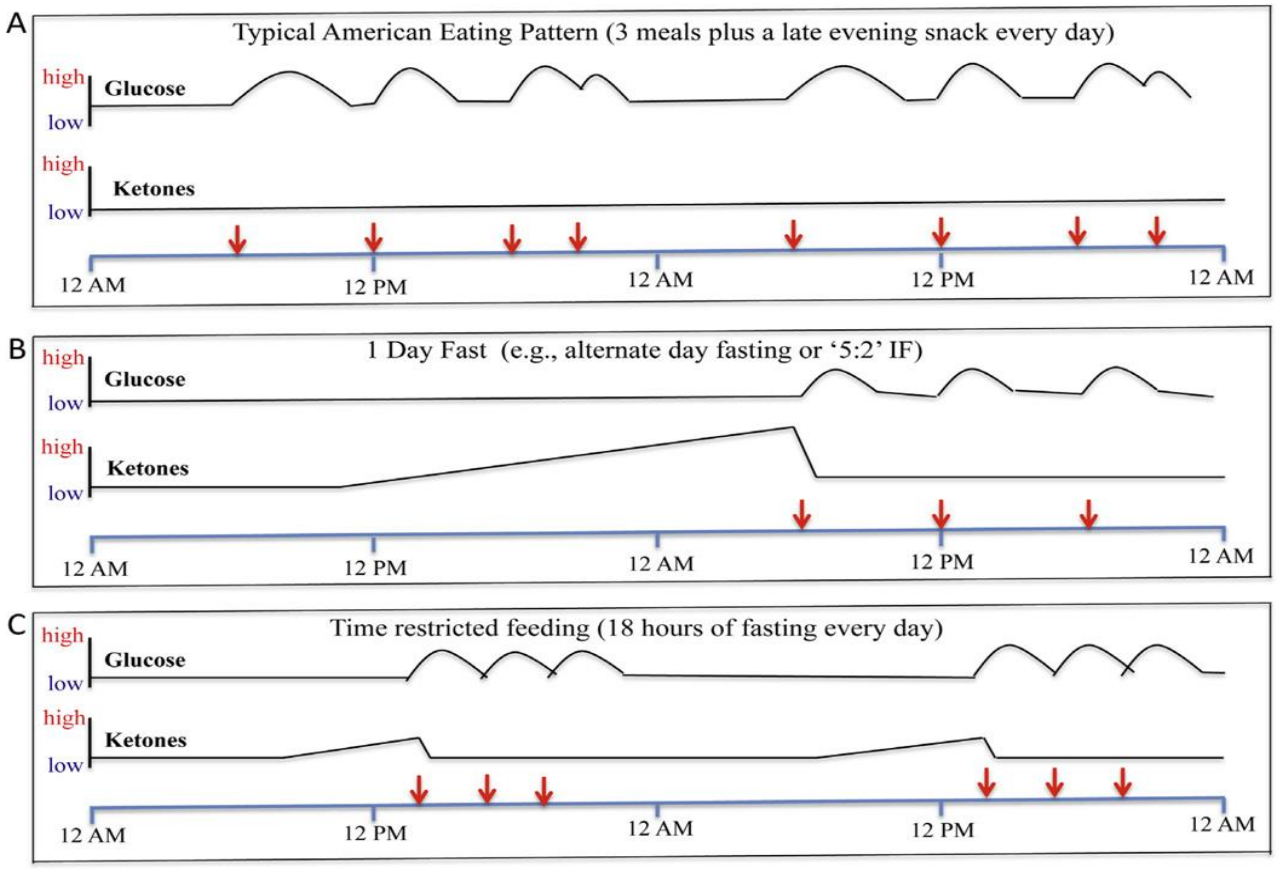

Figure 1. Glucose vs. Ketone levels in different eating patterns. This chart shows three different eating patterns and how glucose and ketone levels respond throughout the day. The red arrows indicate time of feeding. (Figure taken from Mattson et al., 2018).

The Human Body in the Fasted State

There are three factors that affect the fasted state: amino acids, glycogen, and lipids. Amino acids play different roles within the fasted state. Glucogenic amino acids such as alanine and arginine are converted to intermediates used within the Krebs cycle or converted into pyruvates. ketogenic amino acids which include leucine and lysine are converted into acetyl-CoA or acetoacetate. There is also a group of amino acids that can be metabolized by either the glucogenic or ketogenic pathway such as isoleucine and tyrosine (Sanctivores et. al, 2020). During short periods of fasting (1-3 days), the liver utilizes glycogenolysis to release glucose. Glycogenolysis is simply the process in which the body will breakdown glycogen into glucose. However, during a prolonged fasting state, the body is depleted of glycogen stores and will create glucose through a process known as gluconeogenesis (Rui, 2014). Gluconeogenesis is the process in which the body creates glucose.

Glycogen levels decrease throughout a fasted state. When blood glucose levels decrease, glucagon levels rise. When glucagon levels increase insulin secretion decreases. As insulin levels decline glucose and glycogen levels also decrease. In the liver, glucagon binds to its receptors to induce a cyclic-AMP (cAMP) reaction. The enzyme glycogen phosphorylase will eventually turn a glycogen molecule into a glucose-1-phosphate (G1P). The enzyme phosphoglucomutase will then take the G1P and convert it to a glucose-6-phosphate (G6P). The G6P, derived from glycogen, will be hydrolyzed into a glucose and inorganic phosphate to be utilized in the body (Sanctivores et. al, 2020).

When the body undergoes the short-term fasted state and transitions into the long-term fasted state glucose and glycogen are no longer readily available. The body does however have a storage of triglycerides that can be broken down into fatty acids and later into ketones as an alternative fuel source. When the body begins its fasted state, the hormone called hormone-sensitive lipase (HSL) is activated. HSL can be stimulated by various other hormones such as glucagon and epinephrine, which have higher levels when in a fasted state. The hormone glucagon or epinephrine will utilize G-protein coupled receptors and the G-alpha subunit that regulates adenylyl cyclase to create cAMP. This creates a cascade reaction where cAMP will indirectly activate HSL by activation of protein kinase A. Fatty acids will be released from triglyceride leaving three fatty acid molecules and a glycerol. Glycerol can be converted to various substituents and then can be utilized in glycolysis. Fatty acids can be turned into energy by mechanisms of ketogenesis and beta-oxidation. During beta-oxidation, fatty acids will be converted into acetyl CoA and electron carriers such as FADH and NADH. During ketogenesis, acetyl CoA is used and eventually will become acetone and beta-hydroxybutyrate, a ketone (Sanctivores et. al, 2020). Figure 2 illustrates in detail the various metabolic pathways of a state of ketosis. On average, given normal conditions, the body can make 22 ATP from ketone bodies. The organs of the body for the most part can utilize ketones as energy sources. Organs such as the brain, under extreme starvation which takes 24 days, and muscle systems can use ketones as an alternate fuel source (Dhillon and Gupta, 2021).

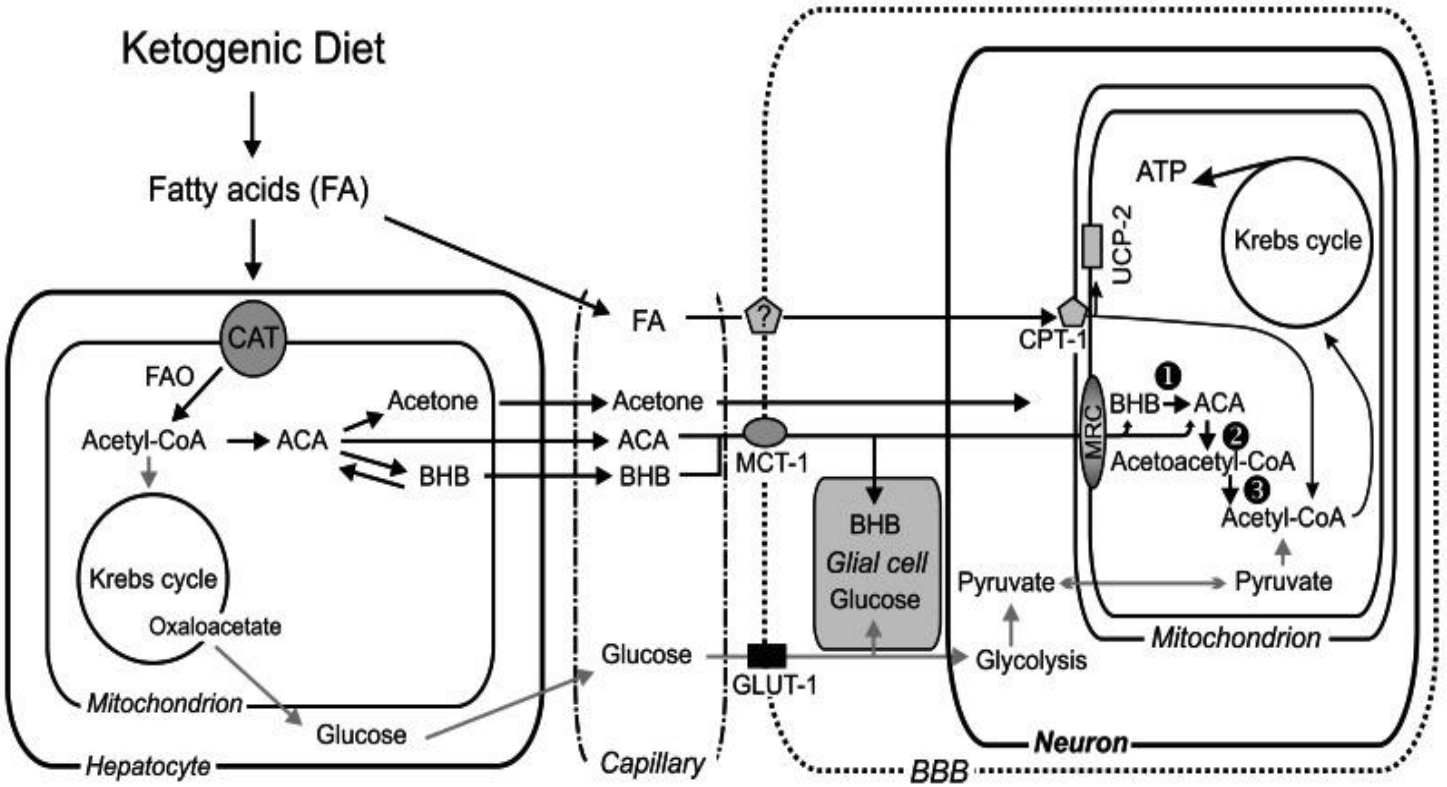

Figure 2: Metabolic pathways involved in Ketosis. This pathway shows the path of fatty acids being utilized for energy for the creation of ATP. Figure taken from Masino et al., 2012.

Insulin Resistance and Type 2 Diabetes Mellitus

Insulin is the main regulator for blood glucose levels and is extremely important for maintaining proper health. Insulin levels fluctuate throughout the day depending on frequency of food intake as well as what type of food is being consumed. Generally, foods high in carbohydrates will result in a greater spike in insulin levels whereas foods high in dietary fat will result in much lower spikes in insulin levels. The hormone insulin is responsible for either storage or usage of sugar (CDC, 2019).

Insulin resistance is normally a sign of prediabetes that may eventually develop into T2DM. The conventional "Western Diet," a diet consisting of high, repeated intake of sugar rich foods and beverages can quickly put an individual at risk for insulin resistance. The process of habitual and repeated overeating these high glycemic foods triggers the pancreas to release higher amounts of insulin. As the process of overeating continues, beta cells become insulin resistant and become desensitized to spikes in insulin levels. The pancreas will ramp up production and secretion of insulin. Insulin will signal to the body that liver and muscles need to store glycogen. Eventually those stores will reach maximum capacity and excess glucose will be stored as body fat. Figure 3 displays the various mechanisms of insulin resistance Weight gain along with a multitude of other factors can develop into full onset T2DM (CDC, 2019).

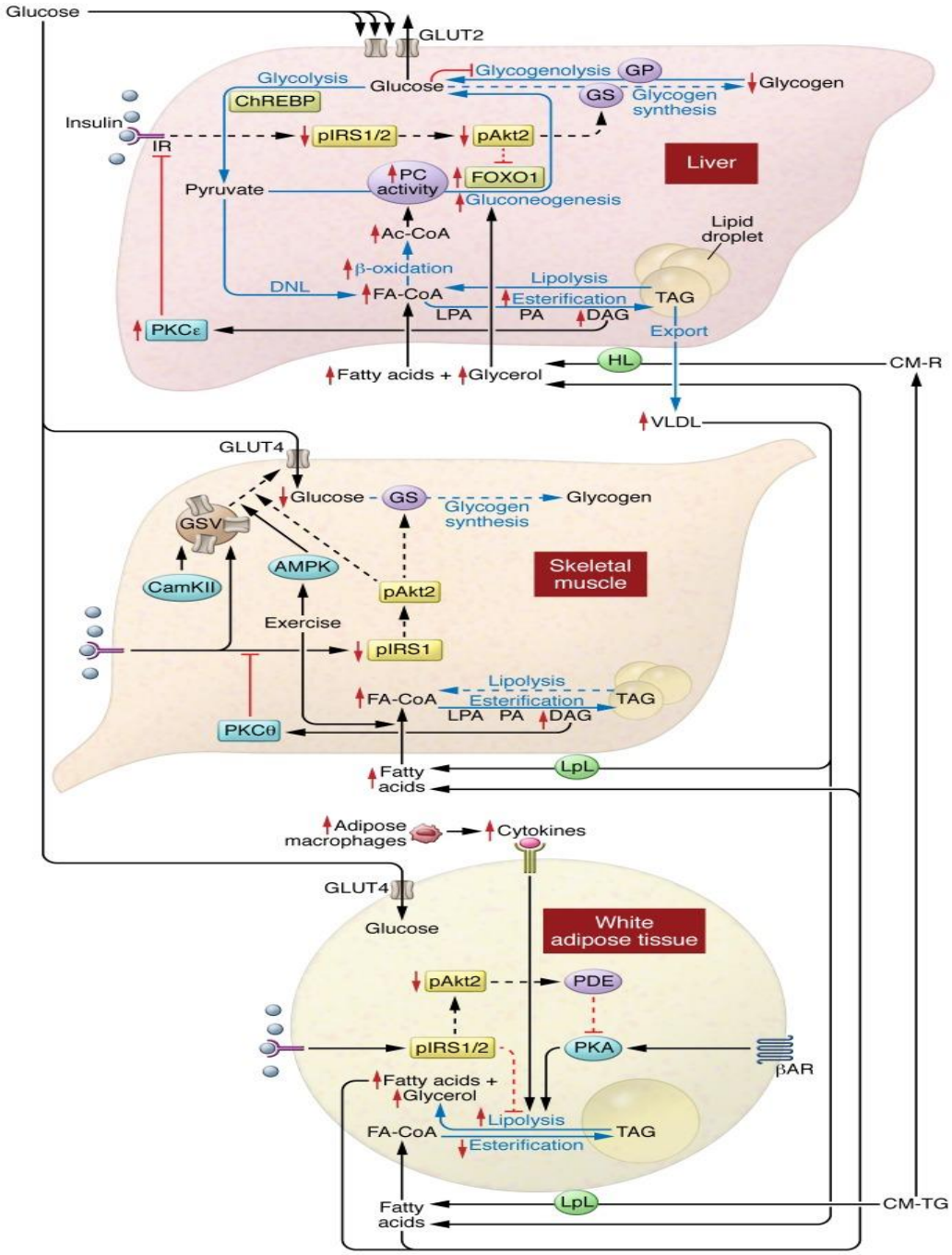

Figure 3: Mechanisms of Insulin Resistance. The pathway begins in the liver where insulin signaling is impaired. It then moves on to skeletal muscle where muscle glucose uptake is impeded. Lastly, in white adipose tissue, fatty acids are released and eventually will increase glucose production. Figure taken from Samuel and Shulman 2016.

T2DM is a common disorder that is caused by a defect in insulin secretion by beta cells of the pancreas or by insulin resistance. There are a multitude of risk factors that include genetic factors such as previous family history, environmental factors such as little to no physical activity, and metabolic factors such as an unhealthy diet (Galicia-Garcia, 2020). Obesity is one of the strongest factors and is strongly associated with insulin resistance. Obesity is also commonly associated with an unhealthy diet and decreased physical activity. On the contrary, physical activity can help delay onset of T2DM by increasing blood flow to muscles, reducing fat from the intra-abdominal region, and improving glucose uptake by almost 40% (Galicia-Garcia et al., 2020). Figure 4 displays a chart of risk factors for T2DM.

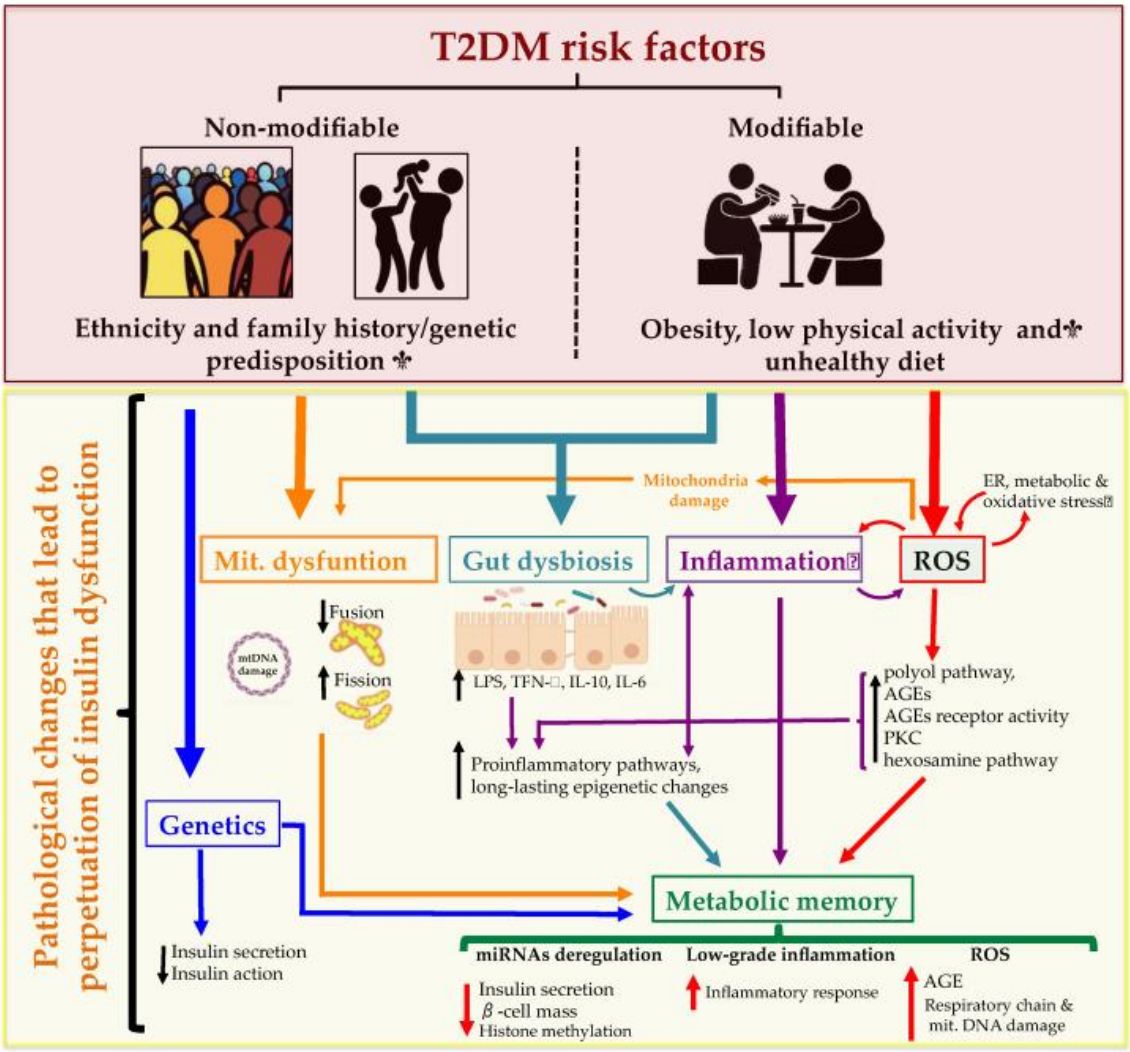

Figure 4: Risk Factors for Developing T2DM. Risk factors can be divided into non-modifiable including ethnicity and family history and modifiable such as diet, physical activity and obesity. A complex combination of both non-modifiable and modifiable are responsible for the development or prevention of T2DM. Figure taken from Galicia-Garcia et al., 2020.

Beginning a Fast

Fasting can come in various forms such as intermittent fasting (IF), brief fasting (BF), and prolonged fasting (PF). Proponents of IF encourage a timed regimen of a 16-20 hour fast followed by an 8 or 4 hour feeding window, respectively. Brief fasting can take place for 24-72 hours whereas prolonged fasts can take place over one week. The goal while practicing fasting for health reasons is to limit insulin secretion, to help improve insulin sensitivity (Anton et al., 2018). During the fasting window, beverages such as black coffee, green tea, plain water, and in some cases zero calorie beverages are allowed (Wilhelmi de Toledo et al., 2019).

A sample regimen for IF following a 16 hour fast, 8 hour feeding window is as follows: Mark the time before the last meal ends. If the last meal ends at 8pm, the 16 hour fast will begin immediately after. When the individual wakes up at 8 am, he would already be 12 hours into the fast. The subject can make a cup of black coffee or zero calorie tea to start the day. By noon time, 16 hours will have elapsed, and the feeding window can begin. If the first meal is taken at noon, the subject would have until 8 pm to eat the next meal, meeting the caloric goals. The cycle will repeat and can vary based off preferred eating time and type of fast. Figure 5 shows the human circadian rhythm while looking at various factors during fasting.

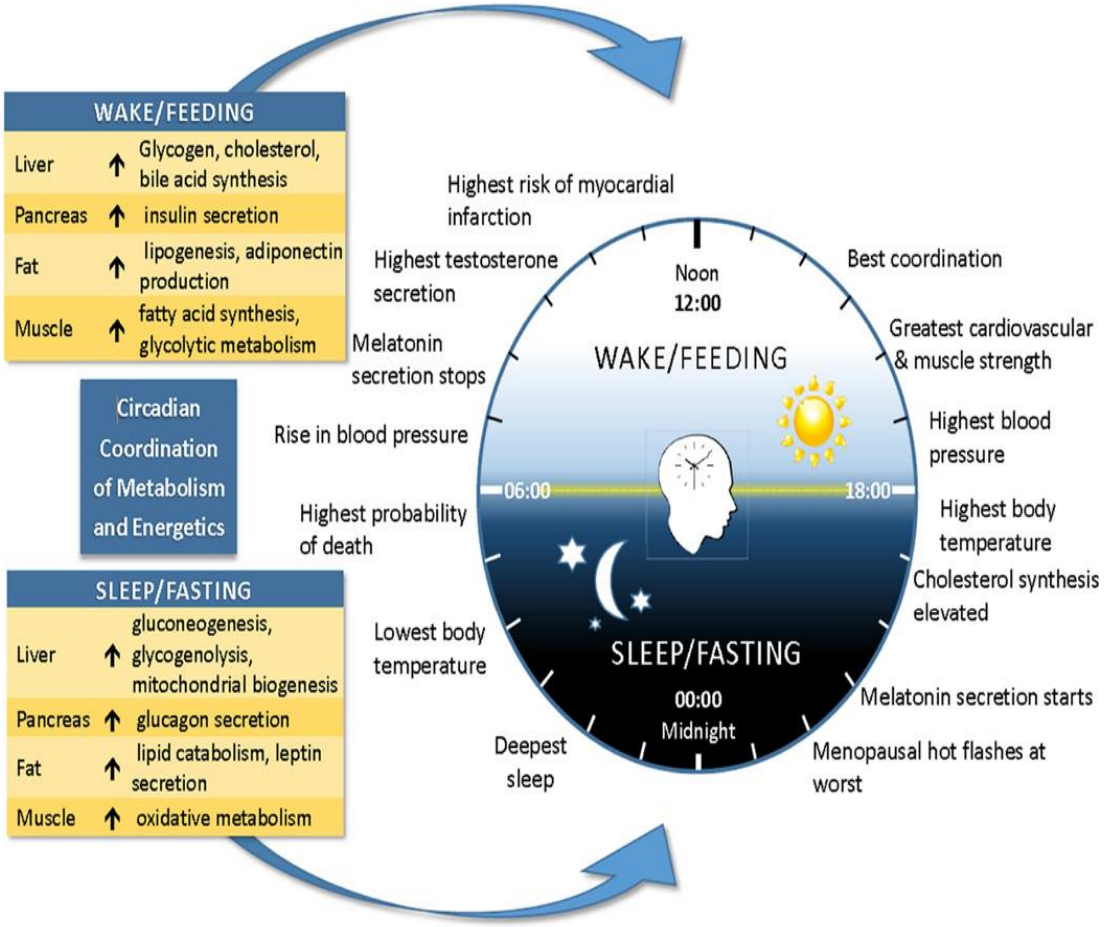

Figure 5: The Fasting Circadian Rhythm. Variables shown include hormone levels, sleeping times, eating times, different physiological processes, and metabolism. Figure taken from Wilhelmi de Toledo et al., 2019.

The Role of Fasting in Reversing Health Related Disease

Fasting, whether IF, BF, or PF, has been suggested to improve many health-related issues. Fasting has been suggested to prevent diabetes, certain cancers, brain disease, heart disease, obesity, arthritis, hypertension, and aging (Longo & Mattson, 2014). Fasting also can improve certain aspects of health. Fasting can benefit positive changes in the gut microbiome, improved fatty liver index, absence of hunger sensation, muscle/protein sparing, and in cases of PF, autophagy (Wilhelmi de Toledo et al., 2020). Figure 6 shows a summary of benefits during fasting and calorie restriction.

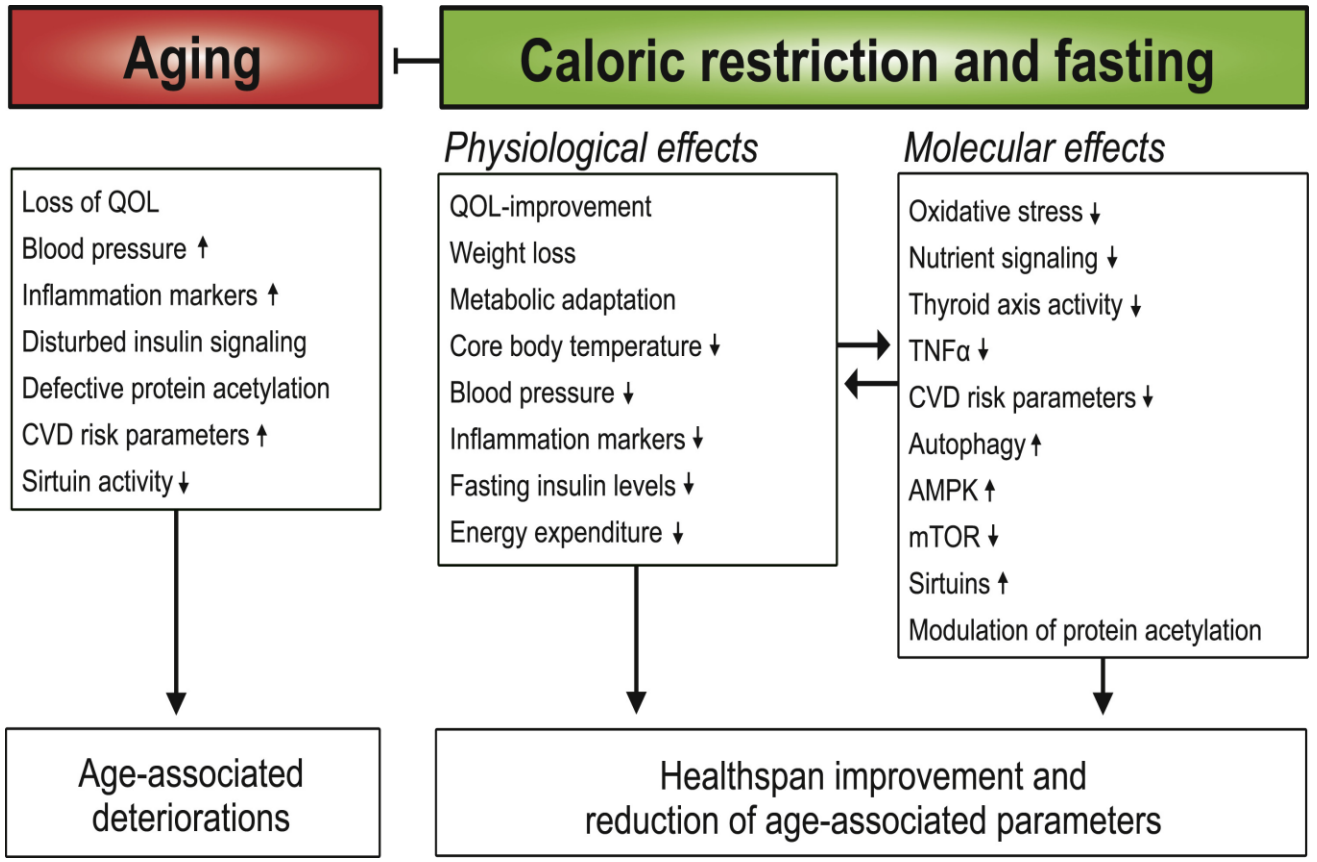

Figure 6: The Physiological and Molecular Effects of Fasting and Caloric Restriction. Displayed on the left, age-associated deteriorations are shown while on the right side, the benefits of both CR and fasting can help reverse the effects of aging. Figure taken from Wilhelmi de Toledo et al., 2019.

SPECIFIC AIMS / OBJECTIVES

There is currently no consensus on the topic of fasting. Conventional wisdom would indicate that eating every few hours is the way to stay healthy and that skipping breakfast could ruin the metabolism. Others would state that fasting, both intermittent as well as prolonged, would have the opposite effect on metabolism. There is a lack of long term randomized controlled trials within the realm of fasting to reverse insulin resistance, especially amongst patients suffering with type 2 diabetes mellitus.

The purpose of this literature review is to:

- Discuss the body's mechanisms in a fasted state
- Discuss background information regarding insulin resistance and type 2 diabetes mellitus, including events that would lead up to it.
- Discuss the benefits of fasting and potential consequences.
- Identify mechanisms or procedures to prevent individuals from becoming insulin resistant and type 2 diabetic.
- Discuss healthier lifestyle choices and potential diets to use along with fasting to implement in the future.
- From the listed objectives, this study hopes to find a solution to ending the pandemic of growing cases of dietary health related diseases, specifically type 2 diabetes.

PUBLISHED STUDIES

Refined carbohydrates, especially sugar, cause a large spike in insulin. Overtime, frequent eating of refined carbohydrates will cause the cells that respond to insulin to become desensitized (Mattson et al., 2017). The pancreas will keep creating insulin to compensate and eventually the individual may become insulin resistant. Insulin resistance is associated with prediabetes and consequently T2DM. Individuals who suffer from insulin resistance also can have a multitude of other issues such as cardiovascular disease, hypertension, myocardial infarction, obesity etc. (Mattson et al., 2017).

A review from the Journal of Advances in Clinical and Experimental Medicine (Golabek and Ilow-B, 2019), concluded that within the current literature, dairy products and moderate intake of alcohol do not have a negative impact on insulin sensitivity. The authors of the studies noted that high intake of refined sugars, especially from beverages, constant fast-food intake, and a diet low in dietary fiber can result in insulin resistance.

On the contrary, a cross sectional study was performed in Mexico that observed 217 individuals with 27% of them being clinically obese (Castro-Quezeda et al., 2019). The results from this study suggested that there were no significant associations between carbohydrate or sugar intake and insulin resistance. The authors did, however, find that the use of fiber in higher quantities increases insulin sensitivity in the peripheral cells.

Several approaches have been suggested in the literature to help improve insulin sensitivity or help combat insulin resistance amongst patients (Hemmingsen et al., 2017). Dieting, exercise, various medications have been the normal recommended treatments to improve insulin sensitivity. A newer, more drastic approach to combatting IR has been suggested to help, namely fasting. Fasting can aid not only in combatting IR but in other ways across various organ systems. Figure 7 shows different examples of effects of IF on various organs.

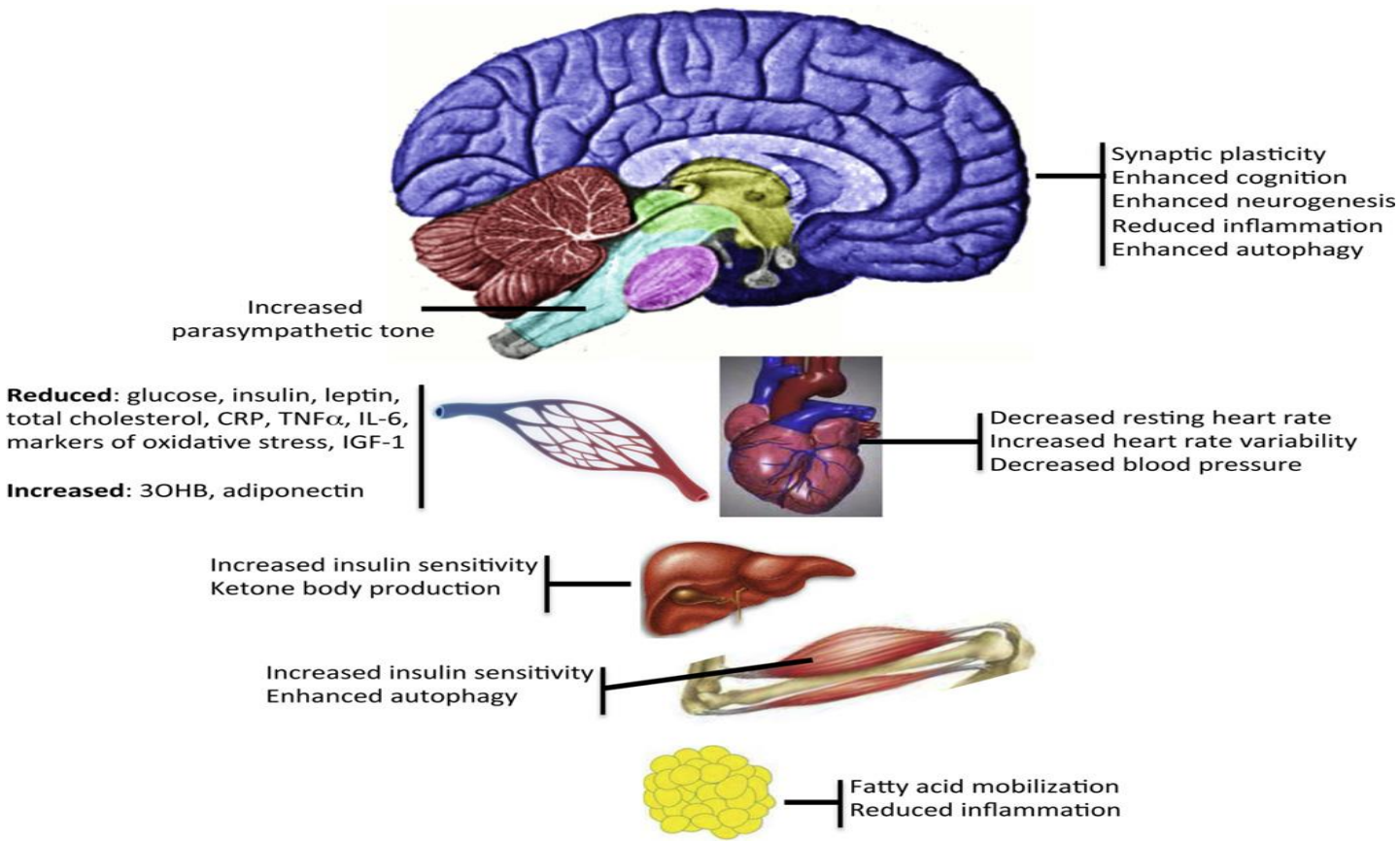

Figure 7: Effects of IF on Organs. IF can affect various organs such as the liver, brain, muscle tissue, fatty acids, and the heart. Figure taken from Mattson et al. 2017.

A case study involving three T2DM patients was conducted to see if fasting could be a therapeutic use as an alternative to insulin (Furmli et al., 2018). The age range for these three patients were 40 years old to 67 years old and these individuals had been suffering from T2DM for at least 10 years and up to 25 years. All patients presented with comorbidities such as hypertension and hypercholesterolemia. After a combination of lower carbohydrate meals and scheduled 24-hour fasts, all three patients showed great success. The need for insulin was eliminated, weight loss was achieved, improvement of HbA1C levels occurred, and the BMI was lowered (Furmli et al., 2018).

One study looked at early time-restricted feeding (eTRF), which is a type of IF, to determine how it affected various health variables in prediabetic men (Sutton et al., 2018). The authors concluded that after a 5-week randomized controlled trial eTRF had improved a variety of variables including, insulin levels, insulin sensitivity, beta cell responsivity to insulin and blood pressure . The study also found that eTRF reduced oxidative stress but had no significant effect on inflammatory markers such as cortisol or IL-6 or glucose and mean glucose levels. Additionally, eTRF was found to overall lower blood pressure but did not affect cholesterol levels (Sutton et al., 2018). Figure 8 illustrates the data regarding factors for glycemic control.

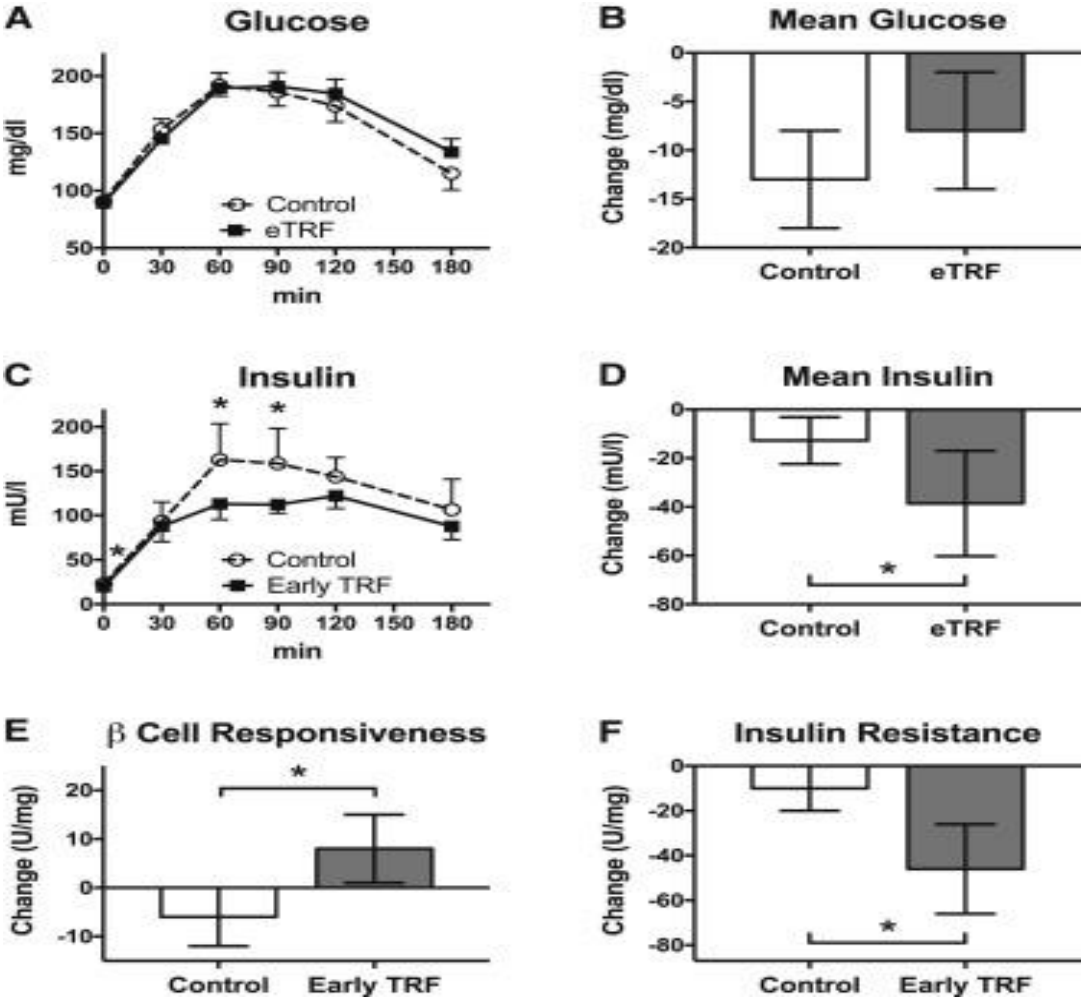

Figure 8: Glycemic Control. eTRF vs Control effect on Glucose, Mean Glucose, Insulin, Mean Insulin, Beta cell Responsiveness, and Insulin Resistance. Figure taken from Sutton et. al 2018.

A review from the Journal of Physiology and Pharmacology looked at 29 studies revolving around the effects of different variations of IF and its effects on weight loss, body composition, glycemic control, and the cardiovascular system (Zubrzycki et al., 2018). Amongst the variations of IF, eTRF, Ramadan, ADF, and cyclic or periodic fasting were included. Across the studies, body weight, fat mass, cholesterol, and triglyceride levels improved in most patients. It was also reported that plasma glucose levels have improved shown by the decrease in concentration of HbA1c levels (Zubrzycki et al., 2018).

Another review from the Journal of Nutrients looked at 9 randomized-controlled trial studies using caloric restriction protocols vs IF protocols (Rynders et al., 2019). The subjects were all overweight female adults, 63 with T2DM, and the duration of fasting/caloric restriction protocols ranged from 8-52 weeks. Despite limitations to the study such as self-adherence, there was no significant difference found in body fat or weight loss between IF and caloric restriction. It was reported in both groups however that glucose levels decreased overall, insulin levels decreased, and insulin sensitivity was improved (Rynders et al., 2019).

A study from the Journal of Clinical Endocrinology and Metabolism looked at the effects of 12 and 60 hour fasts and measure glucose and glutathione metabolism (van der Crabben et al., 2008). At the end of the 60 hour fast, the participants had a 46% decrease in insulin-mediated peripheral glucose uptake. They also found that glutathione concentration also decreased. It was also concluded that fasting did not increase rates of inflammation (van der Crabben et al., 2008). Table 1 displays glucose and glutathione data at basal state after 12 and 60 hours of fasting.

Table 1: Glucose and Glutathione Levels at Basal State. Results of glucose and glutathione levels after 12-hour and 60-hour fasts are displayed as well as % change. Table taken from van der Crabben et al., 2008.

	12 Hours	60 Hours	% Change
Glucose concentration (mmol/liter)	5.1 (4.5–5.5)	3.4 (3.0–3.9)	−30 (−40 to −25)
EGP (μmol/kg·min)	12 (11–14)	9 (8–10)	27 (26–37)
GSH concentration (mmol/liter)	1.14 (0.99–1.23)	1.02 (0.93–1.23)	−9 (−15 to −2)
FSR GSH (%/d)	382 (299–541)	413 (233–470)	−10 (−41 to 24)

A study was conducted that examined ADF in non-obese patients and measured the effects of fasting on body composition, energy metabolism, and body weight subjects (Heilbronn et al., 2005). Subjects underwent an ADF regimen for 22 days. Many health variables such as resting metabolic rate, respiratory quotient, fat oxidation, and carbohydrate oxidation were measured and taken note of throughout the process. After 22 days, the 16 subjects lost 2-3% of their body weight as well as 3-5% of their fat mass. They also found that glucose and the hormone ghrelin did not have any significant changes. They did find that fasting insulin decreased 53-61% within the 16 subjects (Heilbronn et al., 2005). Table 2 displays results at baseline and at the end of the 21 and 22 days fast.

Table 2: Health Variables at Fed State vs. Fasted State. Resting metabolic rate, respiratory quotient, fat oxidation, and carbohydrate oxidation measured towards end of ADF regimen and at baseline. All measured health variables except for RMR were found to be significantly different from the baseline. Table taken from Heilbronn et al., 2005

	Baseline	**Day 21 (fed)**	**Day 22 (fast)**
RMR (kJ/d)	6675 ± 283	6292 ± 268	6329 ± 260
RQ	0.85 ± 0.01	0.86 ± 0.02	.79 ± 0.01
Fat oxidation (g/24 h)	64 ± 8	54 ± 10	101 ± 9
Carbohydrate oxidation (g/24 h)	175 ± 17	184 ± 24	81 ± 16

A study was conducted examining the effects of caloric restriction versus ADF and its differential effects on insulin resistance (Gabel et al., 2019). Amongst the 43 insulin resistant subjects, there was no significant difference in weight loss between ADF and CR. There was a noted decrease in BMI and in fat mass between both protocols. Furthermore, it was reported that ADF produced a greater positive effect on fasting insulin levels as well as an improvement in insulin sensitivity by the last month. There were no noted changes in lean body mass, fat mass, cholesterol levels, or triglyceride levels (Gabel et al., 2019). Figure 9 shows the results of ADF vs CR within this study.

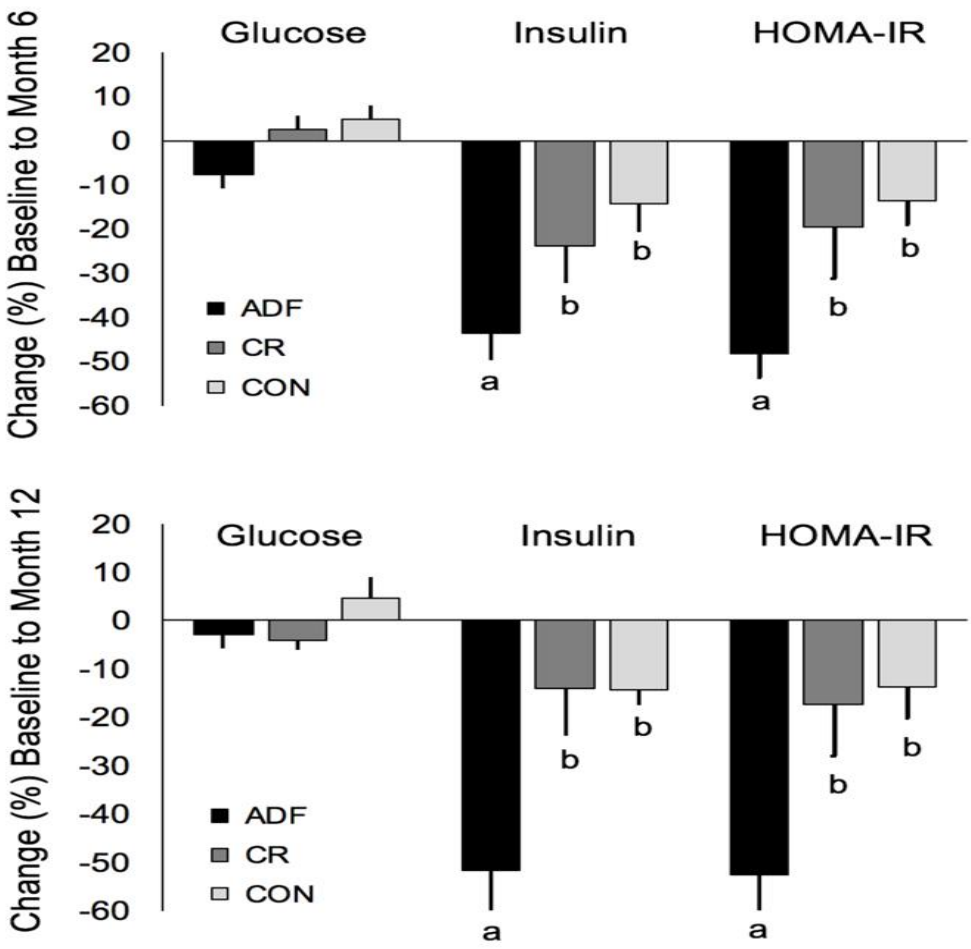

Figure 9: Alternate Day Fasting vs Caloric Restriction vs Control. Glucose levels, Insulin levels, and Insulin Resistance were measured in changes to baseline at 6 and 12 months. Figure taken from Gabel et al., 2019.

In a study involving the effects of a 8 hour feeding window and 16 hour fast, the researchers examined 23 obese subjects (Gabel et al., 2018). The trial duration was 12 weeks and examined effects on body weight as well as risk factors for other metabolic diseases. A dietician was involved to instruct participants of how to record a complete week of food logging and time of intake. The food logs were recorded at the baseline and at the 12th week of the study. These logs were checked for completeness and accuracy. Comparing baseline to the end of the 12th week, the researchers found that fat mass, triglycerides, fasting insulin, homeostatic model assessment – IR and homocysteine levels were significantly different from baseline. Body weight, systolic blood pressure, and fasting glucose did have some change but not significantly different (Gabel et al., 2018). Table 3 includes the results regarding body composition and risk factors for metabolic disease after the 12-week period.

Table 3: Body Composition and Risk Factors for Metabolic Disease. Results of IF fasting following a 16:8 regimen in obese individuals. Factors with an * are significantly different from baseline. Table taken from Gabel et al., 2018.

Body Composition	Baseline	Week 12
Body Weight (kg)	95 ± 3	92 ± 3
Fat Mass (kg) *	42 ± 2	40 ± 2
Systolic Blood Pressure (mm Hg)	128 ± 4	121 ± 3
Triglycerides (mg/dl) *	105 ± 11	93 ± 9
Fasting Glucose (mg/dl)	79 ± 4	82 ± 2
Fasting Insulin (uIU/ml) *	8.3 ± 1.0	5.7 ± 0.7
HOMA-IR *	1.6 ± 0.2	1.0 ± 0.2
Homocysteine (μmol/l) *	9.9 ± 0.6	9.0 ± 0.5

A randomized control trial was conducted to assess the effect of ADF on weight loss amongst obese individuals (Trepanowski et al., 2017). A group of 222 individuals were randomly placed in groups of ADF, daily caloric restriction, and control groups. Amongst the initial group of people, only 69 individuals completed the study in 12 months. Weight loss results were shown not to be significantly different from either of the fasting or caloric restriction regiments. Total weight loss was 6% for fasting and 5.3% for caloric restriction. There were no statistically significant differences between either group for fat-mass or lean mass both halfway through the study and at the end. Blood pressure and heart rate was also not significantly different between either group. High-density lipoprotein levels were increased in both groups while low-density lipoprotein and triglyceride levels did not show statistically significant different outcomes (Trepanowski et al., 2017). Figure 10 shows results of weight loss per diet group.

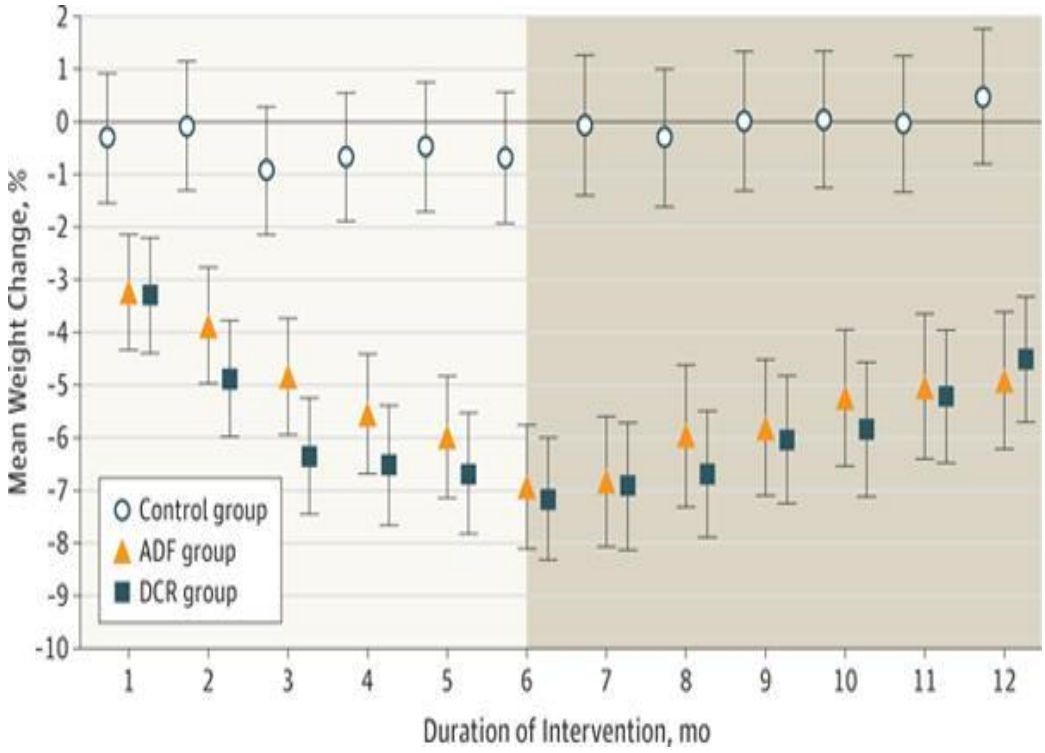

Figure 10: Weight Loss of Fasting vs Caloric Restriction. Mean weight change % over one year. Control group, ADF), and daily CR groups are shown. Figure taken from Trepanowski et al., 2017.

A systematic review and meta-analysis were performed to look at IF as a treatment for obesity (Harris et al., 2018). Within the six studies that met inclusion criteria, the IF regimens included 2-day fasts, 4 days per week fasting, and ADF. The duration of the studies lasted 3 months up to a year. The result from the meta-analyses suggests that IF was an effective treatment for weight loss where the average person lost around 7 kg in body weight. However, the authors concluded that IF showed no significant difference as a treatment when compared to normal caloric restriction (Harris et al., 2018).

A review conducted by the Annual Review of Nutrition examined the metabolic effects of IF, looking at 16 human-intervention studies (Patterson and Sears, 2017). The types of IF observed were ADF, TRF, and religious fasting. The studies included documented an overall decrease in energy consumption by approximately 30%. In additional studies comparing the use of mice, time-restricted feeding showed increase in movement and improvement of circadian rhythms. The authors concluded that fasting reduces basal level concentrations of insulin and glucose (Patterson and Sears, 2017). Table 4 displays in further detail the studies used in the review that indicated obese participants following a modified fasting regimen.

Table 4: Metabolic Biomarkers of Diabetes, Cardiovascular Disease, and Cancer. Summary Table of 9 studies involving obese patients undergoing a modified fasting regimen. NS denotes not statistically significant and ND denotes no data reported. Table taken from Patterson and Sears, 2017.

First author and year	Weight Change	Gluco-Regulatory Markers	Lipids
Williams 1998	Decrease	NS	NS LDL/HDL/TG
Johnson 2007	Decrease	NS	NS LDL/HDL
Varady 2009	Decrease	ND	Decrease LDL and TG NS HDL
Harvie 2011	NS	NS Glucose Decrease Insulin	NS LDL/HDL/TG
Bhutani 2013	Decrease	NS	NS LDL/HDL/TG
Eshghinia 2013	Decrease	ND	NS LDL/HDL/TG
Harvie 2013	NS	NS Glucose Decrease Insulin	NS LDL/HDL/TG
Varady 2013	Decrease	ND	NS LDL/HDL Decrease TG
Hoddy 2016	Decrease	Decrease Insulin and Glucose	ND

DISCUSSION

Insulin resistance is a common health issue that may turn into T2DM. Over the last 50 years, Americans have been led to believe by Harvard scientists paid by the Sugar Research Foundation that diets low in fat but high in carbohydrates were supposedly healthy. Over time, grocery stores became filled with highly processed and refined carbohydrate food items. These foods are naturally easy to overeat, cheap to obtain, and had a long shelf life. These highly processed food items are high in sugar, preservatives, and many contain hydrogenated oils which are comprised of trans fats.

Now, health related diseases such as insulin resistance, hypertension, obesity, T2DM, and high cholesterol have increased in prevalence across the United States. With the record of cases increasing over the past 50 years, it is imperative for scientists and health researchers to find treatments or therapies to help combat and prevent insulin resistance and T2DM.

While the rise of low carbohydrate and higher fat diets such as the ketogenic diet or Paleo diet have recently become popular, a more drastic approach, fasting, has also gained traction. The ketogenic diet works physiologically similarly to fasting. It allows your body to process ketones as fuel and use either exogenous or endogenous fat.

Across the literature, a common result of fasting whether it be IF, ADF, or PF all result in some form of weight loss. Some studies did not specify if weight loss came from water

mass, muscle mass, or fat mass. It is natural for an individual during a fast to lose a significant amount of water mass. With the absence of intake of carbohydrates or food period, the body does not hold onto water as much if the individual were to eat a conventional diet.

One study did report a decrease in BMI in IR patients as well as fat mass between both fasting and caloric restriction groups (Gabet et al., 2019). It should also be noted that authors concluded that ADF produced more significant reduction to fasting insulin levels compared to the CR group of patients. Another study reported subjects having decreased fat mass and increased fat oxidation during an ADF fasting regimen (Heilbronn et al., 2005). The authors noted that on the alternate days of eating, the individuals were not able to consume enough calories to maintain their previous noted weight. In addition, one systematic review found that across 29 studies, fat mass, triglyceride, and cholesterol levels improved in most patients (Zubrzycki et al., 2018). The authors also found that decrease in blood pressure, reducing oxidative stress, improving blood lipid levels, improving beta cell function, and increasing insulin sensitivity were common amongst patients practicing IF.

However, it should be noted that many of the studies that had patients undertake some fasting regimen also had caloric restriction. Given the nature of fasting, caloric restriction

may happen due to the restriction of time during the feeding window. The individual would need to consume higher amounts of calories in a smaller amount of time therefore having the consequence or benefit of satiety with less overall intake of food. Many of the studies concluded that there was no significant difference in terms of weight loss between IF and a calorie restricting diet (Trepanowski et al., 2017; Harris et al., 2018; Rynders et al., 2019). A combination of both may prove to be the most effective for weight loss purposes, which would in turn improve not only overall health but T2DM and insulin resistance.

Despite the non-statistically significant differences in weight loss between IF and caloric restriction, that observation does not necessarily mean that fasting does not have other health benefits. One study found that amongst T2DM patients, scheduled 24-hour fasts were able to completely remove the need for insulin as well resulting in an improvement to Hb1Ac levels (Furmli et al., 2018). Researchers also found that in a 5-week randomized control trial utilizing eTRF, beta cell responsivity, insulin sensitivity, insulin resistance, and blood pressure all improved. Other studies all reported improvements to glucose and insulin levels (Zubrzycki et al., 2018; Rynders et al., 2019; van der Crabben et al., 2008; Gabel et al., 2019; Patterson and Sears, 2017). One study even reported a multitude of benefits such as increased autophagy, reduced inflammation, enhanced cognition, decreased resting heart rate, and increased fatty acid mobilization (Mattson et al., 2017).

All the benefits of fasting, whether they are directly or indirectly related to combating insulin resistance or T2DM, can be useful for an individual trying to become healthier. An individual with insulin resistance or subsequently T2DM may have other health problems like high cholesterol, hypertension, or obesity that fasting has been suggested in the literature to aid in some manner. All the literature reviewed suggests weight loss was achieved and a majority of the studies resulted in fat mass decrease. Along with decrease in fat mass, triglyceride and cholesterol levels also were improved, helping T2DM patients who are also suffering from high cholesterol or obesity. Numerous studies reported improved insulin sensitivity and decreased insulin resistance that is one of the biggest markers for pre-diabetes. Other indirect health benefits such as increased autophagy, reduced inflammation, enhanced cognition, and decreased hunger may give the individual incentive to undergo some variation of a fasting protocol.

One of the downsides to fasting noted in many of the trials was adherence. Adherence is ultimately one of the most important aspects to any type of lifestyle change whether that be exercise, dieting, or fasting. If the individual cannot sustain the regimen of fasting to improve their health, then it proves to be useless. Much like dieting, there is also the issue of rebounding weight. This was noted in one study where after the fast was completed, a follow up case showed that the individuals did not keep healthy habits and gained a lot of their original weight lost back (Trepanowski et al., 2017). Despite the issue of adherence to fasting, the individuals who were able to successfully complete the planned practice of fasting showed successful results and an individual's mental strength to adhere to a

certain practice should not downplay the many benefits and almost no noted negative health risks to fasting. Overall, given the current literature, fasting has a multitude of benefits that can help an individual both prevent or help reverse insulin resistance and T2DM.

CONCLUSION

Education and prevention are key to stop these health-related issues. Individuals should venture and research to see if there is a familial history of IR or T2DM because there are genetic risk factors that could put these individuals in danger. Reducing constant intake of highly refined carbohydrate food and beverages that spike insulin levels and contribute to insulin resistance is a good step for prevention. Exercise, a balanced diet, and the understanding of nutrition especially starting at a young age, could setup the population for success. Building good habits that are reliable and repeatable in the realm of self-care is imperative to curb the growing statistic of IR and T2DM prevalence amongst the future generations.

More research in the subject of fasting is needed. Specifically, there is a lack of randomized controlled trials involving human subjects. There is also a lack of long term randomized controlled trials about fasting. Out of the current literature, there did not seem to be any negative health risks or unwanted side effects of fasting. Some authors of online articles about intermittent or prolonged fasting talk about benefits of autophagy as well as decreased ghrelin levels. There is anecdotal evidence of decreased hunger but no well documented studies regarding measurable decreases in ghrelin or measurable autophagy. Well conducted long-term randomized control trials may bring new information to light about fasting, both positive and negative.

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