

The Effects of Intermittent Fasting on Blood Insulin Levels and Insulin Sensitivity: A Literature Review

Shantel Centner

Abstract

Obesity has become a major concern for healthcare professionals and the general public in the United States over the past few decades. Other nations have recently begun to experience an increase in obesity rates as well. Diabetes also affects many Americans to an alarming degree. Though practitioners and organizations have presented various treatments for those experiencing these metabolic diseases, including medications, restriction diets, calorie counting, and exercise, people still become morbidly overweight and develop Type 2 Diabetes. A new diet-based approach, generally termed intermittent fasting, has been proposed as a very viable treatment option for individuals with these conditions. This literature review sought to test the present theory that intermittent fasting reduces insulin resistance by improving insulin sensitivity. Though findings of the reviewed studies were mixed, the general consensus was that intermittent fasting does positively affect insulin by reducing fasting insulin levels and increasing insulin sensitivity. More research is needed to confirm this conclusion, as well as to investigate other aspects of diet and fasting such as gender, time of day to eat, types of foods eaten, and length of fasting periods, just to name a few. Social implications for intermittent fasting as a potential treatment option have also been discussed.

.Introduction

Rates of obesity have steadily risen in the general American population over time, as shown in Figure 1 below. As healthcare professionals realized how widespread this particular epidemic was becoming, prevention measures and disease treatments developed, such as prescribing patients exercise and dietary changes [1]. Yet 39.8% of the American population today presents with obesity [1]. Diabetes is another common health concern in the American population (see Figure 2). Diabetes is the 7th leading cause of death in the U.S., as seen in Figure 3 [2]. This is concerning when one considers that almost 10% of Americans have been diagnosed with diabetes. Common treatments for diabetic patients include exercise and adjusted eating habits as well, but also usually include prescriptions like metformin and insulin [3]. The continuing prevalence of these metabolic disorders, despite current treatment methods, brings up an important question: What else can be done to help these individuals recover from their diseases? A plausible answer could be intermittent fasting (IF). To explain why IF could be a possible treatment method for obesity and Type 2 Diabetes, this literature review aims to first describe the mechanisms of the insulin pathway in healthy individuals, then the mechanisms of the insulin pathway in obese and diabetic persons, termed insulin resistance, and finally to introduce intermittent fasting (IF) and explain why it may be a possible treatment method for metabolic conditions. Research article results will be examined to determine if there is support for this idea or not. The hypothesis is that intermittent fasting positively affects insulin levels in the blood by reducing fasting insulin levels and increasing insulin sensitivity, which is important when considering how to address these metabolic disorders.

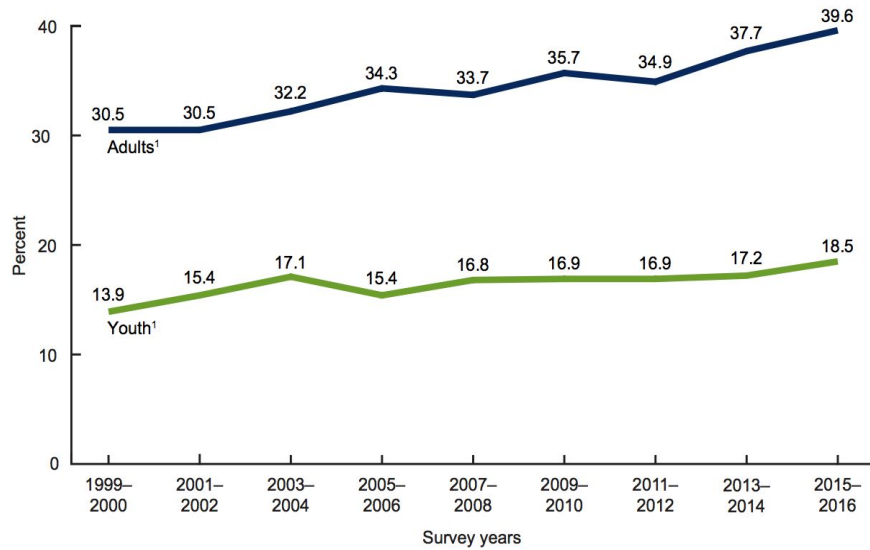
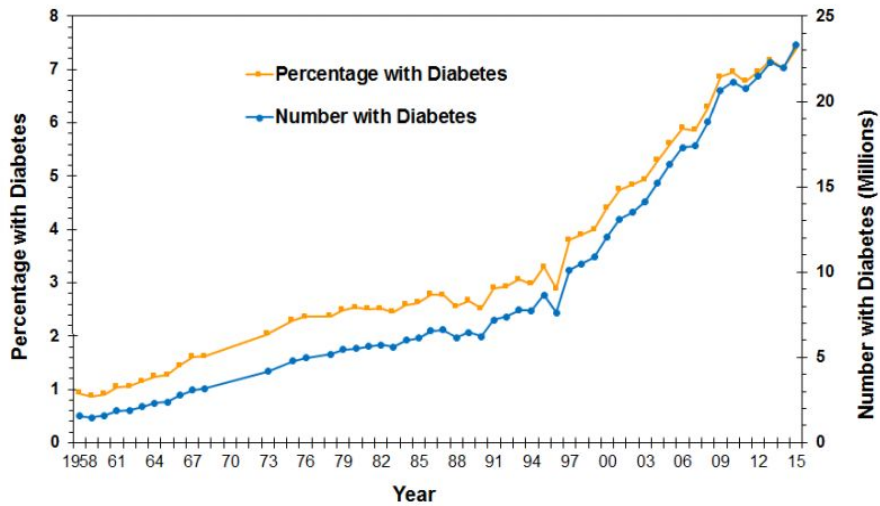


Figure 1: The figure above provides information about the increasing trend of obesity in the American population from 1999 to 2016 [4].

Number and Percentage of U.S. Population with Diagnosed Diabetes, 1958-2015



CDC's Division of Diabetes Translation. United States Diabetes Surveillance System available at <http://www.cdc.gov/diabetes/data>

Figure 2: This image demonstrates the rise in U.S diabetes rates over the course of 57 years [5].

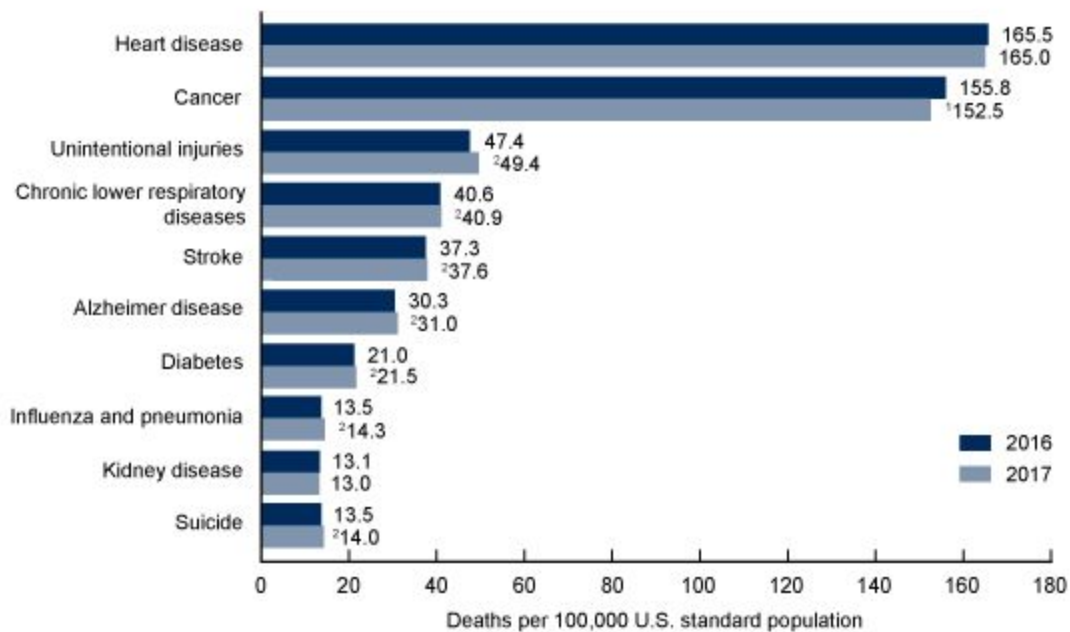


Figure 3: This figure depicts the 10 primary causes of death for individuals in America. Notice how diabetes is ranked 7th on this list [6].

Discussion of Insulin and Glucagon Homeostasis

Blood sugar levels require homeostasis, or balance, for the body to function properly. This balance is regulated by two hormones secreted from the pancreas, insulin and glucagon. Though the focus of this review will be on the hormone insulin, it is important to understand its general function within the human body and the system it plays a role in. Once homeostasis is understood, the mechanisms of insulin action at the receptor will be discussed in detail.

A simple example of glucose homeostasis can be seen in the temperature system of a house. If the temperature is set at 68 degrees, the thermostat system will maintain the house temperature at 68 degrees. If the internal temperature rises above 68, the air conditioning will

turn on and cool the house until the set temperature is achieved. If the house is too cold, the heater will function to raise the temperature of the house to the pre-set 68 degrees.

The Function of Insulin

Glucose homeostasis follows a similar process. After food is ingested through the mouth, the body digests it mechanically and chemically. Fats, sugars, and other macronutrients are absorbed throughout the digestive system. Sugars and carbohydrates (from here on referred to as glucose) are transferred directly into the bloodstream for immediate uptake by the cells. The increase in blood glucose concentrations causes the pancreas to release the hormone insulin from the beta cells [7]. See Figure 4 for an visual of natural insulin level fluctuations during the day after meals.

Insulin is a peptide hormone, made of proteins. The beta cells produce insulin first as a prohormone. This prohormone is then cleaved by enzymes to make the final product of active insulin hormone. The increased concentration of glucose in the bloodstream initiates the secretion of the active hormone [8]. The insulin circulates in the blood and facilitates the uptake of glucose by the cells, specifically targeting the liver, the muscles, and adipose tissue, or fat [9][10]. This uptake reduces the amount of glucose present in the blood. As glucose levels in the blood decrease, the pancreas stops releasing insulin. Excess glucose is processed in the liver and is converted into glycogen, a condensed storage form of glucose [7]. Thus, blood glucose levels are maintained after an influx of ingested food containing carbohydrates and sugars. See Figure 5 for an illustration of this process.

The Function of Glucagon

Over time, the cells utilize the glucose inside them as well as the glucose available in the bloodstream. Blood glucose levels decrease below the proper range, which signals the pancreas to release the hormone glucagon from the alpha cells. Glucagon is another peptide hormone, but has the opposite function of insulin [7]. It causes an increase in blood glucose concentrations by initiating the breakdown of glycogen in the liver and converting it back to glucose. This extra glucose released from the liver into the bloodstream and circulates through the blood to provide energy for cells to continue functioning. As blood glucose concentrations rise, the amount of glucagon secreted by the pancreas decreases. Refer to Figure 5 for the illustrated process.

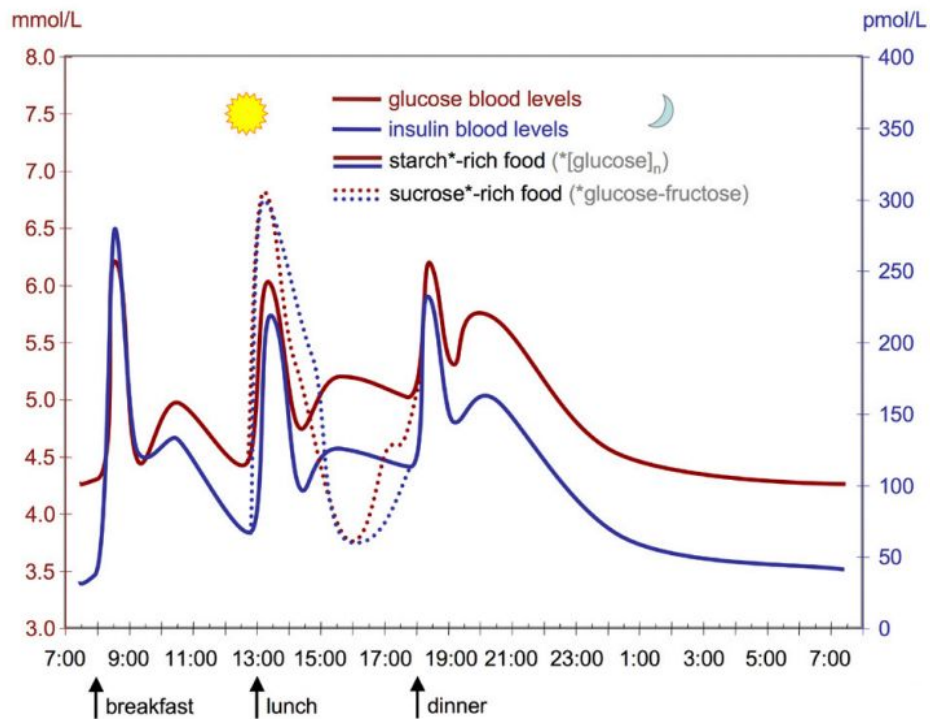


Figure 4: This graph shows how insulin levels fluctuate during the day. It demonstrates the close relationship between ingesting food, the rise in blood sugar levels, and the secretion and action of insulin after meals throughout the day [11].

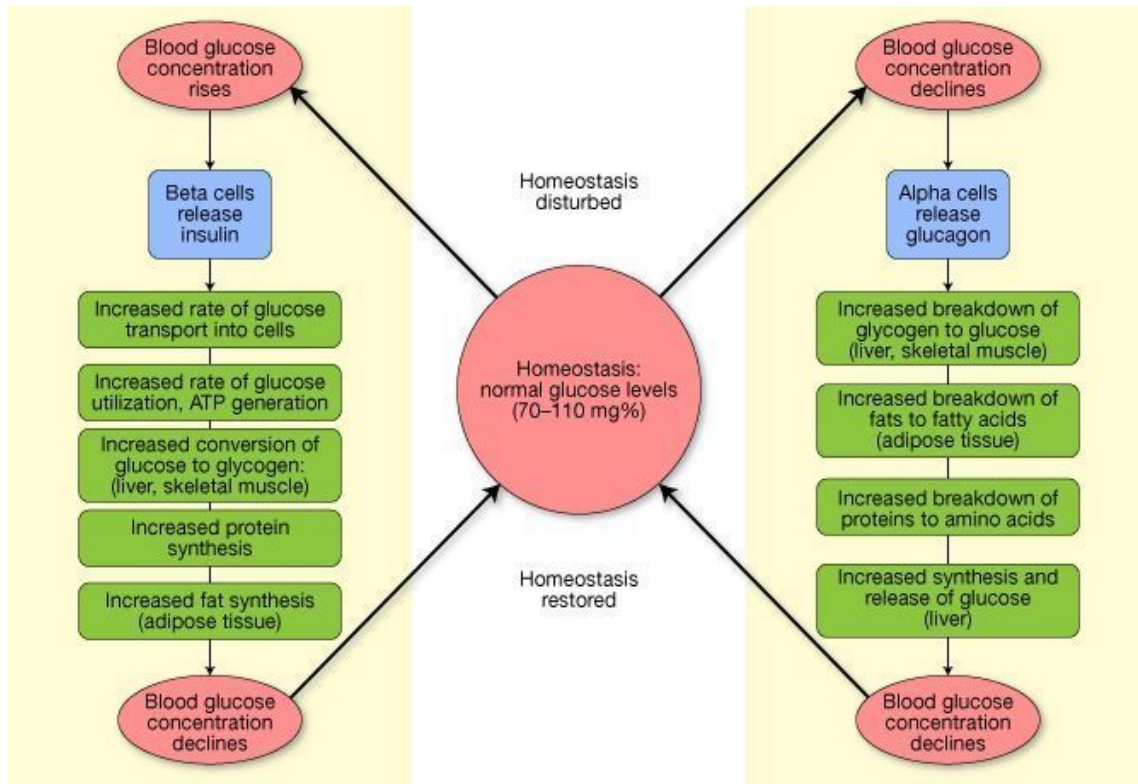


Figure 5: Illustration of how insulin and glucagon maintain homeostasis of blood glucose concentrations. The loop on the left demonstrates the effects of insulin, while the right loop conveys the functions of glucagon [12].

Mechanism of Insulin Pathway in Healthy Individuals

The mechanism by which insulin interacts with somatic cells is quite complicated and involves many steps within the cell. To begin, the insulin receptor (IR) is part of the receptor tyrosine kinase family of receptors. It is made of an alpha subunit and a beta subunit bound by disulfide bonds. Two of these alpha-beta subunit complexes are dimerized together to form the IR. See Figure 6 for a visualization of the insulin receptor [13].

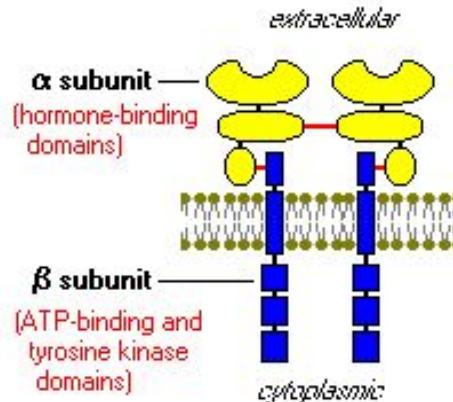


Figure 6: A cartoon image of the insulin receptor. The alpha subunits and beta subunits can be clearly seen in their relation to each other and in the dimerization of the two complexes that make up the receptor. The disulfide bonds are depicted here as red lines [14].

When activated, the receptor goes through a conformational change that activates the tyrosine kinase portion of the receptor protein. The IR experiences autophosphorylation via the activated tyrosine kinase. This autophosphorylation produces sites on the receptor called src homology 2, or SH2, domains [15]. Downstream proteins can bind to SH2 domains and begin the signalling cascade inside the cell.

IR-PDK1 Signalling Cascade

The first downstream protein is Insulin Receptor Substrate 1 (IRS-1). It is also phosphorylated within the cell when it binds to the SH2 domains of the IR. This phosphorylation activates it to produce its own SH2 binding sites [13]. Phosphatidylinositide 3-kinase (PI3K) is the second protein in the signalling cascade. It binds to the sites on IRS-1 and becomes active via phosphorylation as well. PI3K phosphorylates phosphatidylinositol 3,4 bisphosphate (PIP2) into

phosphatidylinositol 3,4,5 triphosphate (PIP3). PIP3 activates the protein kinase activity in the cell by activating 3-phosphoinositide-dependent protein kinase 1 (PDK1) [15] [16].

PDK1-GLUT4 Signalling Cascade

Active PDK1 phosphorylates AKT, which is also known as protein kinase B (PKB). It will be referred to as AKT in this literature review. The phosphorylated AKT is the active form of the protein kinase and is necessary for the translocation of the GLUT4 protein [15] [16]. Active AKT deactivates AKT-substrate of 160 kDa (AS160) by phosphorylating it. This allows the accumulation of RAB-GTP proteins, which are important for the GLUT4 storage vesicles (GSV's) to be released from tether containing UBX domain or GLUT4-Ubiquitin Like 1 (TUG) proteins. GSV's are vesicles covered with GLUT4 proteins that are ready to be embedded in the cell membrane. TUG proteins tether the GSV's to the plasma membrane and prevent the GLUT4 proteins from being expressed on the surface of the cell. Once the RAB-GTP proteins target TUG and release the GSV's, the GLUT4 proteins can be translocated and integrated into the plasma membrane and allow glucose transport into the cell [15].

Insulin is also involved in the formation and recycling of the GLUT4 receptors through further cell signalling cascades. For this literature review, the focus is on the translocation of the GSV's to the membrane to allow for glucose movement into the cell. For an overview of the insulin signalling pathway discussed, please refer to Figure 7.

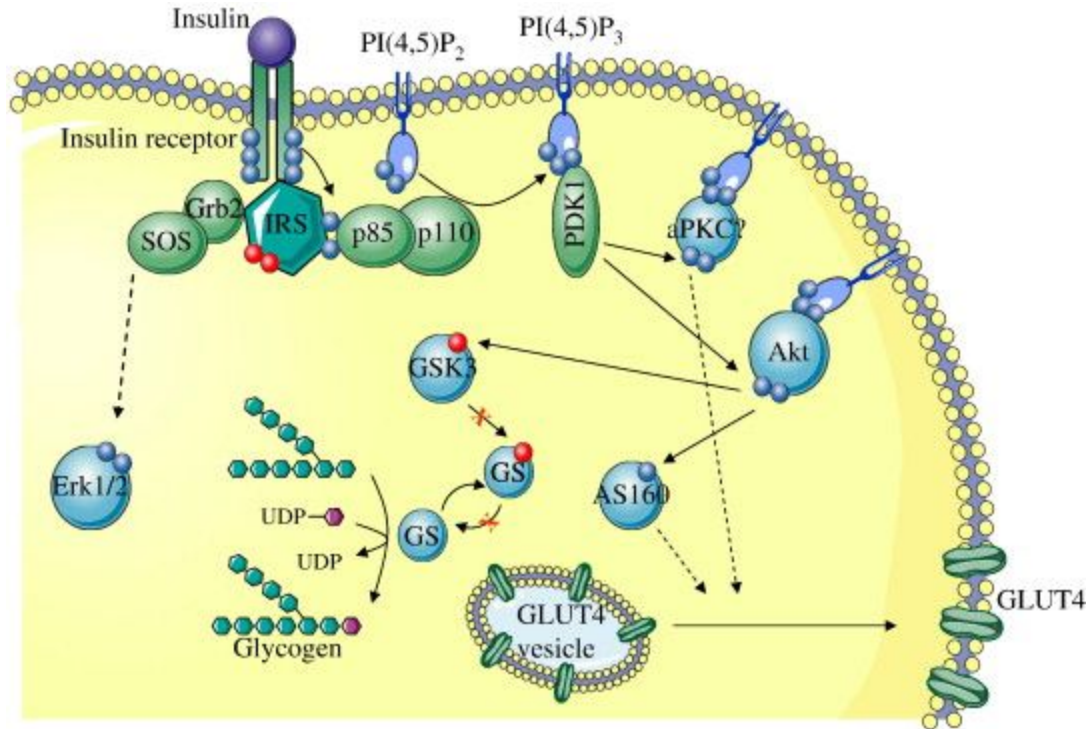


Figure 7: This image provides a general picture of how the insulin signalling cascade works. Not all elements of the image are discussed in this literature review. PIK3 is depicted here in its two parts, p85 and p110 [17].

Mechanisms of Insulin Resistance

Under normal circumstances, when insulin sensitivity is normal, the body responds to glucose and insulin properly. First, food is ingested and digested through the organs of the mouth and stomach. Carbohydrates and sugars are absorbed directly into the bloodstream. The pancreatic beta cells sense the increase in blood glucose levels and respond by releasing insulin. Muscle and somatic cells respond and glucose is transported into the cells by the GLUT4 protein. Any excess glucose is stored in the liver until it is needed between meals, which is considered to

be a natural fasting state. Under normal circumstances, adipocytes, or fat cells, also store excess energy as fat. This occurs when the liver is almost at capacity of its energy storage.

Insulin resistance occurs when an individual consumes too much energy for the body to use, such as eating high-sugar and high-carbohydrate meals, particularly close together over a short period of time [16]. The body's response at the beginning of this eating pattern is normal, as described above. The cells take up glucose, the liver stores the excess until it is needed later. The disruption occurs when an individual eats another high-energy meal before their body uses most of the energy from the previous meal. The cells take in some glucose, but not much. Cells only take what they can hold without bursting. The increased amount of excess blood glucose goes to the liver. Yet the liver can only store so much glycogen before it too is full. The remainder of the energy goes to adipocytes for storage. As the individual continues to overload their body with energy from their meal choices, the adipocytes also come to capacity. The adipocytes become hypertrophied, or enlarged, and begin to crush other surrounding cells, especially the epithelial cells [9] [18]. The damaged epithelial cells release monocyte chemoattractant protein 1 (MCP-1), which initiates the immune response. MCP-1 recruits macrophages to the injury site, beginning the inflammatory response. The hypertrophied fat cells also begin to secrete tumor necrosis factor-alpha (TNF-alpha), an inflammatory cytokine, because they are too large to function properly. The macrophages that have accumulated at the injury site cause the adipocytes to secrete even more TNF-alpha [9] [18].

TNF-alpha binds to proteins in the fat and activate c-JUN NH2-terminal kinase (JNK) and inhibitor kB kinase (IKK). Hormone sensitive lipase (HSL) activity in the adipocytes is

increased. This causes free fatty acids (FFA) to be formed and released into the bloodstream [9] [10].

FFA and TNF-alpha both directly affect the insulin signalling cascade, which plays a vital role in insulin resistance [9] [13] [18] [19]. FFA circulating in the blood are taken up by adipocytes and hepatocytes. The excess FFA are metabolized and results in multiple by-products, the primary one being diacylglycerol (DAG). DAG activates PKC-theta. PKC-theta is an isoform of protein kinase C. PKC-theta activates JNK and IKK. JNK and IKK interfere with IRS-1 via increased serine phosphorylation, specifically on serine 312 in humans, and marking it for degradation [9] [15]. Without IRS-1, the receptor does not function properly and no signal is propagated through the cell. Once IRS-1 is degraded, the IR is internalized and degraded as well [9]. For a visualization of this specific process, refer to Figure 8.

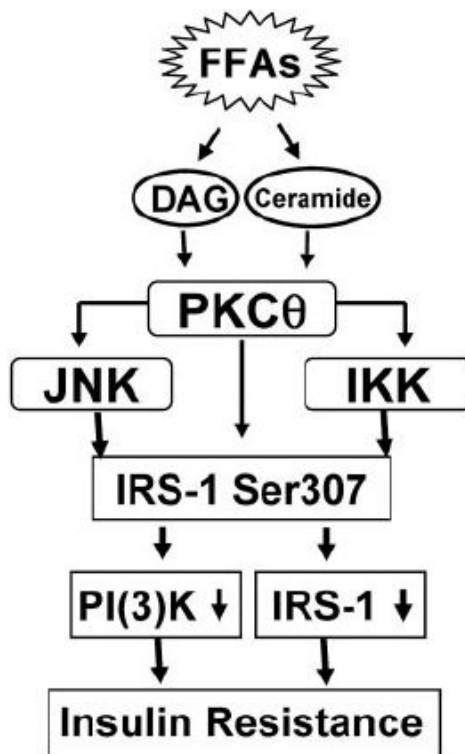


Figure 8: The pathway regarding free fatty acids (FFA) is depicted here [20].

TNF-alpha also directly affects the IRS-1 via two mechanisms. First, it activates IKK and p38 MAP kinase (p38MAPK) to phosphorylate IRS-1 at serine-312. The second effect TNF-alpha causes is the activation of protein-tyrosine phosphatase 1B (PTP1B) to dephosphorylate tyrosine residues on IRS-1 via. It acts locally at the adipose tissue. Figure 9 shows a summary of the effects of TNF-alpha on IRS-1 [9].

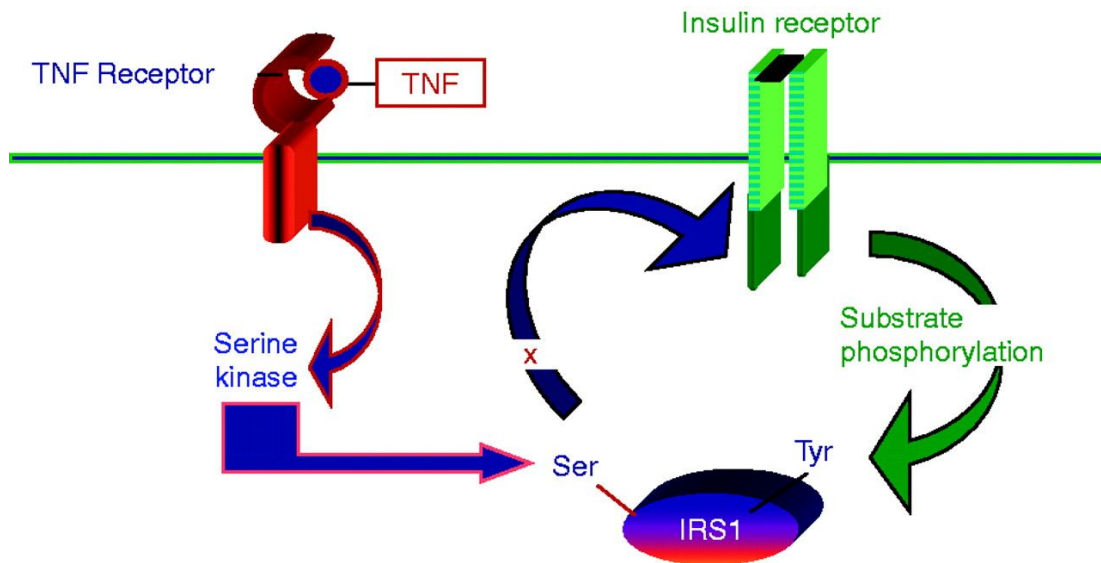


Figure 9: Illustrates the dual affect TNF-alpha has on IRS-1 [21].

Who develops insulin resistance?

Insulin resistance occurs when an individual does not allow their body to maintain blood glucose homeostasis or if their body develops an autoimmune disorder that affects this particular balance, as in Type 1 Diabetes. Patients often approach a doctor when they are overweight, obese, or when they develop/are developing Diabetes Type 2, and discover at that point in time that their blood sugar concentrations are higher than they should be.

Obesity

The state of obesity, or adiposity, is determined by an individual's body mass to body fat ratio, typically calculated as one's Body Mass Index (BMI). To be considered a healthy weight, an adult's BMI must fall between 18.5 and 24.9. Overweight individuals have a body mass index between 25 and 29.9. A BMI of 30 or above is considered obese. Another consideration to determine the adiposity of an individual is abdominal circumference that might indicate a large amount of visceral fat, which is unhealthy [1].

Many other health problems often come with obesity, such as cardiovascular disease, risk of stroke, diabetes development, hypertension, nonalcohol fatty liver disease, sleep disorders, and increased cancer risk, just to name a few [1] [22].

The most common treatments recommended to address obesity is dietary changes and increasing physical activity [1] [22]. Dietary changes include changing the foods eaten as well as eating patterns, such as dieting. Some less commonly known methods are group therapy to address behavior patterns and medications. Bariatric surgery is a more invasive way to deal with obesity [22].

Diabetes

There are two major types of diabetes mellitus, Type 1 and Type 2. Gestational Diabetes will not be discussed in this literature review. Type 1 is the result of an autoimmune response by the body towards the pancreatic beta cells [2]. This results in the decreased production of insulin and thus the body's inability to handle glucose ingested during meals. Type 1 Diabetes

prevalence is low in the American population, with 5% of diabetics presenting with Type 1 [2] [3].

Conversely, Type 2 Diabetes Mellitus is very prevalent in the United States, as almost 90% of individuals with diabetes have Type 2. 30.3 million U.S. citizens currently live with diabetes in general [2] [3]. It occurs when the body develops insulin resistance and is unable to metabolize the glucose ingested by the individual. Obesity usually presents first before Diabetes Type 2. Over time, with continued insulin resistance in the body, the liver and adipocytes are unable to store any more of the excess glucose, so it remains in the bloodstream [2]. Blood sugar levels remain high, the body is unresponsive to the insulin secreted by the pancreas, and Type 2 Diabetes results.

Type 2 Diabetes will be discussed in relation to intermittent fasting in this literature review, as it is one condition that is a result of insulin resistance. Diabetes Type 1 is an autoimmune disease and will not be examined.

Reasoning behind Intermittent Fasting as a Treatment Method

In general, intermittent fasting is the practice of refraining from eating for a period of time, alternating with periods of normal eating, ad libitum. The time frames for fasting can range from several hours to a few days. There are several different types of IF, with varying levels of difficulty based on experience and intensity. Some of the most popular forms of IF are as follows:

Time-Restricted Feeding

Time-restricted feeding refers to a daily pattern of eating where consumption of food occurs during a particular window of time in the day and fasting outside that time-frame. An example this is the 16/8 Plan. Here, an individual eats during an 8-hour window of the day, and fasts the other 16 hours. The feeding period usually occurs earlier in the day. A longer variation of the 16/8 Plan is the 20/4 Plan. The fasting time is increased and the feeding period is shortened. There are other variations of time-restricted feeding, but the 16/8 Plan is the most popular one [24] [25] [26]. This method is considered to be one of the easier forms of IF because it's an alteration of current daily practices by most of society. Most Americans eat three meals a day over the course of 11-12 hours and fast during the evening and sleeping periods. The time-restricted pattern simply shortens the feeding window and lengthens the fasting period.

Alternate Day Fasting

Alternate day fasting is another common way to perform IF and is commonly used in rodent studies of IF because it is easy to implement on test subjects. As evident by the name, alternate day fasting allows an individual to alternate between feeding days and fasting days. A few variations allow for consumption of 500 calories on fasting days. However, this is atypical of alternate day fasting practices. This is considered a more difficult method because of the frequency and duration of fasting time [25] [26].

24-Hour Fasts

A plan similar to alternate day fasting is the 5/2 plan. Eating normally occurs on five days of the week, and fasting on two days of the week. The two fasting days are typically nonconsecutive. On fasting days, it is recommended that an individual eats 500 calories if they are female and 600 calories if they are male. Liquids are recommended as well [24] [25] [26].

The more advanced version, the Eat-Stop-Eat Plan, does not allow eating on fasting days during this regiment. Fasting duration is 24. Non-caloric beverages and water are allowed during this fasting method [24] [25] [26].

Both of these versions of 24-hour fasts are considered challenging and are not recommended for beginners.

The Warrior Diet

The Warrior Diet entails fasting almost all 24 hours of the day, every day, with the allowance of small and very healthy snacks during the fasting period, such as fresh fruits and vegetables, and nuts. The extensive fasting period is followed by a large meal in the evening during a 4 hour period. This method is usually used in conjunction with bodybuilding goals and the paleo diet. It is considered one of the most advanced and difficult forms of intermittent fasting [25].

Meal Skipping

This method is when an individual chooses to not eat a meal. It is not a structured plan and is very flexible based on lifestyle and personal preferences. The person may choose to

abstain from food randomly, or it may be a predetermined choice. This can occur for many reasons as well. Perhaps an event comes up that interferes with eating a meal, or preparing food is not convenient at the time. The individual may also just decide to refrain from eating any particular meal at any time of the week [25]. This is also considered an easier form of IF because of the simplicity of implementation and short duration of fasting time.

Intermittent fasting in general has been proposed as a method of treatment because of the way it might affect insulin resistance in the body [23]. No studies as of yet have determined if one method is better than another for weight loss and weight management. The hypothesis for why IF affects insulin resistance is that the fasting period is a time when the body receives a break from the intake of sugars and carbohydrates. This fasting time requires the body to use its own stores of energy in order to function, as there is no intake of energy [24]. This also provides an opportunity to reduce the excess glucose circulating in the blood. With a decrease in the amount of blood glucose, the pancreas releases less insulin. Without the bombardment of insulin, the cells are able to recover their normal response to the hormone. This time period of fasting allows the body to reset itself and to recover its normal response to the insulin produced by the pancreatic beta cells [23].

Along with regaining insulin sensitivity in the body, IF has been proposed to provide several other benefits. Though specific mechanisms are not yet known for causing most of these possible benefits, some research indicates that IF may improve overall health in the body. More research will be needed to verify the authenticity of many of these proposed benefits. See Figure 10 for a list of some claimed benefits that occur with improved insulin sensitivity.

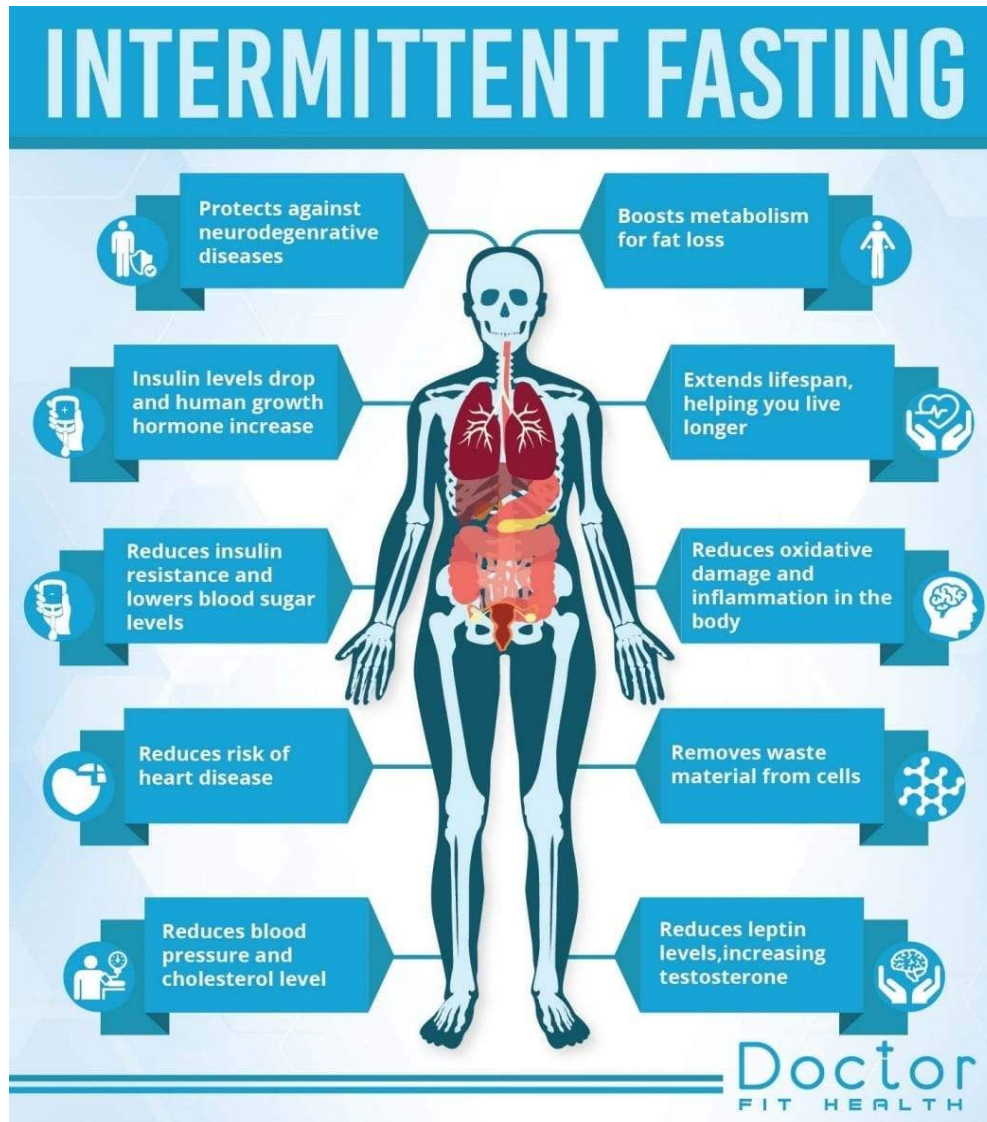


Figure 10: This figure provides a short list of commonly cited benefits of intermittent fasting on the body. Not all benefits are listed in this figure [27].

Findings from Research Literature on the Effects of Intermittent Fasting on Insulin Levels in the Blood and on Insulin Sensitivity in the Body

Regarding the hypothesis about intermittent fasting, this literature review aims to analyze the results of experiments focusing on and including the effects intermittent fasting has on

insulin in the body. For the purpose of this paper, fasting insulin levels and insulin sensitivity will be referred to as insulin for the rest of this section, unless otherwise specifically mentioned. The studies reviewed do not all focus solely on fasting and insulin, but all the literature considered does contain records of how the fasting in their experiments affected the insulin of their respective subjects.

Insignificant Results

Two studies did not find any significant differences in fasting and insulin between the control and test subjects. The first study in this category did not see any normalization of fasting insulin levels or inflammatory markers during the intermittent fasting phase. The average fasting duration for the subjects of this study was 16.82 hours with a standard deviation of 1.18 hours. The fasting regimen occurred over a 3-4 week timescale [28].

The second study analyzed the effects of an 8 hour eating period and a 16 hour fasting period on individuals who already had obesity. The particular goals were to see how risk factors for metabolic diseases and body weight changed after the time-restricted pattern of IF over a 12-week period. Fasting insulin levels and fasting glucose levels were not significantly different from those of the control group for this study [29].

Although both studies concluded that IF had benefits, neither determined that there was any significant impact on insulin levels or insulin sensitivity in their subjects and recommended that further studies confirmed these results. This leads to the conclusion that IF is still a new subject and requires many studies to determine how much it impacts the metabolism of diabetics and obese individuals.

Mixed Results

The first study with mixed results focused on a comparison of intermittent fasting, referred to as intermittent energy restriction in the article, to continuous energy restriction. Continuous energy restriction is when an individual eats less calories than their body requires on a daily basis. The article was a review of other studies and compared the results of continuous energy restriction dieting to results of intermittent energy restriction. The overall conclusion in regards to insulin sensitivity in this paper was there were no significant differences in insulin between the control and test groups, but there were significant differences within each group [30].

Insignificant improvements were seen in another study focused on intermittent fasting benefits for patients with Type 2 Diabetes. The fasting period was one week in length under heavy scrutiny by the researchers to assure no issues or harm came to the participants. Results were measured and examined four months after the study started. While other aspects such as weight and blood pressure improved, there were only insignificant improvements in insulin sensitivity [31].

The third study with mixed results examined how intermittent fasting affected individuals of a healthy weight and those who were overweight or obese. The researchers concluded that the effects of fasting are beneficial for overweight and obese individuals, but harmful for normal, healthy individuals [32].

A fourth study relevant to this literature review discussion has not been concluded yet, but is noteworthy as it appears that the conclusions of this research will add to the results of other studies on this topic [33].

These studies with mixed conclusions provide further insight into how new the topic of IF is in science and literature and indicate that more research is needed before IF can be applied as a normal treatment method for obesity and Type 2 Diabetes. Some knowledge gained through these studies shows how individualized the effects of intermittent fasting can be [30], that maybe improvements to fasting insulin levels take time or vary on a personal basis of the patient [31], and that IF may be most beneficial for patients with metabolic disorders only and may not be the best practice for healthy people to partake in [32].

Significant Results

The remaining articles generally agreed that there was a positive effect on insulin by some form of intermittent fasting.

Antoni and team wrote an overview article comparing different types of intermittent fasting to energy-restriction methods of weight loss and discussed the general effects of each. They concluded that intermittent fasting was comparable to energy-restriction as an approach to weight loss and may provide increased benefits in some ways that energy restriction practices cannot. However, many of the studies they reviewed were conducted on rodents with few containing human subjects. More research on people needs to be done in order to make more of a conclusion, but they found promise in intermittent fasting methods in positive metabolic effects, including insulin, and weightloss [33].

A second research team investigated the effects of various diets on Type 2 Diabetes reduction in young people by reviewing studies of other researchers. One diet method was modified intermittent fasting, in which an individual ate normally on three to six days of the

week and fasted after their set ad libitum period. This team, after reviewing studies discussing intermittent fasting, concluded that intermittent fasting does increased insulin sensitivity. They also concluded in their overview that decreasing carbohydrate intake in general, regardless of dieting choice, decreased Type 2 Diabetes risks in young individuals. Intermittent fasting falls into the carbohydrate reduction category by the lack of food intake, including carbohydrates on fasting days [34].

Mattson, et al, discussed how intermittent fasting influenced general health and diseases. They examined studies on intermittent fasting in both animals and humans and how it changed metabolic biomarkers and various diseases. Most of the effects were positive and significant. The animal studies indicated that intermittent fasting does decrease blood insulin levels and increases insulin sensitivity. More research needs to be done to confirm this in humans, but studies reviewed so far are pointing in the same direction as the results of the animal studies [35].

Another research group compared the metabolic effects of intermittent fasting to those of daily calorie restriction regarding the of preventing Type 2 Diabetes. Caloric restriction was reported to have a greater effect on weight loss than intermittent fasting, but comparable results in the decrease in fasting insulin levels and insulin resistance in the body. The effects of intermittent fasting on insulin was significant. They compared other metabolic biomarkers as well and concluded that intermittent fasting could potentially be an alternative weight loss method to caloric restriction, but more research is needed to confirm their conclusion [36].

Li, et al, looked at intermittent fasting as a solution to weight control and wanted to investigate the mechanisms behind the effects of intermittent fasting on the body. During their research, they also noted that intermittent fasting reduces insulin resistance. They focused on an

alternate day fasting pattern specifically. Their findings support the idea that intermittent fasting positively influences insulin [37].

Sutton, et al, looked at a form of intermittent fasting called early time-restricted feeding and how it impacts insulin sensitivity, oxidative stress, and blood pressure apart from weight loss. Early time-restricted feeding is a form of intermittent fasting that confines eating to earlier in the day to align with the circadian rhythm. Individuals on this dieting regiment don't eat after three p.m. Sutton's team found that all factors investigated, including insulin sensitivity, were positively impacted. Other factors they did not initially examine were also found to be positively impacted, such as appetite and other cell functions [38].

Case studies

There were two case studies as well, one with three subjects [39] and the other with one subject [40]. Both concluded that intermittent fasting does positively impact insulin by reducing fasting insulin levels and increasing insulin sensitivity in long-time diabetic patients. These case studies provide good, focused insight into intermittent fasting on the level of individual patients. However, the sample size is very small and results from these should be measured carefully against studies with larger subject cohorts.

Application for Society

Because of the prevalence of obesity and diabetes in our culture and its spread across the globe, society needs to consider alternative methods to treat obesity and Type 2 Diabetes. It seems possible, based on the literature so far, that IF could be an alternative approach to address

these metabolic conditions. Before it can be fully implemented, more research needs to be conducted on IF and its effects on the human body. Education on multiple levels will also be necessary if scientists do conclude that IF is a viable method for addressing metabolic conditions.

Research certainly needs to continue in the investigation of IF. There are still many questions that need to be addressed before implementation into society is possible. Such questions include: What time of day should these patients eat? What kinds of food do they need to consume or avoid? Do they need to exercise while they are practicing IF? Does age and gender have any effect on the practice of IF? What time span should patients fast? How individualized does treatment need to be? Do different people respond differently to different types of intermittent fasting? Should they continue when they no longer need to see a doctor for their ailment? These and many other questions need to be answered by the scientific community so that patients can practice IF in the healthiest and most educated way possible.

Once more information is gained about IF, and if it is utilized as a possible treatment course for the obese and diabetic, then education will be the next step at the forefront of this movement. Educating current and future doctors who specialize in treatments with obesity and diabetes would be the first place to begin the education process, as they will be most heavily involved in spreading and implementing this treatment technique. Without being taught about intermittent fasting and the details behind it, medical professionals won't be able to recommend it as a treatment option. Educating other medical professionals not directly associated with

treating metabolic conditions would be another aspect of enlightening healthcare providers. Once they learn about and understand it, secondary doctors will be able to guide patients to the proper specialist and to inform their clients about intermittent fasting as best they can. One more benefit to informing medical care providers about IF is their ability to monitor and support patients who need to practice IF. It's important for healthcare practitioners to support their patients in improving their health socially as well as scientifically. With providers' support and monitoring to ensure the patient does not stray in a direction that is not healthy for them, patients will have a better support network and an easier time communicating with their doctor and adhering to the treatment plan.






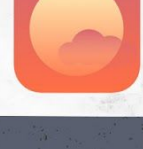
Educating the public would be another part of introducing IF as a normal treatment practice to society. Once science has confirmed it to be more than a fad diet, the findings can determine how strong it is as potential treatment method. Individuals need to understand what it is, how it works in a general sense, and to provide support for patients who need it as a therapy for their health. In educating society, more awareness about IF treatment is provided for individuals who need their health addressed and they can more easily find their way to get that treatment. It will also be a more accepted practice if more people are aware of it. With the facts present for the public to see and with more people possessing awareness of it as a method of treatment, over time there will be support and knowledge of IF and it will be viewed as a normal approach to treating health.

As teachers and scientists educate people in the medical field and in the general public about the benefits of intermittent fasting and its application as a treatment method for obesity and diabetes, groups should also undertake the task of developing support programs for patients seeking treatment via IF. In these programs, patients can meet others who may be going through the same remedy and can find resources to aid them if needed while they practice IF. They can share their stories, learn about recent research on IF, and get tips and ideas to help them stick with the treatment plan if they find themselves struggling with the schedule or adjusting to the types of foods they eat.

Such support tools could include websites and organizations. There are currently some support groups and websites for individuals who wish to practice IF. They include a description of what intermittent fasting is, the different types of IF, how to properly practice IF, common questions about this practice, tips, and other resources for those who are interested and curious. Other possible tools are smartphone apps that can direct and monitor fasting practices for an individual to help them adhere to their treatment plan. These apps could also be used to keep patients' healthcare providers updated on their patients' progress and as a communication source between patients and providers. See Figure 11 for a list of current IF fasting apps available to the public.

21 DAY HERO
TOP 6 FASTING APPS

RATINGS

	<p>BodyFast</p> <ul style="list-style-type: none"> - 10 fasting plans - Fasting and weight tracker - Trophies for achieving goals - Individual plan by the coach (for premium) 	<p>4.7 Available on the iPhone App Store</p> <p>4.6 Available on Google play Google play</p>
	<p>FastHabit</p> <ul style="list-style-type: none"> - Fasting tracker - Fasting history - Streak tracking - Possibility to manually add fasting history 	<p>4.7 Available on the iPhone App Store</p>
	<p>My Fast</p> <ul style="list-style-type: none"> - Fasting and weight tracker - Progress bars - Fasting history - Goal setting functionality 	<p>4.6 Available on the iPhone App Store</p> <p>4.1 Available on Google play Google play</p>
	<p>Track Your Fast</p> <ul style="list-style-type: none"> - Fasting tracker - A widget that shows current fast - Basic weight tracking 	<p>3.7 Available on Google play Google play</p>
	<p>VORA</p> <ul style="list-style-type: none"> - Fasting tracker - Extensive fasting stats and analytics - Possibility to manually add fasting history - Social networking 	<p>4.3 Available on the iPhone App Store</p> <p>4.4 Available on Google play Google play</p>
	<p>ZERO</p> <ul style="list-style-type: none"> - Fasting tracker - Notification setup - 7 days of fasting history - Functionality to export the fasting history 	<p>4.7 Available on the iPhone App Store</p>

WWW.21DAYHERO.COM/IF

Figure 11: This image illustrates 6 apps currently available to the public that help individuals with their fasting schedules. It also gives short descriptions of the services each app provides [41].

Conclusion and Future Perspectives

Though findings from the literature reviewed are mixed, the general consensus is that intermittent fasting does positively affect insulin by reducing fasting insulin levels and increasing insulin sensitivity. In the future, a greater number of more controlled experiments with a focus on how intermittent fasting affects fasting insulin levels and insulin sensitivity are needed in order to make a more definite conclusion. Further research will be necessary to answer several other questions and to determine if IF can be used as a treatment option for diabetic and obese individuals. If the plausibility of IF as a course of treatment is determined to be possible, education and further research would need to be performed to initiate application into society. So far, intermittent fasting seems to be a possible way to address the metabolic conditions rampant in the American population. Hopefully the proposed dietary plan can be used to alleviate these health issues in the United States and progress to other nations experiencing trouble with obesity and Type 2 Diabetes.

Works Cited

1. “Overweight and Obesity.” National Heart Lung and Blood Institute, U.S. Department of Health and Human Services, www.nhlbi.nih.gov/.
2. “About Diabetes.” Centers for Disease Control and Prevention, Centers for Disease Control and Prevention, 2017, www.cdc.gov/.
3. “Diabetes Basics.” American Diabetes Association, American Diabetes Association, 2019, www.diabetes.org/.
4. “NCHS Data Brief No. 288.” *NCHS Data Brief No. 288*, Centers for Disease Control and Prevention, Oct. 2017, www.cdc.gov/nchs/data/databriefs/db288.pdf.
5. *Number and Percentage of U.S. Population with Diagnosed Diabetes, 1958-2015*. Centers for Disease Control and Prevention, Apr. 2017, www.cdc.gov/diabetes/statistics/slides/long_term_trends.pdf.
6. “Mortality in the United States, 2017.” *Mortality in the United States, 2017*, Centers for Disease Control and Prevention, Nov. 2018, www.cdc.gov/nchs/products/databriefs/db328.htm.
7. Piro S., Urbano F., Folli F., Finzi G., Marselli L., Marchetti P. (2018) The Endocrine Pancreas. In: Belfiore A., LeRoith D. (eds) *Principles of Endocrinology and Hormone Action*. Endocrinology. Springer, Cham
8. White M.F. (2018) Receptor Tyrosine Kinases and the Insulin Signaling System. In: Belfiore A., LeRoith D. (eds) *Principles of Endocrinology and Hormone Action*. Endocrinology. Springer, Cham

9. Capurso, Cristiano, and Antonio Capurso. "From excess adiposity to insulin resistance: the role of free fatty acids." *Vascular pharmacology* 57.2-4 (2012): 91-97.
10. Musi, Nicolas, and Rodolfo Guardado-Mendoza. "Adipose Tissue as an Endocrine Organ." *Cellular Endocrinology in Health and Disease*, edited by Alfredo Ulloa-Aguirre and P. Michael. Conn, Elsevier/AP, 2014, pp. 229–237.
11. Suckale, Jakob, and Michele Solimena. "Pancreas islets in metabolic signaling-focus on the beta-cell." *Front Biosci* 13.7156 (2008): 71.
12. Paul, Izak. "Blood Sugar Regulation." *Biology*, edited by Richard Robinson, vol. 1, Macmillan Reference USA, 2002, pp. 87-89. Gale Virtual Reference Library, http://link.galegroup.com.libproxy.uwyo.edu/apps/doc/CX3400700057/GVRL?u=wylrc_uwyoming&sid=GVRL&xid=8706730a. Accessed 11 May 2019.
13. White M.F. (2018) Receptor Tyrosine Kinases and the Insulin Signaling System. In: Belfiore A., LeRoith D. (eds) *Principles of Endocrinology and Hormone Action*. Endocrinology. Springer, Cham
14. "Physiological Effects of Insulin." *Physiological Effects of Insulin*, Colorado State University, Feb. 2019, www.vivo.colostate.edu/hbooks/pathphys/endocrine/pancreas/insulin_phys.html.
15. De Meyts, Pierre. "The insulin receptor and its signal transduction network." *Endotext* [Internet]. MDText. com, Inc., 2016.
16. White, Morris F., and Kyle D. Copps. "The Mechanisms of Insulin Action." *Endocrinology: Adult and Pediatric (Seventh Edition)*, by J. Larry Jameson and Leslie J De Groot, 7th ed., W.B. Saunders., 2016, pp. 556–585.

17. Fröjdö, Sara, Hubert Vidal, and Luciano Pirola. "Alterations of insulin signaling in type 2 diabetes: a review of the current evidence from humans." *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease* 1792.2 (2009): 83-92.
18. Favussin, Eric, and Steven R. Smith. "Role of the Adipocyte in Metabolism and Endocrine Function." *Endocrinology: Adult and Pediatric (Seventh Edition)*, by J. Larry Jameson and Leslie J De Groot, 7th ed., W.B. Saunders., 2016, pp. 627–647.
19. Ruderman, Neil B., and Gerald I. Shulman. "Metabolic Syndrome." *Endocrinology: Adult and Pediatric (Seventh Edition)*, by J. Larry Jameson and Leslie J De Groot, 7th ed., W.B. Saunders., 2016, pp. 752–769.
20. Gao, Zhanguo, et al. "Inhibition of insulin sensitivity by free fatty acids requires activation of multiple serine kinases in 3T3-L1 adipocytes." *Molecular endocrinology* 18.8 (2004): 2024-2034.
21. Catalano, Patrick M. "Obesity, insulin resistance, and pregnancy outcome." *Reproduction* 140.3 (2010): 365-371.
22. Cowley, Michael A., et al. "Obesity: The Problem and Its Management." *Endocrinology: Adult and Pediatric (Seventh Edition)*, by J. Larry Jameson, J. Larry and Leslie J De Groot, 7th ed., W.B. Saunders., 2016, pp. 468–478.
23. Longo, Valter D., and Mark P. Mattson. "Fasting: molecular mechanisms and clinical applications." *Cell metabolism* 19.2 (2014): 181-192.
24. Fung, Jason, and Andreas Eenfeldt. "Intermittent Fasting for Beginners – The Complete Guide – Diet Doctor." *Diet Doctor*, 16 Mar. 2019, www.dietdoctor.com/intermittent-fasting.

25. Gunnars, Kris. "6 Popular Ways to Do Intermittent Fasting." *Healthline*, Healthline Media, 4 June 2017,
www.healthline.com/nutrition/6-ways-to-do-intermittent-fasting#section7.
26. Cole, William. "Intermittent Fasting: A Complete Guide to Benefits, Diet Plans and Meals." *Mindbodygreen*,
www.mindbodygreen.com/articles/intermittent-fasting-diet-plan-how-to-schedule-meals.
27. "Fat Protein Carb's." *Fat Protein Carb's*, Blogger, 7 Apr. 2019,
fatproteincarb.blogspot.com/index.html.
28. Arnason, Terra G., Matthew W. Bowen, and Kerry D. Mansell. "Effects of intermittent fasting on health markers in those with type 2 diabetes: A pilot study." *World journal of diabetes* 8.4 (2017): 154. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5394735/>
29. Gabel, Kelsey, et al. "Effects of 8-hour time restricted feeding on body weight and metabolic disease risk factors in obese adults: A pilot study." *Nutrition and Healthy Aging* Preprint: (2018) 1-9. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6004924/>
30. Harvie, Michelle, and Anthony Howell. "Potential benefits and harms of intermittent energy restriction and intermittent fasting amongst obese, overweight and normal weight subjects—a narrative review of human and animal evidence." *Behavioral Sciences* 7.1 (2017): 4. <https://www.ncbi.nlm.nih.gov/pubmed/28106818>
31. Li, Chenying, et al. "Effects of a one-week fasting therapy in patients with type-2 diabetes mellitus and metabolic syndrome—A randomized controlled explorative study." *Experimental and Clinical Endocrinology & Diabetes* 125.09 (2017): 618-624.
<https://www.ncbi.nlm.nih.gov/pubmed/28407662>

32. Kessler, Christian S., et al. "A nonrandomized controlled clinical pilot trial on 8 wk of intermittent fasting (24 h/wk)." *Nutrition* 46 (2018): 143-152.
<https://search-proquest-com.libproxy.uwyo.edu/docview/1985638397?pq-origsite=360link>
33. Antoni, Rona, et al. "Effects of intermittent fasting on glucose and lipid metabolism." *Proceedings of the Nutrition Society* 76.3 (2017): 361-368.
<https://www-cambridge-org.libproxy.uwyo.edu/core/journals/proceedings-of-the-nutrition-society/article/effects-of-intermittent-fasting-on-glucose-and-lipid-metabolism/8803CC1517F53CEF2BF8BFDC06A816D6/core-reader>
34. Gow, Megan L., et al. "The effectiveness of different diet strategies to reduce type 2 diabetes risk in youth." *Nutrients* 8.8 (2016): 486.
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4997399/>
35. Mattson, Mark P., Valter D. Longo, and Michelle Harvie. "Impact of intermittent fasting on health and disease processes." *Ageing research reviews* 39 (2017): 46-58.
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5411330/>
36. Barnosky, Adrienne R., et al. "Intermittent fasting vs daily calorie restriction for type 2 diabetes prevention: a review of human findings." *Translational Research* 164.4 (2014): 302-311. <https://www.ncbi.nlm.nih.gov/pubmed/24993615>
37. Li, Guolin, et al. "Intermittent fasting promotes white adipose browning and decreases obesity by shaping the gut microbiota." *Cell metabolism* 26.4 (2017): 672-685.
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5668683/>

38. Sutton, Elizabeth F., et al. "Early time-restricted feeding improves insulin sensitivity, blood pressure, and oxidative stress even without weight loss in men with prediabetes." *Cell metabolism* 27.6 (2018): 1212-1221.
<http://vh7qx3xe2p.scholar.serialssolutions.com/?sid=google&auinit=EF&aualast=Sutton&atitle=Early+time-restricted+feeding+improves+insulin+sensitivity,+blood+pressure,+and+oxidative+stress+even+without+weight+loss+in+men+with+prediabetes&id=doi:10.1016/j.cmet.2018.04.010&title=Cell+metabolism&volume=27&issue=6&date=2018&page=1212&issn=1550-4131>
39. Furmli, Suleiman, et al. "Therapeutic use of intermittent fasting for people with type 2 diabetes as an alternative to insulin." *BMJ case reports* 2018 (2018).
<http://casereports.bmj.com/content/2018/bcr-2017-221854.long>
40. Ku, Michael, Megan J. Ramos, and Jason Fung. "Therapeutic fasting as a potential effective treatment for type 2 diabetes: A 4-month case study." *Journal of Insulin Resistance* 2.1 (2017): 1-5. <https://insulinresistance.org/index.php/jir/article/view/31/77>
41. Sinkus, Tauras. "21 Day Hero." 21 Day Hero, 2018,
21dayhero.com/top-6-intermittent-fasting-apps/.
42. Fung, Dr. Jason. *The Obesity Code: Unlocking the Secrets of Weight Loss*. Scribe, 2016.