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COMPARISON OF VARIOUS INTERMITTENT FASTING DIETARY INTERVENTIONS TO THE KETOGENIC DIETARY INTERVENTIONS AND ITS EFFECTS IN MITIGATING HUNGER IN OBESE ADULTS

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Thesis

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Abbreviations

ad libitum (ad-lib)
Alternate Day Modified Fasting (ADMF)
Alternate day fasting (ADF)
AMP-activated protein kinase (AMPK)
arcuate nucleus (ARC)
β-Hydroxybutyrate (β-OHB)
body mass index (BMI)
Branched amino acids (BCAAs)
Caloric restriction (CR)
Carbohydrates (CHO)
central nervous system (CNS)
Cholecystokinin (CCK)
CREB regulated transcription coactivator 2 (CRTC2)
Dorsomedial nucleus (DMN)
Free fatty acids (FFA's)
Fat mass (FM)
Fat free mass (FFM)
Glycated hemoglobin (HbA1C)
Glucocorticoids (GCs)
Glucagon-like peptide-1 (GLP-1)
Intermittent fasting (IF)
Kilocalories (kcal)
ketogenic diet (KD)
ketogenic low carbohydrate diet' (KLCD)
low carbohydrate diet' (LCD)
low-density lipoproteins (LDL)
medium carbohydrate, low fat, calorie-restricted, carbohydrate counting diet (MCCR)
methylacetoacetyl CoA thiolase (MAT)
Pancreatic Polypeptide (PP)
paraventricular nucleus (PVN)
Peptide Tyrosine (PYY)
reactive oxygen species (ROS)
sirtuin (SIRT1)
succinyl CoA-oxoacid transferase (SCOT)
Time-Restricted Eating (TRE)
Time-Restricted Feeding (TRF)
Very-low calorie ketogenic diet (VLCKD)
Very low energy diet' (VLED)

Abstract

There have been many dietary strategies that can be used for fat loss and the most recent popular dietary interventions have been intermittent fasting and the ketogenic diet. Intermittent fasting (IF) dietary interventions and the ketogenic diet (KD) are popular diets that claim to promote weight loss which has also been speculated to have enhanced benefits than caloric restriction. Although these dietary strategies are growing in popularity, it is unclear if the intervention can manage hunger, which may increase adherence. The purpose of this paper is to systematically review the literature on the impact of IF protocols compared to KD used for weight loss. This comparison is to evaluate if they have any beneficial effects on managing hunger. The criteria were English-written original research articles published in peer-reviewed journals that had investigated weight loss interventions on their effects hunger. A brief definition of hunger is the regulation of energy balance. Fourteen articles met the inclusion criteria and were selected for this review. Scrutiny of the data suggests that neither IF nor KD was more efficient than the other in mitigated hunger. More research is needed to understand if comparing the IF to a KD has any positive outcomes in managing hunger.

Chapter 1

Introduction

Although obesity is largely a preventable disease, there are at least 650 million people worldwide that are afflicted by it (Castro et al., 2018). This is despite the seemingly simplistic formula to achieve weight-loss, using a calorie-restrictive diet. Besides caloric reduction, interventions to treat obesity such as surgeries and medications have been used to reduce fat mass (Castro et al., 2018). Thus, while the formula for weight-loss may seem simple, its implementation faces challenges because of the lack of success in weight management. Obesity continues to grow around the world, resisting public health efforts to encourage healthy eating and activity (Witkowski, 2007). This led researchers to examine why do individuals overconsume food and gain weight. Understanding the psychology of why people overeat may be helpful to improve adherence to dietary interventions. It has been well-established that overweight and/or obese people have a stronger desire to eat and often lack self-control for overeating (Castro et al., 2018)**.**

Obesity is not simply a caloric equation because the common strategy to combat obesity is to decrease calorie consumption, increase calories expended, or ideally a combination of both. This formula has been in place for years, but the obesity crisis is still on the rise. There are a multitude of causal factors for this epidemic and most health professionals treat all persons with obesity similarly. Unfortunately, these strategies are somewhat unsuccessful for some groups and one reason for its lack of success is that calorie reduction increases hunger which can lead to a lack of dietary adherence (Lean & Malkova, 2016). Thus, it is necessary to define hunger which has two classifications, and they are homeostatic hunger or hedonic hunger. The desire to eat can be driven by various stimuli, such as the need to meet homeostatic energy is called homeostatic hunger. The palatability or desirability of certain food items is referred to as hedonic hunger, which can be triggered by one's susceptibility to environmental food cues (O'Neil et al., 2012). The area of the body that interprets homeostatic hunger and/or hedonic hunger is the brain. (Lutter & Nestler, 2009)**.** Essentially, the brain sends signals that there is a need for energy and thus a person is motivated to seek food**.** In response to homeostatic hunger, there is homeostatic eating. The operational definition of homeostatic eating is defined as eating is the response to the perceived energy needs of the brain (Schweitzer, 2008). It is difficult to assume that the obese population that are investigated are exhibiting a homeostatic hunger, hedonic hunger, or just having an appetite. Appetite is sometimes used synonymously with hunger. However, the definition of appetite is “the system that influences energy consumption and is associated with the motivational states of hunger” (Gibbons et al., 2019). If a dieter is unable to manage their hunger, whether homeostatic or hedonic, the ability to have eating restraint is lowered and compliance to diet protocol is diminished (Johnstone et al., 2008).

Unfortunately, caloric restriction may increase hunger leading to eventual failure of attempted weight loss. (Beaulieu et al., 2020). Some may be cautious on implementing an IF protocol because of fear of becoming hyperphagic due to the increase of hunger. However, a study conducted by Beaulieu et al. (2020), comparing IF and CR revealed that there was no significant difference in hunger. Although, this was only one study it shows promise that hunger and the drive to eat were not exacerbated.

Food cravings can be psychological in nature and there have been studies investigating the hunger state with brain imaging (Goldstone et al., 2009; Stice et al., 2013; Uher et al., 2006). The potential benefit of these research studies is that they investigate the interaction between the nutritional state with different foods, and how the brain recognizes the potential reward driven by the food stimuli. Not everyone experiences food cravings the same and individual differences must be taken into consideration. White et al. (2002), stated that food cravings should be separated into the desire to eat, which is considered hunger, or a wanting for a particular food, which is considered a craving. Understanding the difference between the two may give a different perspective regarding obesity and the lack of adherence to weight-loss protocols. Weight-loss practitioners that are having difficulty managing their food cravings have difficulty sticking to hypocaloric diets.

Various strategies can be used qualitatively to understand if a patient is experiencing hunger, food cravings, or disinhibition when implementing a weight loss protocol including eating inventory

(Stunkard & Messick, 1985), visual analog scale (VAS) (Flint et al. (2000), Tinsley et al. (2018), food craving inventory (White et al., 2002), and the three-factor eating questionnaire (Stunkard & Messick, 1985). A measure used in clinical studies that rates hunger, fullness, and satiety is the VAS (Flint et al., 2000). However, according to Flint et al. (2000), a notable concern is that with increasing age there is a weakening of the inverse relationship between hunger and fullness present in young adults.

There are other factors that may cause overeating which influences obesity. For instance, the reason why a person chooses to overeat needs to be investigated. Understanding the physiological as well as the psychological influences of hunger irregularities that lead to excessive food consumption is crucial and thus may prove to help dietary adherence (Johnstone et al., 2008). Therefore, being unable to mitigate hunger may explain why people have difficulty adhering to a traditional caloric restriction (CR) regimen and why new strategies need to be introduced. Some recent strategies to fight obesity, the ketogenic diet (KD) and various forms of intermittent fasting (IF), may hold promise for better management of hunger (Hoddy et al., 2020).

Many people have used the KD as a weight loss protocol, but that was not its initial intended application. In the early 1920s, neurologists Lenox and Cobb began using the KD to treat refractory epilepsy in both children and adults. An additional benefit observed was body weight reduction (Di Rosa et al., 2020). KD involves consuming majority of calories from fats, moderate amount of protein, and restricting carbohydrates (CHO) to no more than 50 grams per day (Gibson et al., 2015). Essentially, the reduction in CHO is to induce the metabolic state of nutritional ketosis so the body will primarily use fat for energy (Masood et al., 2021b).

IF describes many dieting strategies such as time-restricted eating or feeding (TRF), alternate day fasting (ADF), and the 5:2 diet (ad-libitum eating 5 days and 75% caloric restriction 2 days). These different protocols do not instruct people on what to eat but rather provide a time frame on when to eat or restrict eating. Emerging studies have suggested that ADF which implements an every-other-day eating restriction, may improve not only weight-loss but have positive influences on metabolic health risk factors (Klempel et al., 2010). Unfortunately, IF may not be appealing to all because of the extended periods of restricted eating. Non-compliance of an IF protocols may be due to not being adapted to the intervention. For most, people are conditioned to eating 3 meals a day and attempting to limit their eating to an eating window to only a few hours may be difficult. An especially challenging fasting protocol is the ADF, which allows ad-libitum eating but only every other calendar day (Grajower & Horne, 2019). TRE is another popular IF protocol and an example is no food intake for 16hrs and having an eating window of 8hrs. This eating strategy is influenced by the circadian rhythm with a feeding window that is usually in the range of 8-12 h (Chawla et al., 2021); however, windows as short as 4 h have been employed (Tinsley et al., 2017). The increase in popularity of KD and IF diets raise the question: although popular, do these dietary strategies help adherence by managing hunger?

Purpose

The purpose of this review is to compare various IF diet protocols to the KD on the effects of influencing hunger control in obese/overweight adults. The rationale for this review is that so many weight-loss diets fail because of the lack of adherence, therefore the investigation of these dietary strategies uncovers a beneficial impact on regulating and/or managing hunger. The hypothesis is managing hunger would be equivocal between the two weight-loss dietary interventions which are IF and the KD.

Chapter 2

Literature Review

IF has many variations and there is not a standardized term for its use (Anton et al., 2018; Mattson et al., 2017). The term IF encompasses many regimens, and it is defined as a host of eating strategies with the common element which is a time-related restriction of eating according to Mattson et al. (2017).

The list below contains a few of the most frequently used forms of IF:

- **Intermittent Fasting (IF)** is the more commonly practiced technique. This pattern makes use of fasting for a period, typically for 12 hours or more. As a shorthand, the ratio between fasted/non-fasted states is shown (e.g., 16:8 refers to 16 hours fasted, 8 hours eating).
- **Time-Restricted Feeding (TRF)** is a pattern that typically reserves eating for a certain period of a day, within 8-12 hours. The exact period can change based on the practitioner's schedule.
- **Alternate Day Fasting (ADF)** can be considered a more drastic approach to fasting. This type of fasting, as the name implies, alternates between a total caloric fast (i.e., strictly water and other non-calorie beverages) on fasted days, and unrestricted eating days (i.e., "cheat" days). Some proposed benefits of this form of IF are health improved body response to insulin and it may increase autophagy.
- **Alternate Day Modified Fasting (ADMF) –** According to Anton et al. (2018), ADMF allows the s consumption of less than or equal to 25% of baseline energy needs on "fasting" days, alternating with ad libitum food consumption on non-fasting days.
- **5:2 diet –** This is a modified fasting pattern that allows for the regular consumption of calories 5 days out of the week. However, 2 days are scheduled restrictive days. These days

limit calorie goals to approximately 25% of total daily energy needs. The presumed benefit of this regimen is that short bouts have a greater degree of compliance (Patterson et al., 2015).

IF in rodent studies that reduced daily eating patterns had a beneficial effect on many metabolic markers (Chaix et al., 2019; Chaix et al., 2014; Hatori et al., 2012). IF can be used as a form of caloric restriction. Caloric restriction can aid in weight loss and reduce certain metabolic anomalies in obese population (Franz et al., 2014; Van Gaal & Scheen, 2015).

Success with diet protocols is often dependent on a person's adherence and IF should be viewed as a tool, not a law, that considers the needs of the individual. The potential reason some prefer one protocol of IF to another is due to ease of dietary adherence and/or personal preference.

Proposed physiological effects of IF

Several mechanisms have been proposed to explain how IF practices can effect changes in a person's physiology. One of the most discussed mechanisms is how IF reduces free radical production from metabolic processes due to extreme caloric deficits. Another avenue of research suggests that IF can help to stimulate adipose browning which helps the gut microbiota to proliferate, which has been shown to help with weight reduction (Li et al., 2017). Lastly, some research showing that the processes that come with behavior changes can reduce glycated hemoglobin (HbA1c) levels, as well as regulate a person's Circadian rhythms. The last hypothesis is of interest as it alludes to a natural way for a person to "reset" their bodies, in the sense of adjusting eating and sleep patterns, which can be of benefit for weight loss and hunger reduction.

Oxidative Stress Hypothesis

Decreased caloric intake results in less overall energy. This reduction in energy causes the mitochondria to produce fewer free radicals through cellular metabolism; this is known as the Oxidative Stress Hypothesis (Merry, 2004). Oxidative stress refers to the imbalance between the number of antioxidants and free radicals in the body. Sources of free radicals can be internal, as byproducts from metabolic processes, or external from pollutants such as radiation or smoke inhalation (i.e., x-rays, smoke, ozone, etc.). Regardless of the source, they can damage the cellular structures of the DNA down to the structural proteins. Antioxidants are substances that are created endogenously by the body, as well as obtained exogenously from various foods; these substances help to neutralize free radicals' harmful effects.

Given that IF is a form of caloric restriction, and any form of caloric striction attenuates oxidative stress, albeit temporarily leading to adaptive protective responses (Sohal & Weindruch, 1996). This is in turn eventually protects cells from future reactive oxygen species (ROS) and, in essence, a protective adaptive response (Wegman et al., 2015). The adaptive response is not exclusive to IF but to VLCD’s and semistarvation diets as well. This being said, IF is just another tool that can be utilized to reduce oxidative stress. This protective response potentially is an underlying mechanism in IF (Wegman et al., 2015). The presumption is that the mitochondria aid in this protection and is the main site where endogenous ROS production and mitochondrial transcription are regulated when fasting (Haigis & Yankner, 2010; Ristow & Zarse, 2010). Some studies have shown that IF practices can reduce markers of oxidative stress and improve clinical findings (Cienfuegos et al., 2020; Gabel et al., 2018) and it could be used as an alternative to daily caloric restriction (Ravussin et al., 2015). These findings provide support that IF, a form of CR, is another dietary tool to reduce oxidative stress.

Modifiable Lifestyle Changes Hypothesis:

An increase in body weight can be prevented or managed by implementing a lasting and sustainable healthy lifestyle habits. Diet strategies, as well as, increasing physical activity, require behavior modification. These behavioral modification does not have to be done in conjunction but are promising in reducing the feelings of hunger. In most cases, the over consumption of hyperpalatable foods are usually high in calories and low in nutrients but switching to a higher nutrient dense diet may aid in weight loss and increase satiety. In a study conducted by Fuhrman et al. (2010), they found when their participants was given a diet that was high in micronutrients they were satiated and there was higher degree of adherence to the protocol. This study also revealed that those that do not incorporate a higher micronutrient diet experience more sensations of hunger.

Exercise is another modifiable lifestyle change that may have positive outcomes on improving satiety. Although within the literature the positive effects of exercise it is not conclusive on satiety regulation, it may depend on the individual to investigate for themselves. A systematic review that was conducted by Hubner et al. (2021) illustrated that there are positive effects of exercise and physical activity interventions on some hunger markers but there is a need for further research.

Another influence factor that may mitigate hunger is sleep. Sleep has been reported that if it is not optimal it may increase in ghrelin which is a hormone that stimulates hunger. This may then lead a person to eat to staff off the feeling of fatigue. On average, if a person has better sleeping patterns, it has been associated that their appetite regulating hormones are regulated optimally (Papatriantafyllou et al., 2022). This aspect of sleep quality and duration on its influence on hunger have been well documented and it is a modifiable lifestyle change that can be used to structure a successful weight loss protocol.

Circadian Rhythm Hypothesis

Circadian rhythms may be commonly referred to as a “biological clock.” These rhythms are an internal regulatory mechanism that maintains homeostasis and coordinates the physical, behavioral, and mental processes that follow a 24-hour cycle (Queiroz et al., 2021). The circadian rhythm influences the anabolic and catabolic pathways; the premise is that, at various times of the 24h day, and these processes are optimal when they are aligned (Asher & Sassone-Corsi, 2015; Bass, 2012; Chaix et al., 2019; Mattis & Sehgal, 2016; Panda, 2016; Qian & Scheer, 2016; Scheer et al., 2010). Since IF is an umbrella term, its beneficial effects on circadian rhythms may vary. The proposed benefits are dependent on the length of the IF protocol. Some studies have shown that obesity and abnormal metabolic changes have been associated with disruptions in the circadian system (Arble et al., 2010; Scheer et al., 2009). A study conducted by Scheer et al. (2013) the circadian system regulated hunger in their participants. It has been proposed that aligning food intake with circadian rhythms may be a good strategy for reducing hunger and help with weight loss, and this is where IF may be influential (Świątkiewicz et al., 2021). However, additional studies investigating the circadian rhythm and other forms of IF and its impact on hunger are limited and further research is needed.

Gut Microbiota Hypothesis

Recent evidence on the gut microbiota and its role of influencing obesity suggests that changes in dysbiosis, and the reduction of microbial diversity can promote insulin resistance (Lynch & Pedersen, 2016). The gut microbiota includes many beneficial bacterial species that can affect human physiology and play roles in a variety of metabolic processes (Lynch & Pedersen, 2016). If the gut microbiota is compromised, it can lead to a reduction in short-chain fatty acid synthesis. These fatty acids are essential to support the integrity of the gut barrier. Also, pancreatic β-cell proliferation and endogenous insulin production are affected by changes in the microbiota (Tan et al., 2014; Tang et al., 2015). Additionally, dysbiosis may inhibit the synthesis of other metabolites, like branched amino acids (BCAAs) and trimethylamine. This inhibition may disturb glucose homeostasis, increasing abnormal health outcomes (Neis et al., 2015; Shan et al., 2017). A study by Li et al. (2017) showed the benefits of fasting on metabolic markers. The study revealed that IF promotes the browning of white adipose tissue and decreases obesity by altering microbiota profiles (Li et al., 2017). Most studies that have researched fasting and the gut microbiota are from animals. Thus, until more studies are conducted in this area, evidence for the role of gut microbiota as a mechanism for IF is still preliminary and speculative.

IF and Its Proposed Effects on Metabolism

A potential result of IF is it aids the body by shifting its main energy source from glucose to fatty acids. It has been documented that people who obese have an inability to effectively oxidize circulating lipids (Kim et al., 2000). Being able to metabolize fat is one of many factors in lowering the rate of obesity. The way our bodies obtain the energy from fatty acids, it must be convert the fatty acids into ketones. (Anton et al., 2018). This process is referred to as the metabolic switch and it is theorized that being able to shift from glucose metabolism to fatty acid oxidation which are derived from ketones may help body recompositing in obese individuals (Vasim et al., 2022). IF may be another practical method than daily caloric restriction (Anton et al., 2018). IF aims to deplete glycogen stores in the hepatocytes and when they are depleted it accelerates adipose tissue lipolysis producing fatty acids and glycerol (Anton et al., 2018). The switching when the body starts to transition from ketone production and utilization has been proposed to occur between 12 to 36 hours after food consumption. This could help with fat metabolism, however, there are several factors that may impact this theorized metabolic switch and it is the quantity and quality of the food consumed, and the amount of stored glycogen in the liver. The depletion of liver glycogen not only happens during fasting but also in energy expenditure according to Anton et al. (2018). Furthermore, Anton et al. (2018) stated that once glycogen is depleted the body metabolizes FFAs, which are released into the blood. FFA's that are released in the blood stated by Gano et al. (2014), are then transported into hepatocytes where they are metabolized by β-oxidation to produce ketones, β-Hydroxybutyrate (β-OHB), and acetoacetate, which may in turn, induce mitochondrial biogenesis (Evans et al., 2017). The ketones can be used by muscles and neurons that are highly metabolically active. A function of ketone bodies is the ability to serve as a source of energy during fasting and during prolonged periods of moderate to high-intensity physical activity (Evans et al., 2017). The ability of skeletal muscles to use ketone bodies can aid in the preservation of lean muscle mass (Varady, 2011).

Proposed Effects of IF on Liver glycogen

Depending on the length of IF the liver glycogen will be decreased significantly. It has been estimated that the glycogen in the liver over a 24hr fast could be reduced by ~65% (Magnusson et al., 1992). Most of the understanding of how IF affects liver glycogen is through non-human subjects, mostly mice. However, in humans during food deprivation or several hours of a fast, liver glycogen stores may be depleted and glycogenolysis begins within the hepatocytes. The hepatocytes would synthesize glucose for extrahepatic tissues (Anton et al., 2018). Numerous studies have investigated IF's effects on the liver during a fasted period (Chaix et al., 2014; Hatori et al., 2012). A study by Belkacemi et al. (2012), showed that rats that followed a TRF regimen had improved insulin sensitivity and glucose levels. The control rats and the TRF rats had their calories equated and the researcher's concluded that IF had a beneficial effect on glucose tolerance. Another study by Hatori et al. (2012), showed that TRF prevented the buildup of lipids in the liver seen in mice that had a high-fat diet. The mice in this study also had their calories equated and the researcher’s inferred that a TRF feed mice had favorable biomarkers compared to the controlled mice. In contrast to the positive results these studies had, Park et al. (2017) observed young rats that were given an ad-lib high-fat diet, compared to rats that were fed the same diet for only three hours each day for five weeks. The ad-lib diet rats showed high rates of insulin resistance despite having lower body fat. The transition from the liver using glucose to ketones is mediated by regulating proteins called sirtuins (Liu et al., 2008). A function of sirtuin (SIRT1) suppresses glucose synthesis by preventing CREB-regulated transcription coactivator 2 (CRTC2) mediated gluconeogenesis. This intracellular signaling molecule is upregulated when the body undergoes the switch from glycogenolysis to ketone production. This leads to the degradation of CRTC2 due to deacetylation (Walker et al., 2010). Another function of SIRT1 is the repression of cholesterol synthesis and lipolysis by regulating the activity of cholesterol catabolic pathways (Walker et al., 2010). SIRT1 also regulates the oxidation of fatty acids by the liver (Purushotham et al., 2009; Rodgers et al., 2005). These mechanisms are seen in animal studies, and they may have a similar response in human trials however, future investigations are needed to draw any conclusions.

Proposed Effects of IF on Muscle Glycogen

In humans, approximately 80% of glycogen is stored in skeletal muscles and the rest is stored in the liver (Hawley et al., 1997; Ivy et al., 1988; Jensen et al., 2011). Skeletal muscles store the most glycogen and are the major consumer of energy. In the absence of glycogen, muscles will use ketones during fasting. It has been said that energy surplus combined with physical inactivity can lead to an increase in body mass (Bak et al., 2018). However, there are limited studies that have investigated the effects of IF on human muscle tissue.

IF may result in a radical change in metabolism and cellular physiology. There may also be a reduction in overall adiposity and subsequently insulin resistance due to the decreased caloric intake, as well as metabolic reprogramming. A systematic review conducted by Yuan et al. (2022) that investigated effects of IF diets on glucose and lipid metabolism and insulin resistance in patients with impaired glucose and lipid metabolism concluded, that IF diets may in fact may be effective and be utilized as a therapeutic option for patients with this impairment.

However, other studies have shown IF within itself has little or no effect on muscle glycogen according to Maughan et al. (2010). However, in a study conducted on animals, after 24 hours of IF muscle glycogen was reduced by one-third (Nutter, 1941). The author's opinion is if this outcome could be translated into human subjects this may increase insulin sensitivity to skeletal muscles. A study conducted by Schrauwen et al. (1998) results demonstrated that obese subjects are capable of rapidly adjusting fat oxidation when glycogen stores are lowered. It may be beneficial to combine both IF and exercise to stimulate muscle glycogen use. According to Wu et al. (2006), IF and exercise stimulate mitochondrial biogenesis and mitochondrial stress resistance in skeletal muscles.

Although fasting has been implemented for years its mechanisms are not fully understood. Furthermore, IF is a potential dietary strategy that has yielded positive results but and it may not be suitable for everyone. More studies are needed in this area of nutritional research.

IF and Adherence

Any IF protocol may take a while to get accustomed to and some may feel that going without food for a set period may be difficult. This may lead to a lack of dietary adherence. to. Some of adverse outcomes may be feelings of low energy, increase food cravings, and a hyperphagic response

(Skaznik-Wikiel & Polotsky, 2014). According to Skaznik-Wikiel and Polotsky (2014), people fail because of the lack of self-control to go without food attempting depending on the length of the fasting regimen. All fasts are not created equal and prolonged fasts should be mentioned. An operational definition prolonged fast is an extreme form of caloric restriction which can last from two days and can go upward to the most of extreme and last for months (Wilhelmi de Toledo et al., 2020). A study conducted by Wegman et al. (2015) discovered that some of their study participants were unable to consume the required number of calories on feasting days. There have been some studies that had alternative outcomes of prolonged fasting. Kuo et al. (2013) observed negative outcomes with their participants when participating in a prolonged fasting intervention which led to insulin resistance or even muscle atrophy. The hormone responsible for this adverse effect is glucocorticoids (GCs) and Kuo et al. (2013) further state glucocorticoids relay their signal through the glucocorticoid receptor (GR) which is found intracellularly in skeletal muscle tissue.

Although the studies are conflicting when it pertains to how IF affects skeletal muscle, insulin resistance at the skeletal muscle level. Insulin sensitivity can be achieved with a calorie-reduced diet (Johnson et al., 2016) and exercise (Venkatasamy et al., 2013). Although the mechanisms of IF are favorable in animal studies and it may not have a similar response in human trials, future investigations are needed to draw stronger conclusions.

Genesis of the Ketogenic Diet

Epilepsy was considered a disease of excessive eating in the 19th century. Epileptic seizures were treated in the era of Hippocrates by fasting and it was somewhat effective in this regard. However, fasting regimens could not be maintained for extended periods by some epileptic patients. In 1921, Dr. Russell discovered that a high-fat diet resulting in ketonemia may in fact help patients with seizures (Kim, 2017). The diet is known today as the KD. Interestingly, the KD was known as the ketone-producing diet. In the course of his practice, Dr. Wilder reported three refractory epileptic patients whose symptoms of seizures were dramatically reduced using this intervention (Wilder, 1921) The KD did not gain notoriety until the late 20th century because the new anticonvulsant medication was developed to manage seizures. These new medications over shadowed the KD because people did not have to change their eating preferences, thus reducing the KD's popularity (Roekenes & Martins, 2021).

Presently the KD has developed additional identities including the medium-chain triglyceride diet, the modified Atkins diet, and the low glycemic index treatment. These diets share a common goal of bringing about nutritional ketosis, but each utilizes different ratios of fat, CHO, and protein to accomplish a task. As with any dietary protocol, adherence is key to its success.

It is notable to mention, that the use of antiepileptic drugs is no longer the only option to reduce epileptic seizures, a KD is now being considered a viable therapeutic alternative (Cervenka et al., 2017). The therapeutic potential of KD has extended into dietary weight-loss interventions (Boden et al., 2005), as well as the initial treatment of some cancers (Erickson et al., 2017). The KD has evolved and is still being used for therapeutic use and is becoming mainstream for a weight loss intervention .

Ketogenic Diet (KD)

A KD is a diet that is high in fat and low CHO and within time places the body into a metabolic state of ketosis. As previously mentioned, the process of ketosis happens during times of fasting when the body has depleted most of its stores of glycogen and switches to an alternative source of fuel which is synthesized from fatty acids. This fuel source is derived from fatty acids and they are called ketone bodies, acetoacetate, βeta-hydroxybutyrate (βHB), and acetate (Roekenes & Martins, 2021).

The human bodies preferred fuel source is glucose derived from CHO and low blood sugar will lead to low insulin secretion and low circulating concentrations of plasma insulin (Boden et al., 2005). Plasma concentration is not the only reduction that is taking place but lipogenesis as well. As glycogen stores become depleted there will be an increase in the synthesis of ketone bodies. The ketones are produced in the mitochondria of the liver cells and the synthesis of ketones bodies are derived through a process called ketogenesis. The rate at which the ketones are utilized is called ketolysis (Kim, 2021). A person that continually stays in this state can reach nutritional ketosis which is defined as having a plasma concentration of serum β-hydroxybutyrate levels between ≥ 0.3 mmol and 0.5 mmol (Gibson et al., 2015; Harvey et al., 2019). Through the process of ketosis, the body breaks down fatty acids which are liberated from the adipose tissue, additionally this process also occurs during periods of fasting or adrenergic stress. Adrenergic stress is a process that is mediated by stimulating the adrenergic receptors and the activation of the post-receptor pathways. The breakdown of adipocytes by lipolysis is influenced by three hormones β-adrenergic, catecholamines, and glucagon. These three hormones are stimulated during periods of fasting and it is suppressed post-prandially (Sumithran & Proietto, 2008). This is to illustrate that this alternative fuel source can be transported to the various other tissues of the human body when it is deficient in glucose.

The KD has garnered a lot of attention in the research field as a weight-loss tool but there is not a clear definition of what constitutes a ketogenic diet. The macronutrient profile of a KD roughly constitutes 5% to 10% CHO, 30% to 35% protein, and majority of the macronutrient composition is from fats and it can range from 55% to 60% (Masood et al., 2021a). The initial weight loss from a KD may be up to 10 lbs. in 2 weeks or less according to Masood et al. (2021b). Although that amount of weight loss seems promising it is mostly due to a diuresis through glycogen depletion from the liver and skeletal muscles. To illustrate, the premise of the KD is to enter ketosis by CHO restriction; however, the level of CHO intake required to attain ketosis has been loosely defined in some studies and they have used various macronutrient compositions to reach that metabolic state (Deemer et al., 2020; Di Rosa et al., 2020).

Potential Effects of the Ketogenic Diet on hunger

Adjusting macronutrient components has been shown to effect hormones, hunger modulation, and metabolic pathways (Freire & Alvarez-Leite, 2020). KD and ketosis have been shown to suppress hunger (Paoli et al., 2015). Interestingly, if ketosis is sustained a person may not have an increase in hunger and weight-loss may still be achieved. (Gibson et al., 2015). However, the KD does not negate the fact that a caloric deficit must be sustained to continue weight loss. Hunger control is necessary for weight-loss dietary adherence and research has supported the notion that KD suppresses hunger even though substantial weight loss is achieved. Several research studies support this result (Coutinho, With, et al., 2018; Lyngstad et al., 2019; Martins et al., 2020; Nymo et al., 2017), and according to one study, up to 17% of initial body weight has been reduced during a KD (Nymo et al., 2017).

Ketogenic Diet and Hunger Hormones

The KD may influence the hunger hormone ghrelin. Ghrelin is classified as an orexigenic hormone (Cummings et al., 2002; Doucet et al., 2000; Sumithran et al., 2011) that stimulates appetite (Cowley et al., 2003; Kojima et al., 1999). Ghrelin appears to be blunted when a KD is adopted, and nutritional ketosis is present according to several research studies (Castro et al., 2018; Coutinho, With, et al., 2018; Gibson et al., 2015; Lyngstad et al., 2019; Martins et al., 2020;

Mohorko et al., 2019; Nymo et al., 2017). The KD may have effects on other satiety-related hormones but the mechanism and how it influences these hormones are still in the need of further research. However, the satiety-related hormones that the KD may influence are cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), and peptide YY (Paoli et al., 2015). When the body is deprived of CHO as an energy fuel source the production of insulin is limited and glycogen stores are diminishing, and this process inhibits lipogenesis which prevents the accumulation of fat (Roekenes & Martins, 2021). Unfortunately, to date, there is not a clear understanding of the mechanisms within a KD that regulates hunger.

Adverse Effects of the Ketogenic Diet

The KD is a very restrictive dietary regimen and if done incorrectly, may increase overall chronic disease risk because some may consume excessive amounts of proteins and fats (Bronzato & Durante, 2017). Which can lead to an increased risk of cancer or cardiovascular disease. Additionally following a KD eliminates or extremely reduces entire staple food groups which can be problematic because it limits the ability of obtaining essential vitamins and nutrients. Thus, extremely reducing CHO intake may have negative consequences on bone health, and increases the risks of certain types of cancer, and/or cardiovascular disease (Li & Heber, 2020). Additionally, restricting CHO reduces the amount of dietary fiber which may increase the chance of constipation (Martins et al., 2020; Seimon et al., 2019).

Potential Mechanisms the Ketogenic Diet may Suppress Hunger

Although KD may influence certain gut hormones, the exact mechanisms that suppresses hunger are not fully understood (Deemer et al., 2020). Paoli et al. (2019) have researched the KD and postulated the roles of ketosis and hunger management. The complex interplay that ketosis has on anorexigenic and orexigenic signaling has been investigated. These researchers extrapolated that the ketogenic diet suppresses hunger by influencing the gut microbiota however these assumptions are still under investigation. Paoli et al. (2019) hypothesized that ketosis is the main agitator for hunger suppression expressed in a KD. According to Paoli et al. (2019), this suppression of hunger and the reduction of ghrelin is only evident when the individual remains in a ketotic state (Paoli et al., 2019).

Adaptation to Ketosis

Ketone bodies can increase within approximately 3 days if a person is without food. In this starvation mode, ketone levels can rise and reach to a level of around 8 mmol/L after 5–6 weeks (Robinson & Williamson, 1980). In the absence of glycogen, the skeletal muscle will utilize ketones for a limited time until skeletal muscle will convert to using free fatty acids as its fuel source during this dietary intervention (Owen & Reichard, 1971), but the brain will continue to use ketone bodies and does not switch to alternative fuel source like skeletal muscles (Robinson & Williamson, 1980).

Low Carbohydrates Diets Compared to the Ketogenic Diet

In 1972, the low carbohydrate diet was introduced as a proposed strategy for weight loss (Oh et al., 2019). Although low-carbohydrate dietary interventions involve a reduction in CHO, there is not a clear consensus on what defines a low-carb diet. Low-carb diets and KD are successful in weight loss and a reduction in insulin production (Ebbeling et al., 2018) and this is achieved by being in a caloric deficit. The deficit must be done overtime with any diet to achieve weight loss. The only macronutrient of concern with low-carb dieters is CHO and with other macronutrients generally consumed ad libitum (Oh et al., 2019). A spectrum of low CHO diet could be achieved in a few ways: Very low-carbohydrate can constitutes obtaining less than 10% carbohydrates or

20 to 50 gm/day, low-carbohydrate requires obtaining less than 26% carbohydrates or less than 130 gm/day, a moderate-carbohydrate consist of 26% to 44% of caloric needs. The protocol for KD essentially restricts CHO to 20-50g daily to induce nutritional ketosis, allowing 10% protein, and 80% fat (Oh et al., 2019).

Energy balance and Obesity

Energy balance is achieved when the number of calories consumed is equivalent to the number of calories expended. A proposed mechanism consistent with the laws of thermodynamics of weight gain is when caloric intake exceeds caloric expenditure, which yields a net positive energy balance. A chronic caloric surplus is the main cause of obesity. Conversely, eating fewer calories than the body requires, will lead to weight loss. This is defined as eating with a negative energy balance. It should be noted that energy balance can be achieved in people who are sedentary or active; the caveat is adequate calories must be in supply.

The macronutrients that humans ingest can be stored in the body in several ways. Excess calories are preferentially stored as fat, but other macronutrients can be stored differently. For example, ingested alcohol goes through a number or processes before it is metabolized. The liver is the main organ which metabolizes alcohol and in moderation can be used for energy, or in excesses lead can lead to ectopic fat deposits, and in turn lead to development of alcoholic fatty liver disease (Steiner & Lang, 2017). CHO can be stored in the liver or the muscles in the form of glycogen. Glycogen that is stored the liver can, in most circumstances, be depleted after an overnight fast (Anton et al., 2018). Glucose is the preferred fuel source, and it is used immediately as an energy source; the human body has limited mechanisms to store the excess glucose and it will convert it into fat (Glimcher & Lee, 2009). This stored form of energy can be used later if the body needs it (Hellerstein et al., 1991). If excess fat is consumed it is stored as fat, and this process occurs efficiently and at a low metabolic cost (Hruby & Hu, 2014). When protein is consumed it can converted into a few different fuels sources and they are glucose, ketones, or fat (Gannon & Nuttall, 2010; Hildebrandt et al., 1995). Protein can, along with any other macronutrient, be converted into fat if eaten above caloric needs.

Causal components of energy intake and expenditure in the rise of obesity.

Macronutrients, besides water provides a specific number of calories per gram. Protein provides 4 kcal/g, CHO 4 kcal/g, fat 9 kcal/g, and alcohol 7 kcal/g. The way humans store the foods that are converted into energy is in the form of fat and/or glycogen. But, for Proteins, depending on the length of a fast proteins are oxidized and broken down to produce energy (Wang & Wu, 2022).

When energy intake exceeds energy output an increase in body mass is inevitable in most cases (Goran, 2000). The general belief is that the over consumption of food, combined with a sedentary lifestyle, laid the foundation for the surge in rates of obesity in modern society. The true origin of obesity is complex because it houses an interrelation of other factors that contribute to the development of this disease. Thus, singling out any one factor is extremely difficult. Some factors that can be considered, for example, is the increase in energy intake and energy expenditure are cultural, behavioral, and biological and influencing these factors is reliant on individual variances in genetics, hormones, and possibly cultural. Thus, there are many roots of the obesity epidemic, and it will take research geared specifically to the individual to tailor a custom plan to aide in their weight-loss experience.

Obesity

Obesity can be simplistically defined as an excess body weight using the height-to-weight ratio and the body mass index (BMI) is an assessment that can be used to indicate obesity and the classification of being obese is when the BMI is 30 or more (Wendee, 2012). Although this definition is true obesity has a far more complex etiology linked to a profound increase in adiposity, which has metabolic implications (Gordon-Larsen, 2008).

Obesity affects so many and over a third of population is affected it (Ng et al., 2014; Stevens et al., 2012) and although it is multifactorial disease it is highly preventable (Hruby & Hu, 2014).A drastic climb in obesity has seemed to have stabilized in most developed countries in adults, but in some of these countries, there has been a drastic increase in morbid obesity seen. The operational definition of morbid obesity is having a BMI ≥40 kg/m2 and any form of obesity has a negative outcome on quality of life (Yazdani et al., 2020)

Physical inactivity and its Role on Influencing Obesity

One strategy to reduce obesity to increase energy output by increasing physical activity according to some researchers (Goran et al., 1997; Maffeis et al., 1997). Obesity has been correlated with low levels of physical activity or, no activity (Shook et al., 2015). The factors that increase sedentary behavior can be linked to the increase utilization of technology, for example, an increase in screen time, motorized scooters, and motorized bikes. The sedentary position assumed during screen time, like watching television, or working on a laptop, is usually done in a sitting or reclining position. Thus, the number of calories utilized during these types of activities is minimal. Motorized scooters and bikes reduce the labor necessary to power those devices. These motor-powered devices also have limited the number of calories used because these activities use to be powered by human movement. These interventions have decreased the physical activity of daily living (Haskell, 1996).

Factors that Influence Satiety or Hunger

Hypothalamus

The hypothalamus is part of the central melanocortin system; its function is to regulate food intake as well as to regulate short-term and long-term dietary intake through the production of diverse orexigenic and anorectic neuropeptides (Suzuki et al., 2012). Containing several nuclei which include the arcuate nucleus (ARC), the ARC assists the hypothalamus in regulating feeding and metabolism (Myers & Olson, 2012). Additionally, the ARC combines two mechanisms which are hormonal and nutritional metabolic signaling. These signals emanate from the peripheral circulation, also including the peripheral and central neuronal inputs. These three units generate and coordinate a feedback response. The ARC then receives appetite signaling through feedback with the help of several amino-acid neurotransmitters. The hypothalamus is considered one of the key organs that aids in regulating whole-body energy homeostasis (Suzuki et al., 2012). The functions of the hypothalamus are not limited to the aforementioned regulator processes, but they also have influences on the circadian rhythm, temperature, and sleep (van der Klaauw & Farooqi, 2015).

Peptide Tyrosine (PYY)

This hormone called peptide tyrosine reduces hunger. It was discovered by isolating the porcine upper intestine (Tatemoto & Mutt, 1980). During periods of fasting PYY concentrations are low and after a meal the hormone increases. It peaks between 1-2 hours and stays elevated for several hours. This hormone and its response suggest it plays a role in satiety. It has been reported that PYY regulates energy expenditure by delaying gastric emptying, reduces acid secretion, and inhibits gallbladder contraction, and pancreatic exocrine secretions (Ashby & Bloom, 2007; Sloth et al., 2007). It has been reported that in obese subjects, circulating PYY levels are lower compared to their normal weight counterparts (Alvarez Bartolomé et al., 2002; Batterham et al., 2003).

Pancreatic Polypeptide (PP)

As the name suggests, this hormone is released from the pancreas in response to the ingestion of food This hormone also synthesized of 36 amino acids and belongs to the peptide family (Śliwińska-Mossoń et al., 2017). A hormone that has effects in delaying gastric emptying, lowering pancreatic exocrine secretion, and preventing gallbladder contraction is pancreatic polypeptide (PP) (Kojima et al., 2007). Moreover, this hormone reduces the energy demand, thereby decreasing the amount of food intake (Śliwińska-Mossoń et al., 2017). In rodent studies, this hormone influenced decreasing food intake ("Pancreatic polypeptide reduces appetite and food intake in humans," 2003).

Glucagon-Like Peptide-1 (GLP-1)

Glucagon-like Peptide is a hormone that aids in reducing food intake and suppresses glucagon secretion as well as delayed gastric emptying (Cummings & Overduin, 2007). After a meal there is a rise in circulating GLP-1 which is not elevated during a fasted state. Emergent research had suggested the GLP-1 is increased during anticipation of a meal (Vahl et al., 2010).

Glucagon

Essentially, a hormone helps regulate blood glucose is called glucagon. This hormone is made within the alpha cells of the pancreas. This hormone helps increase blood sugar levels and aids in not allowing blood sugar levels to drop too low. Certain activities stimulate the production of glucagon and they are fasting, exercise, and composition of meals that are very low in CHO (Heppner et al., 2010; Jones et al., 2012). According to Al-Massadi et al. (2019) glucagon suppresses hunger pangs and influences lipid metabolism.

Cholecystokinin (CCK)

Cholecystokinin (CCK) hormone is secreted postprandially enteroendocrine cells in the proximal small intestine called I cells. The region of the human body that secretes this hormone is the small intestine. CCK is elevated postprandially and it takes place within 15 minutes to reach a substantial concentration after ingestion (Liddle et al., 1985). An Additional function of this hormone is to stimulate the release of enzymes from the pancreas and gall bladder. This stimulation promotes intestinal motility and delays gastric emptying. Research conducted on this hormone has suggested that it may work in concert with leptin. This interaction has been presumed to acute short-term inhibition of food ingestion and aid in long-term reduction in body weight (Owyang & Heldsinger, 2011).

Amylin

Amylin is a hormone that is released simultaneously with insulin and the response of this hormone is due to the ingestion of a meal. Amylin functions as an anorectic hormone and evidence indicate it circulates to a greater extent in obese population compared to lean individuals (Reda et al., 2002; Reinehr et al., 2007).

Insulin

Insulin is a hormone that is synthesized by the ß cells of the pancreas and once the food is ingested, it is rapidly mobilized (Polonsky et al., 1988). Another function of insulin is that it acts as an anorectic signal that emanates within the central nervous system CNS (Porte & Woods, 1981). The brain has the greatest amount of insulin receptors, specifically within the hypothalamic nuclei.

Leptin

Leptin is a hormone that is secreted by the adipocytes. The amount of circulating leptin is proportional to the amount of fat mass an individual has (Considine et al., 1996). The peak level of leptin is at night because it follows a diurnal and pulsating pattern (Saad et al., 1998). Leptin also has an anorectic effect which is mediated through the ARC. Leptin has influences on attenuating food intake (Schwartz et al., 2000), and amplifies energy expenditure (Pelleymounter et al., 1995). It has been shown that obese individuals usually have higher levels of leptin compared to normal-weight individuals and this higher level of leptin leads to leptin resistance. Moreover, this can lead to leptin resistance which can diminish the utilization of leptin. Thus, the body will have the inability to transport leptin (Banks, 2001).

Chapter 3

Methods for the systematic review of intermittent energy restriction and the ketogenic diet

This systematic review utilized the PRISMA Checklist 2020 (see Appendix 1). This review is not being published therefore it was not registered with PROSPERO. Neither ethical permission nor budget was required for conducting the review.

Inclusion and exclusion criteria

Study designs included in this review were human clinical trials (randomized controlled trials, nonrandomized trials, cohort studies, and experimental design studies). Only original research studies were included. The participants considered for this review were human male and/or females between 18 and 65 years of age, of any racial make-up, and with a BMI classified as overweight and/or obese. The only singular outcome of interest in this systematic review was the feelings of hunger. Studies were included if they assessed subjective ratings of hunger using VAS questionnaires, which is widely used scale for measuring the experience of hunger, three-factor eating questionnaire (TFEQ), food craving questionnaire, and/or the food craving inventory. Exclusion criteria were adults with fluctuating body weight, who have previously been in a weight reduction program, patients with chronic infections, cancer, or a history of eating disorders, individuals who had bariatric surgery, pregnant women, and those planning a pregnancy or breastfeeding were excluded. Also, any form of religious fasting was not included in this systematic review because the pattern of eating is not replicable to the commonly used forms of IF for dietary purposes.

Evaluation Instruments

VAS usually consist of 100 or 150-mm lines and participants are asked to place a vertical mark across the line corresponding best to their feelings, with the scale ranging from 0 (not at all) to 100/150 (extremely) (Flint et al., 2000) Although the TFEQ incorporates measures of restraint (21 items), disinhibition (16 items), and hunger (14 items), this review focused on the hunger index. Responses are scored 0 or 1 and summed. Higher scores denote higher levels of hunger, respectively (Stunkard & Messick, 1985). The only area of concern for this review is hunger. Additionally, only articles that were in the English or translated into the English language and that were published between 2000 and 2021 were selected for this systematic review. The author justification for the delimiting the years was to attempt to include only recent evidence. The justification for the language was due to the author only reads English.

Search strategy

Lehman College One Search and PUBMED were searched from the inception date of each database to December 2021. MeSH, a medical subject heading, and free text searches using Lehman One Search and Google Scholar were applied. To obtain desired studies, limitations were set to include humans (patients, subjects, participants, etc.) and only English publications were reviewed. The screening was performed to review former systematic reviews to select pertinent key words and headings for each section. Title, abstract, and keyword fields and phrases were utilized. I used Boolean operators (“AND”, “OR” and “NOT”). The following example shows the specific key words (or MeSH terms) used for the search Alternate day fasting* OR alternat* calori* diet* OR alternate day diet* OR alternate day modified fast* OR intermittent fast* OR intermittent energy fast* OR intermittent energy restrict* OR intermittent calori* restrict* OR time restricted feed* OR ketogenic diet* OR high fat diet* AND hunger* OR satiety*

I filtered the studies by human studies, study language, publication year, and type of publication. I also manually checked Google scholar and the reference lists of relevant systematic reviews, literature reviews, and other relevant publications to identify relevant studies that were not covered by the database searches.

Selection of studies

The author imported all records from the searches to EndNote 2.0, a software package used to manage bibliographies and references. Duplicates were removed. All relevant records were promoted to full-text examination against the inclusion and exclusion criteria. The full texts of all relevant studies were obtained, and screened and reasons for exclusion were recorded.

Data extraction and analysis

The titles and abstracts that were used including the search strategies that were implemented were reviewed by the author. The author used the inclusion and exclusion criteria to retrieve and analyze the text of applicable and probable studies. The author included additional articles from other sources. Some studies had data that was presented in figures and authors of some studies were contacted to request data, but no reply was received. The author extracted the following data from each study, summarized in Appendix 2: author, year, sample size, participant characteristics (sex, age, BMI), duration, and design of the intervention.

Many different definitions were used to describe the length of the duration of the interventions in the studies addressed in this review. Durations of interventions were expressed in weeks, and all data provided in other units of time were converted to weeks (1 month = 4.3 weeks; 1 year = 52 weeks).

Results

Study Selection

This systematic review search resulted in fourteen publications that met the inclusion criteria. A total of 20 publications potentially could have been entered into this review, but six were excluded because the publications did not meet the inclusion criteria for body mass or did not use a validated subjective measurement tool (Johnston et al., 2004; Jospe et al., 2020; Martens et al., 2020; Nickols-Richardson et al., 2005; Saenz et al., 2021; Varady et al., 2013). Of the 14 studies included in this review, 4 utilized a KD (Castro et al., 2018; Johnstone et al., 2008; Nymo et al., 2017; Saslow et al., 2014), while the remaining 10 used an IF protocol (Beaulieu et al., 2020; Bhutani et al., 2013; Coutinho, Halset, et al., 2018; Harvie et al., 2013; Hoddy et al., 2016; Kalam et al., 2021; Klempel et al., 2010; Kroeger et al., 2018; Sundfør et al., 2018; Teong et al., 2021). The majority of the studies were not specifically designed to assess physiological and behavioral adaptations to the interventions. This hindered the screening and review process as an explicit reference to comparisons between initial and sustained exposures to the study manipulations were often lacking in the narrative text and data reporting making conclusions regarding adaptation impossible.

Characteristics of studies included Randomized and Non-Randomized and Participants

14 of the publications were outpatient and 1 study was inpatient (Castro et al., 2018). 8 studies were RCT's (Beaulieu et al., 2020; Bhutani et al., 2013; Coutinho, Halset, et al., 2018; Harvie et al., 2013; Kroeger et al., 2018; Saslow et al., 2014; Sundfør et al., 2018; Teong et al., 2021) and 6 studies were non-RCT's (Castro et al., 2018; Hoddy et al., 2016; Johnstone et al., 2008; Kalam et al., 2021; Klempel et al., 2010; Nymo et al., 2017). Sample sizes in the different studies ranged from 16 – 116, for a sum of 723 participants across all studies. When both sexes were included in the studies, most of the participants were women (569). In 3 of the studies, participants were exclusively female (Beaulieu et al., 2020; Harvie et al., 2013; Teong et al., 2021) and in 1 study the participants were exclusively male (Johnstone et al., 2008). The characteristics of ages in the 15 studies were similar and ranged from 30-55. The overall duration of the interventions varied from 8 to 52 weeks, with the most common duration of 8 and 12 weeks. Information relating to the participants in each study is provided in Appendix 2.

Physical Activity

Research has illustrated that exercise training increases fasting hunger and postprandial satiety (King et al., 2009). 6 publications measured Total Daily Energy Expenditure (Beaulieu et al., 2020; Bhutani et al., 2013; Hoddy et al., 2016; Kalam et al., 2021; Klempel et al., 2010; Kroeger et al., 2018). 5 allowed self-report of PA (Castro et al., 2018; Harvie et al., 2013; Nymo et al., 2017; Saslow et al., 2014; Sundfør et al., 2018) 2 did not report PA (Johnstone et al., 2008; Teong et al., 2021) and 1 measured exercise efficiency (Coutinho, Halset, et al., 2018).

Dietary interventions

4 publications were ketogenic-based protocols (Castro et al., 2018; Johnstone et al., 2008; Nymo et al., 2017; Saslow et al., 2014). Castro et al. (2018) was a Cohort study; Johnstone et al. (2008)

compared LC ketogenic diet to a MC ketogenic; Nymo et al. (2017) was a longitudinal intervention study; lastly, Saslow et al. (2014) compared a low carbohydrate KD to a medium carbohydrate, low fat, calorie-restricted, carbohydrate counting diet. Each of these studies used a different KD intervention. Castro et al. (2018), and the dietary protocol set by the researchers followed the 2015 European Food Safety Authority guidelines on the ingestion of CHO (Efsa Panel on Dietetic Products & Allergies, 2015). The dietary intervention consisted of 5 steps, and the first 3 steps consisted of a VLCK diet with the number of calories ranging from 600-800 kcal/day, with the allotted amount of CHO from vegetables in the amount of <50 g daily. The amount consisted of 10 g of fats from olive oil. Protein ranged between 0.8- 1.2g per kg of body weight to ensure adequate protein needs to mitigate the loss of fat-free mass. The researchers provided their patients throughout the ketogenic phase of intervention with vitamins and minerals, such as potassium, sodium, magnesium, calcium, and omega-3 fatty acids. The reason that was given for the supplementation of these vitamins and minerals was they were following the recommendation that was set by the international Tasks for Scientific Cooperation. These steps were maintained until the patients lost the targeted amount of weight-loss. If the participants lost the required amount of weight in the proceeding steps 4-5, the caloric intake was increased to 800- 1500 kcal/day, still maintaining a low-calorie diet. This protocol was not only a KD it was in addition to a low-calorie content. It is the hypothesis of this author that the low-calorie content would not have any positive relation in managing hunger.

Johnstone et al. (2008) ketogenic intervention utilized The Human Nutrition Unit at the Rowett Research Institute which provided all food and drinks consumed during weight-loss and weight maintenance periods for their participants. The very low carbohydrate diet macronutrients consisted of 30% protein, carbohydrate 4%, and 66% of energy from fat.

In the study conducted by Nymo et al. (2017), which was a KD intervention, the protocol's macronutrient composition was 42% CHO, 36% protein, and 18% fat. The calorie allotment was 500/600 calories per day for females and males, respectively. To ascertain if the participants were in fact in nutritional ketosis their urine acetoacetic acid concentration was measured weekly, by using Ketostix reagent strips. If participants were not ketotic in more than one time, participants were removed from the researcher’s analysis.

Saslow et al. (2014) dietary intervention was based on a an LCK (low-calorie) KD, and it was taught to the participants by the primary author of the study. The participants were instructed in this group to reduce their CHO intake between 7-10 days to 20-50 grams of CHO’s a day. There was no limit set on protein but was recommended by the researchers to eat a normal amount. Lastly, the remaining amount of calories left over was to be used for fats.

The 10 publications used various IF interventions and 25% of caloric needs on fasting day and non-fasting day ad libitum were implemented (Beaulieu et al., 2020; Bhutani et al., 2013; Klempel et al., 2010) Beaulieu et al. (2020) compared IF to CR with no control group; Bhutani et al. (2013) was a RCT that Randomized that had a ADF group; an ADF+exercise group; and a control group. The publication by Coutinho, Halset, et al. (2018) which was a cohort study employed 3 non-consecutive days of partial fasting per week allotting 550 and 660 kcal/day for women and men. The research study by Kalam et al. (2021) which was an experimental study with no control group allowed 600 kcal “fast day” alternated with ad libitum on feeding day. 1 publication instituted fasting 24 hours 3 non-consecutive days and feeding day ad libitum. 1 publication allowed 30% caloric needs on 2 consecutive fasting days and allowed ad libitum on feeding days (Harvie et al., 2013). The Harvie et al. (2013) intervention was RCT that compared IF with CR, IF with CR but allowing substantial amount of protein and fat, and CR group. However, this intervention did not have a control group. 1 publication allowed 25% of energy needs on a fast day and 125% of energy needs on the feast day (Kroeger et al., 2018). The research conducted by Kroeger et al. (2018) was a cohort study.

The Methodology for Assessing Hunger

A VAS was used to assess hunger in 10 of the studies (Beaulieu et al., 2020; Bhutani et al., 2013; Coutinho, Halset, et al., 2018; Harvie et al., 2013; Hoddy et al., 2016; Kalam et al., 2021; Klempel et al., 2010; Kroeger et al., 2018; Nymo et al., 2017; Sundfør et al., 2018) 2 of the KD publications in this review used the VAS as their assessment for hunger (Johnstone et al., 2008; Nymo et al., 2017). 2 studies used the Three Factor Eating Questionnaire (Saslow et al., 2014; Teong et al., 2021) and only 1 study used the Food Craving Questionnaire (Castro et al., 2018). 3 publications used test meals/meal challenges to assess subjective hunger ratings (Beaulieu et al., 2020; Coutinho, Halset, et al., 2018; Hoddy et al., 2016).

Results

These studies data reveal how subjective feeling of hunger affected their participants should be viewed with a degree of caution because they had no control group and they are Hoddy et al. (2020); Kalam et al. (2021); Klempel et al. (2010) and Nymo et al. (2017). These studies that showed a transient increase at the beginning of the intervention was Klempel et al. (2010) and Nymo et al. (2017). In Klempel et al. (2010) subjective feeling of hunger was increased in the first week and then it decreased by the second week and remain low. Similarly, in the Nymo et al. (2017) study, hunger scores were elevated but it was during third day and the thirteenth week of the intervention. This assessment was also taken in the fasted state. A potential hypothesis of increased hunger at the third day of the intervention could be that the KD was a novel way of eating for all the participants. This intervention did not address postprandial subjective feeling of hunger. It's the author's opinion that this is a potential bias that was very evident in this study was opposing a KD intervention.

It also should be noted that the only study that had a hyperphagic response was by Klempel et al. (2010). The participants were instructed to consume 25% of their caloric needs on fast days and to eat ad-libitum non-fasting days. The researcher's observed that their participants had hyperphagic response on the non-fasting days in response to the lack of food on their fasting day. This response is a potential pitfall for non-adherence to this type of intervention.

Most of the studies only assessed subjective feeling of hunger at one time point**.** It would be better if there were multiple time points to assess hunger because most people have a desire to eat multiple times a day it would increase data reliability. These studies Johnstone et al. (2008); Kroeger et al. (2018)used a VAS to measures subjective feeling of hunger and it was done postprandially 5 minutes before participants went to bed. This form of instruction resembles self-reporting dietary intake as it has been documented within the literature is not the most reliable form of data. How is the researcher's supposed to know in fact that the participants are filling out before going to bed and not days later? Two studies Kalam et al. (2021) and Nymo et al. (2017) also used VAS to assess subjective feeling of hunger but they also implemented a standardized meal. They measured the participants responses at 30 min intervals until they reached 150 mins. These measurements were done systematically which leaves little room for error. Conversely, in the Kroeger et al. (2018) study allowing the participants to be responsible to measure their subjective feeling of hunger without researcher's supervision may under report their experiences or fail to report in a timely manner.

A study that did not address when they had their participants fill out their questionnaire regarding hunger was Saslow et al. (2014). The investigators in this study did not state when the questionnaire was taken, where the questionnaire was given, and how many times was the questionnaire filled out during the intervention. These are crucial questions that needed to be addressed which leaves some doubt within the interpretation of results.

Discussion

This systematic review aimed to compare two different weight-loss interventions which are IF and KD for the efficacy of hunger management. The authors findings when looking at each study independently between IF and KD had varied responses on mitigating hunger in obese adults. The primary goal of this review was to compare IF and KD and if any of these dietary interventions for in obese adults can mitigate hunger. Searching through the literature there were no studies conducted that compared IF and KD directly. What was done was analyzing studies that implemented either an IF and/or KD diet within the given population which assessed for subjective responses to hunger.

To the best of the author's knowledge, this is the first systematic review to s compare IF and the KD on the effects of controlling hunger in obese /overweight adults. Most studies that had investigated different outcomes of IF and the KD have not compared the two interventions and only assessed hunger as the outcome.

Hunger

Bhutani et al. (2013) observation in their 12-week study was a decrease in hunger pre and post treatment within the ADF no exercise group but not in the ADF+exercise group. Interesting to note, during their assessment for subjective feelings of hunger was lower in the ADF group but towards the end of the intervention subjective feeling of hunger were identical in both groups. Unfortunately, in this study there was not a control group to infer the difference in subjective feelings of hunger because the comparison was done between two groups utilizing an ADF protocol thus getting a fuller understanding in the variations in subjective feelings of hunger cannot be elucidated. Nonetheless there are a few speculations regarding why the difference in hunger in the ADF+exercise group compared to ADF. The ADF combined with exercise may had an influence in subjective feelings of hunger because exercise increases energy expenditure which may had increase the participants desire to eat. There is research supporting exercise increases the desire to eat and/or suppresses the desire (Douglas et al., 2017). If this study was to be replicated, it would be interesting if the researchers would have detailed what was the hunger levels of the participants before they began their intervention. Questions such as "are you always hungry" would have been interesting to know. If the participants are always hungry and the during the intervention it did not change, then the intervention could be viewed as unsuccessful**.** In the study by Klempel et al. (2010) showed hunger scores were elevated during the first week in the ADMF group but there was no control group to compare these results. Also, the researchers allowed the participants to self-select their feeding window while during this time energy restriction was lowered which could have affected their feeling of hunger. The author's assumption on the increase in hunger may be due to the adaption process to the dietary intervention. Continuing the experiment, hunger decreased and remained low throughout the rest of the investigation. Although these three studies reported decreases in hunger (Beaulieu et al., 2020; Coutinho, Halset, et al., 2018; Hoddy et al., 2016), Kalam et al. (2021) intervention was an ADF combined with a low-carbohydrate diet which observed no change in subjective feelings of hunger in their participants. Interestingly, Harvie et al. (2013) observed the IECR (intermittent fasting with carbohydrate restriction) group had an increase in hunger and a desire to eat during the one-month assessment compared to the IECR+PF however after the month assessment both groups had experienced a reduction in subjective feeling of hunger and desire to eat but at the end of the intervention hunger scores did not differ between the three group. In the comparative study conducted by Kroeger et al. (2018) revealed that hunger decreased in the ADF high-weight-loss group but remained unchanged ADF low-weight-loss group. A study conducted by Sundfør et al. (2018) found there was increase in subjective feelings of hunger in IF group compared to the CR. Conversely, the study conducted by Teong et al. (2021) observed that both CR and IF decreased the susceptibility to hunger. A potential hypothesis why the study conducted by Sundfør et al. (2018) saw an increase in the perception of hunger was their IF intervention was a low calorie diet on two days during the week. This essentially would lower dietary adherence because of the sparseness of the fast coupled with an extreme caloric reduction. The CR group was able to consume a good amount of calories each day while achieving a caloric deficit. This intervention would be preferable to achieve dietary adherence. To restate, not all IF interventions are the same and individual experiences may differ. The subjective hunger assessment used by 2 of the KD protocols were VAS Johnstone et al. (2008) and Nymo et al. (2017) Nymo et al. (2017) LCKD intervention observed that the subjective feeling of hunger increased immediately following the initiation of the weight loss phase and then again at the cessation of the weight loss phase. There are two potential explanations for the increase of hunger at the beginning of the weight-loss phase and at the end of the weight-loss phase. One it could be the adaptation process of the intervention or two the intervention had the additional component being low in calories as well, so it is difficult to extrapolate what aspect of the intervention affected hunger within the participants. Comparing the results of LCKD Nymo et al. (2017) LCKD to the Johnstone et al. (2008) study it was observed that subjective feelings of hunger was reduced in the low carbohydrate (LC) ad libitum KD compared to the medium carbohydrate (MC) ad libitum non-KD. A potential explanation why participants LCKD felt significantly less hunger is due the satiation properties of protein, which this intervention had 2 high days of increase protein intake. The LC groups consumed less calories compared to the MC group. Again, this observation is indicative that the KD can mitigate hunger. One study that assessed hunger with a different measure tool was Castro et al. (2018). The method that was used was food craving inventory, and these types of observation methods did see decreases in hunger. Although this study observed decrease in hunger there was no control group to assess any correlation. However, the investigators in this study did observe a negative correlation between ketones and subjective rating of hunger. The investigators in this study also notice that testing the levels of ghrelin that there were no changes. In this study, it is difficult to infer what lowered the subjective feeling of hunger. A study result that was contradictory to Johnstone et al. (2008) intervention was Saslow et al. (2014). In this study the assessment tools that was used to measure subjective feeling of hunger was The Three Factor Eating questionnaire. The results were that there was no difference in hunger between the LCKD group compared to the MCCR group. Interesting to note, the LCKD was consuming more calories than the MCCR, and more calories does not equate to less hungry, in the case of this experiment. A potential reason that hunger did not decrease in the LCKD was the composition of the extra calories could have been in the form of oils. According Stull et al. (2008) liquids increased subjective feelings of hunger compared to solids. Except, in this study conducted by Saslow et al. (2014) the composition of the extra calories was not investigated, and an inference cannot be given. If the calories were in the form of liquids, then potentially hunger could have remained unchanged. Conversely, if the extra calories were from foods that need to be chewed, it may have lowered the perception of hunger. According to Stull et al. (2008) liquid and solid foods elicit differential responses to subjective feeling of hunger. They have stated liquids have been reported to elicit stronger feelings of hunger when compared to eating solids. This notion should be taken with a degree of caution because subjective feeling of hunger could be reduced with liquid meals if the content within the beverage has sufficient amount of fiber (Stull et al., 2008).

Macronutrients

It has been stated gut appetite hormone may have some influenced by macronutrient composition and if manipulated optimally may impact the desire to eat and energy intake which may be a factor in reducing the obesity epidemic. The studies in this review addressed to investigate if the macronutrient composition had any effect on managing subjective feeling of hunger. Although most of the IF protocols followed a similar macronutrient profile, the results in managing hunger varied. Five studies had no change in the subjective feeling of hunger. Two of the IF studies Coutinho, Halset, et al. (2018) and Harvie et al. (2013)) showed no change in subjective feelings of hunger and the macronutrient composition from these separate studies were identical. The macronutrient composition in Nymo et al. (2017)was 30–35% fat, ∼20% protein, and 45–50% CHO and within the Harvie et al. (2013) protocol was 25% protein 45% low glycemic CHO 30% fat**.** The assumption proposed by the author of this manuscript is that in the Coutinho, Halset, et al. (2018) and Harvie et al. (2013) intervention the participants were following a 5:2 IF intervention which may not be viable to adapt to the IF protocol and this could be the reason that there was no change in the subjective feeling of hunger**.**

The remaining two studies that had no change in hunger were also IF protocols but followed an ADF regime and they were Teong et al. (2021) and Kalam et al. (2021). In Bhutani et al. (2013), macronutrient composition was 30% kcal from fat, 15% kcal from protein, and 65% CHO. Their preliminary results revealed no change in hunger in the comparison groups but a decrease in hunger in the ADF group only. Potentially, the results in the reduction of hunger in the ADF group could be due to the participants only engaging in activities of daily living and not extracurricular activities such as exercise, which the intensity of the exercise may increase subjective feelings of hunger. The macronutrient allotment could have been sufficient in the ADF group so, that there was no increase feeling of hunger.

Kalam et al. (2021) was an IF intervention and their macronutrient composition was 30% CHO, 35% protein, and 35% fat. Surprisingly, with 35% of this diet intervention is from protein and protein has been claimed to be satiating but, there wasn't a significant decrease in hunger or satiety in this study. A potential reason for the no change in hunger could have been the length of the IF. This intervention had participants consume three meal replacements which was 200 calories each during the weight-loss period. During the non-fasting days, participants were allowed to consume five meal replacements which totaled 1000 calories. It is the opinion of this author that the diet phase was a very low-calorie non-palatable diet, which would not foster adherence and sustainability in most people. Dietary restriction for the sake of weight-loss within itself is difficult to maintain. Most people correlate dietary foods as bland and boring and, in this intervention, substituting food with a shake can easily lead to poor adherence if this protocol is adopted mainstream. During their maintenance phase, the participants consumed three meal replacements and were allowed to eat ad libitum low carbohydrate/high protein foods after consuming all their meal replacement shakes. This protocol design did not consider the needs of the participants and this weight-loss strategy, although temporary, would not be successful, and therefore their subjective feeling of hunger remained the same. It seems that the participants did not and could not adapt to this intervention because of the higher levels of hunger and dropouts.

The only KD study that elicited a transient increase of hunger in the beginning and then a decrease towards the third week was the Nymo et al. (2017) intervention**.** The macronutrient profile was CHO 42%, protein 36%, and fat 18%. The researchers also required that the participants also obtained 4% of dietary fiber. This study also was not a conventional KD it obtained ketosis by very low-caloric consumption. Regarding Nymo et al. (2017) findings, the author's assumption of the study is that the temporary increase in hunger was due to the adaption process.

Klempel et al. (2010) was an IF intervention which had two different set of macronutrient compositions profiles. Profile #1 which was: non-fasting days Protein 18 ± 1%, CHO, 47± 3%, Fat 36 ± 6%. While on the days of fasting which was profile #2 their macronutrients were Protein 23% ± 1 CHO 52 %± 0, and Fat 25 %± 1. Protein in the fasting days could have been by design to help increase satiety. In this dietary intervention, the researchers did observe and mention that the increase and then the decrease in hunger was potentially due to participants adapting to the intervention, and the author of this manuscript agrees with their assumption.

Seven publications in this review reported that hunger decreased six (IF) and three (KD). The IF publications had similar macronutrient compositions with slight variations. Teong et al. (2021) had a maintenance macronutrient composition of 50% carbohydrate, 15% protein, 35% fat, Hoddy et al. (2016) had protein 16%, CHO 48%, and fats 36, Kroeger et al. (2018) 30% of energy as fat, 55% as CHO and 15% as protein, Coutinho, Halset, et al. (2018)20% protein, 30% fat, and 50% CHO, and 55% kcal from carbohydrate and Beaulieu et al. (2020) 50–55% carbohydrate, 30–35% fat, and 15–20% protein. The IF macronutrient profile was simple to obtain while the KD intervention had variations in their protocol requirements.

These were the results of the macronutrient composition of the KD. Johnstone et al. (2008) macronutrient composition for the LC ketogenic diet contained protein 30%, CHO 4%, and Fat 66%, and the MC non-ketogenic diet contained protein 30%, CHO 35%, and Fat 35% mandatory maintenance diet 13%, 30%, and 57% of energy as protein, fat, and CHO, respectively. An interesting observation from this study's macronutrient composition was in the percentage of protein they allowed. It has been stated that protein increases satiety and therefore this could be a potential reason for the reduction of subjective feelings of hunger. The maintenance diet that Johnstone et al. implemented lowered the protein and increased the CHO which I assumed would change the subjective feeling of hunger but throughout the study, the feeling of hunger was decreased. A point of concern with KD interventions is the ability to sustain the protocol.

Saslow et al. (2014) the macronutrient composition of the weight-loss intervention was not stated but each group had to follow a set of dietary instructions. The LCK portion of the intervention was encouraged to reduce carbohydrate intake over 7–10 days to between 20–50 grams of carbohydrates a day, and the researchers reinforced that the reduction in CHO should not come from fiber. Additionally, participants were encouraged to eat a normal amount of protein so muscle mass could be maintained. The comparison group was instructed to consume 45% to 50% of their calories from CHO and keep protein and fats the same before they started the intervention. This intervention was roughly 13 weeks in duration and both groups were able to achieve a decrease in subjective feelings of hunger. Although there was a difference in macronutrient composition between groups, there was no difference is subjective feelings of hunger.

Castro et al. (2018) research study there was no prescribed macronutrient profile; however, the participants in this study had different phases. In phase 1, the participants were to consume 5 times a high protein preparation containing 15 g protein, 4 g carbohydrates, 3 g fat, and 50 mg docohexaenoic acid. Each serving of this concoction provided 90-100 calories. In the following phase, participants started a low-calorie diet which ranges from 800–1500 cal/day. In the last phase of the intervention, the participants consumed between 1500 and 2000 cal/day, and this was done so that the participants could maintain their weight loss. Unfortunately, in this study, a complete macronutrient breakdown was not accessible. Nonetheless, a variety of macronutrient combinations can be utilized to promote satiety. However, it is the author's opinion that measures to obtain a caloric deficit to achieve weight loss may not be necessary for all adult obese populations. Nonetheless, this dietary strategy is a valid option. A reduction in hunger was obtained in this study.

Teong et al. (2021) macronutrients 50% carbohydrate, 15% protein, and 35% fat on fasting IF participants consumed their prescribed breakfast at 8 AM (~30% of energy requirements). The researchers did not have a macronutrient breakdown for this amount of energy requirements. In this study, the participants fasted for 3 nonconsecutive days on 30% of their caloric needs and had a decreased sensation of hunger. However, this study's comparison group was CR, and the researchers found no difference in subjective feelings of hunger between groups. Were both groups considerably hungry before the start of the intervention and there was no difference during and after the intervention? The statement no difference in subjective feelings of hunger by the researchers needed further clarification**.** This study revealed no difference and no increase in subjective feeling of hunger which is encouraging for both IF and CR for this intervention.

The summary of the findings is macronutrient composition in most of the IF studies was similar and was centered around whole foods Could it be that the participants deviated from their normal diet and adopted the intervention which promoted a healthier and regimented system that influenced their behavior and, in most cases, did not increase their subjective feeling of hunger? Interestingly, none of the studies had their participants increase their protein intake. Protein has be touted to increase satiety and reduce feelings of hunger (Leidy et al., 2010). Was the amount of protein in this intervention enough to increase satiety? These are just a few questions that should be considered in future research studies in the subject matter of hunger management. (MUST REDO TO REFLECT PowerPoint PRESENTATION).

Food distribution/Self-report

Providing all the meals to participants in a researcher study can challenging depending on the length and duration of the intervention. Various issues can arise such as the cost of the items and the delivery system utilized to name a few. Being able to supply the food may enhance adherence and sustainability if the foods that are being eaten for weight-loss purposes are palatable and filling. Amongst the fourteen publications, only seven either fully or partially distributed food to their participants. (Bhutani et al. (2013), Beaulieu et al. (2020); Hoddy et al. (2016); Kalam et al. (2021); Klempel et al. (2010) Kroeger et al. (2018); Teong et al. (2021); and Johnstone et al. (2008)).

Self-reports were another assessment tool used for accountability from thirteen of the fourteen publications. The one publication that did not use a self-reporting system was a KD intervention conducted by Castro et al. (2018). The potential reason why Castro et al. (2018) participants used a self-reporting system since they were participants and had no additional access to foods. Self-reporting has come under scrutiny because of its lack of accuracy but can be useful as a supplemental assessment tool (Blundell et al., 2012). It is this author's opinion, that when assessing subjective feelings of hunger, the self-report should reflect the intensity of a specific feeling state or aspect of eating motivation. This in turn would give the investigators clear and concise information on what may affect someone's desire to overconsume. The added benefits of self-reporting done in this way can reliably differentiate between stimuli in an unbiased fashion that can gain access to relevant feeling states and motivations in some populations when used within an appropriate study design that can elicit favorable analysis.

In sum, all diets are not created equal and understanding the limitation of the dietary intervention is crucial for adherence and sustainability. Two of the studies implemented a very low-calorie diet in which most of their nutrients were from a supplemental shake or protein concoction. There are two questions that the author believes should be addressed in future research: “Are any of the foods that were given to these participants something that they could continually consume for healthier lifestyle, or the goal only weight loss?” “How closely did these foods that were provided to the participants match they consume regularly?” These questions in future research studies.

Behavioral Interventions

Most studies may have had better retention of their dietary interventions if they had behavioral counseling within their design to help participants overcome their weight-loss difficulties. This thought has been expressed by public health agencies regarding this sentiment (Lemstra et al., 2016). Three of the publications that did not receive any behavioral interventions were Beaulieu et al. (2020); Johnstone et al. (2008); and Nymo et al. (2017). Although the rest of the publications did have some form of behavioral modification, they had a degree of variation.

In the study conducted by Bhutani et al. (2013), behavioral assistance was only given to the ADF group in their study. They were only instructed on how to measure energy intake by reading food labels, reducing portion sizes, and choosing low-fat protein and dairy options. A survey conducted by Goyal and Deshmukh (2018) stated that 52.5% consumers do not read the ingredients’ or understand what they are reading. It is hopeful and it is the author’s opinion that reading labels to enhance meeting macronutrient needs is an important tool to learn and may foster dietary adherence. In Castro et al. (2018) intervention, the participants received dietary instructions, individual supportive counsel, and encouragement to exercise regularly using a formal exercise program in all visits. This form of support should be given by all participants to all clients to help build a healthy lifestyle, however, the access to support is not available to all in some populations. Coutinho, Halset, et al. (2018); Hoddy et al. (2016); and Kalam et al. (2021); Klempel et al. (2010) and Teng et al. (2011) participants received weekly dietary counseling to monitor their weight loss which is the minimal support given in this review but Coutinho, Halset, et al. (2018); Klempel et al. (2010); and Teng et al. (2011) gave their participants additional behavior modifications to receive dietary counseling from a trained dietitian which may enhance dietary adherence.

Kroeger et al. (2018) was the only publication that did not give their participants any kind of behavioral intervention, but the completers received three months of free weight-loss counseling and a twelve-month gym membership at the end of the study. Sundfør et al. (2018) and Saslow et al. (2014) received similar behavioral interventions with slight differences. Saslow et al. (2014) participants received one hour which was focused on learning skills to support behavior change and diet maintenance. While Sundfør et al. (2018) participants also received behavioral methods to improve compliance they were also supported in ways to improve weight loss maintenance. Additionally, they learned how to plan meals and activity schedules, which aids in improving problem-solving skills to mediate barriers and reduce the stimulus that may control overeating and create a positive atmosphere for healthy eating, homework, and exercise. Also, it gives the participants the skills how to know the difference between hunger and cravings. Lastly, the participants received the support of individualized consultations sessions which ranged from 30 and 60 mins at each follow-up.

Nymo et al. (2017) participants only went over their food logs with a trained dietician for 20 minutes with a dietitian every week. This is also another study that the support system is substandard. However, the investigator did not elaborate if the trained dietician gave additional support. The assumption is given from what was presented in the publication.

In summary, behavioral counseling is a viable tool to assist obese adults who are having difficulty with a weight-loss intervention. These tools give them the added support to meet their goals. It could benefit any dietary strategy and promote better adherence.

Withdrawal and dropouts from the studies

All studies that are being addressed in this review had participants withdrawing from their studies. The focus in this review is to only address participants that withdrew from their respective studies because of nonadherence to the protocol because of dissatisfaction or non-compliance. Therefore, the studies that meet these requirements are Beaulieu et al. (2020); Coutinho, Halset, et al. (2018); Harvie et al. (2013); Hoddy et al. (2016); Kalam et al. (2021); Klempel et al. (2010); Kroeger et al. (2018) and Nymo et al. (2017).

Harvie et al. (2013) was a comparison intervention and had dropouts; two from the IF group and three were from the CR group. Both groups had problems adhering to the diet. In the CR group, their food choices were not scrutinized as much as the IF groups. It would be of interest to investigate and ask the CR group a question about what would have made their weight-loss group more favorable.

Nymo et al. (2017) was the only KD intervention in this study where participants withdrew because of dissatisfaction with the intervention. The intervention attrition was one male, and he that he did not like the diet. Very low-calorie diets can be a useful tool, but some may not tolerate it well, and healthcare practitioners should prepare their clients for the potentiality of this occurrence.

Dietary interventions that had a comparison group had dropouts in both groups as seen in Harvie et al. (2013) and Kroeger et al. (2018). Although, more participants dropped out of the IF intervention than the CR. Coutinho, Halset, et al. (2018) had the same issue, where one participant from his IF group and one from the CR group withdrew because they both did not like the diet. A follow-up question would have what could the researchers have done to improve their experience.

In Hoddy et al. (2016) the participants disliked the food that was provided to them. Presumably, if the foods were more palatable, that the participants potentially would have completed the research study.

These three studies (Kalam et al.; Klempel et al.; Kroeger et al.) had the same reactions from their participants of just not liking the intervention. Six withdrew from Kalam et al. (2021), two dropped out from Klempel et al. (2010), and no detailed amount was illustrated in the Kroeger et al. (2018) study but it was stated most withdrew because of dissatisfaction with the intervention.

In sum, not all dietary interventions are for all people, health care practitioners that are helping their clients to lose weight should take the needs of the individual and incorporate it into the diet plan. Therefore, no matter what dietary intervention may be utilized, dietary adherence may be an issue. It is the author’s opinion that a trial-and-error period should be implemented to get understanding about what dietary protocols are best for the subjects.

Strengths and Limitations from this Review

PRISMA guidelines and their methodology can be considered a strength in this review. The guidelines were instrumental in conducting the search strategy, study selection, and the extraction of data. Strengthen conducting this systematic review is that many of the studies used the VAS subjective assessment of hunger. The VAS is a measurement that is used widely used in nutritional research (Tinsley et al., 2018).

Limitations of this review are: Not all the studies in this review were RCT's. Another limitation is not addressing the hormonal responses to hunger, although the premise of this review was to only assess subjective assessment of hunger. The meaning of hunger did not exactly take on the same definition in all the studies. In fact, none of the studies gave an operational definition of hunger. A clear and consistent definition of this word is necessary for congruency in studies. Most studies only assessed hunger only at a one-time point on fast days No studies directly compared KD to IF, although in this review sufficient publications are comparing IF to CR in the obese and overweight population. Only assessing articles that were relevant to the research question were between the years 2001 -2021 and this was a limitation to this review because there could have been articles in the previous years that could have been useful data for this systematic review. Most of the subjects in the studies for this review were female, thus the generalizability may not be applicable to the generalizability of a complete population. However, this is not novel, because most participants that engage in weight-loss interventions are predominantly women (Teng et al., 2011). Another limitation was that the studies implement the subjective assessment of at different time intervals. Studies had participants fill out their VAS before going to bed, while others had the assessments done after breakfast. There needs to be cohesiveness between the studies to draw practical conclusions. Individual experiences with hunger are not easily quantifiable and measurements that are used to obtain a quantitative measure validly and reliably are not easily accomplished because the use of questionnaires to obtain responses are completed before and after consumption of the substance tested, and then again at regular time intervals (e.g., every 30 min) or a couple of hours or until the next meal, and an example of which is the (Blundell et al., 2010). According to Livingstone et al. (2000), subjects that are responding to the questionnaire do not fully understand the usage and may not answer appropriately. Many of the studies that were not considered in this review used different subjective parameters to assess hunger and did not use the gold standard of assessment which is the VAS. It would be necessary to conduct another review that encompasses all subjective hunger assessments to obtain better understanding if IF or KD has any beneficial effects on managing hunger. The generalizability for in this review for younger adults is limited, the average age was 35-45. Further research in the younger adult population is needed. Furthermore, this review did not directly assess the quality of all primary studies but relied on the assessment reported by the study authors. Moreover, we did not include meta-analyses.

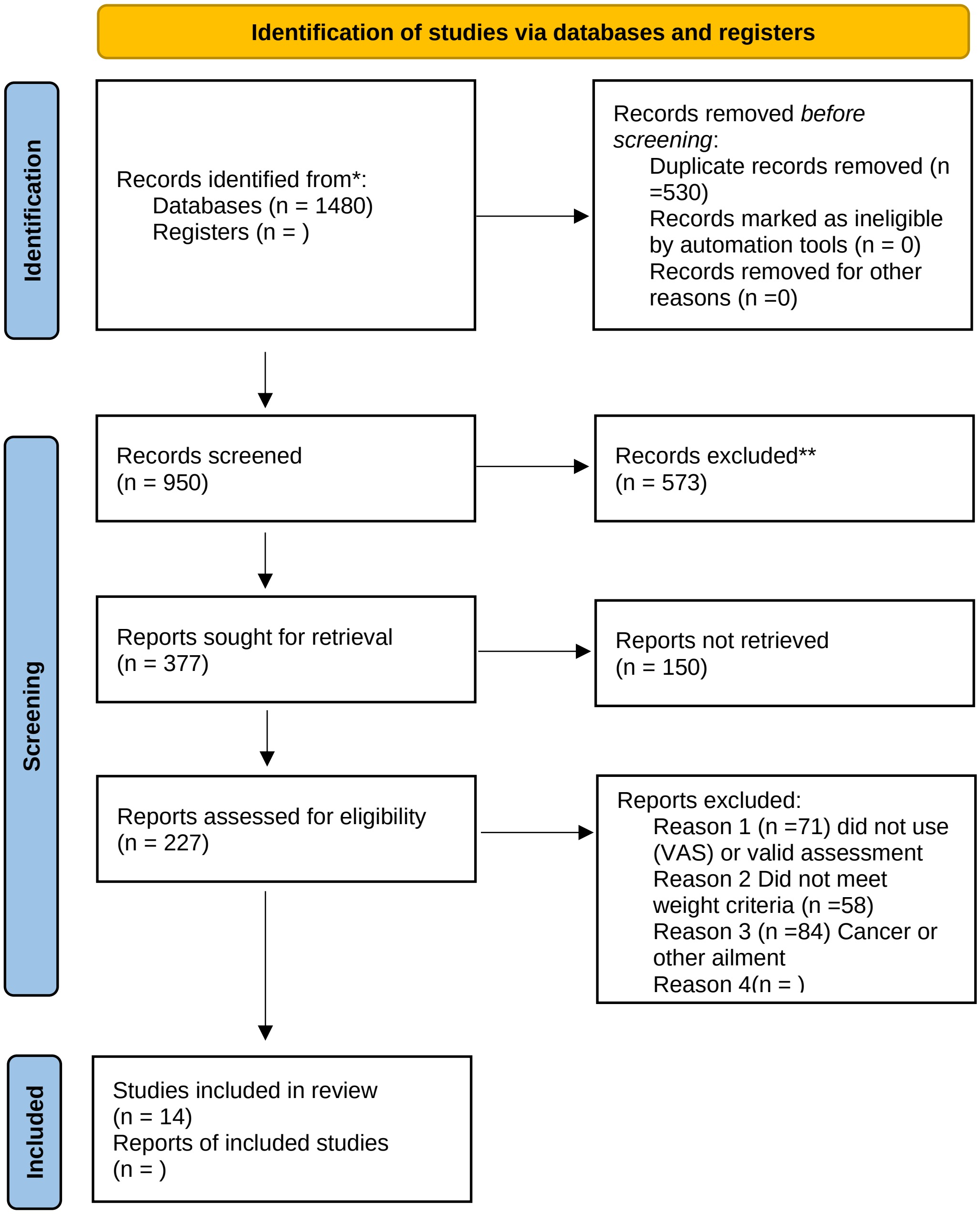
Moreover, this author believes that all relevant publications to the authors knowledge were found and identified; although broad search terms were used, among different research databases. Second, there are several factors may have introduced bias in our findings. A glaring bias is the inclusion of only publications written in English. The third limitation of the literature is that some of the studies were conducted in countries outside of the United States. This is important because other populations may differ with respect to weight reduction and the acceptability of food items from dietary guidelines.

Conclusion

IF or the KD was not superior over the other in managing hunger. The results regarding subjective feeling of hunger in the studies assessed in ranged from no difference, decreased, increased, or remained the same. The basic food substrates that have a positive impact on managing hunger is protein and fiber. Sleep quality and even getting enough micronutrients as well has had positive influences on managing hunger as well. Although most of the research have been done of the effect of protein and satiety and its effects on managing hunger. It seems when the participants had to hit a targeted macronutrient goal, or follow a dietary program, in most cases, hunger was managed. Whether the intervention IF, KD, CR , the foundation of the intervention should be adherence.

More systematic and high-quality clinical studies are necessary to compare the effects of IF and KD and managing hunger. So, when it pertains to a dietary intervention, no one example is good for everyone; it depends on the right intervention, for the right individual, at the right time. Whether the dietary intervention is IF or KD these two different protocols do not seem to have any positive or negative impact on hunger.

Appendix 1
PRISMA Flow Chart



For more information, visit: http://www.prisma-statement.org/

Appendix 2
Characteristics and results of included studies

Study	Population	Sample size	Intervention	Duration	Assessment	Outcome
Beaulieu et al. (2020)	Obese/Overweight Women mean BMI 29.1 ± 2.5 Mean age CR 34 ± 9 Mean age IF 35 ± 11	n-46	Random assignment to IF or CR. IF, on fast days, volunteers consumed 25% of their daily energy requirements from total diet replacement products provided by the researchers CR volunteers consumed 75% of their daily energy requirements each day from commercially available products provided by the researchers	12 weeks	Visual analogue Scale	IF intervention and the continuous restriction diet both can have positive impact on dietary restraint, craving control, and lessen susceptibility to hunger and binge eating.
Bhutani et al. (2013)	Obese adults mean BMI Combination 35 ± 1, ADF 35 ± 1, Exercise 35 ± 1, Control 35 ± 1 Combination 45 ± 5, ADF 42 ± 2, Exercise 42 ± 2, Control 49 ± 2	n-64	Randomized, controlled, parallel arm feeding trial 1) combination group; 2) ADF group; 3) exercise group; 4) control group.	12-week	Visual analog scale and TFEQ	Hunger decreased while satisfaction and fullness increased in the ADF group only. Restrained eating increased ($P < 0.05$) and uncontrolled eating decreased ($P < 0.05$) in the combination and ADF groups. No change in hunger, satisfaction or fullness was observed in the combination group post-treatment.
Castro et al. (2018)	Obese Patients Mean BMI 35.5 ± 4.4 Mean age 47.2 ± 10.2	n-20 8M/12F	Very low ketogenic diet Cohort study	17.39 weeks	Food cravings questionnaires	VLCK a decrease in food and alcohol cravings, increases in physical activity, reduction of sleep abnormalities, and improvement in sexual functioning
Coutinho, Halset, et al. (2018)	Obese adults Mean BMI: IF 36 ± 4 kg/m2 CR 35.1 ± 4.2 Mean Age IER 39.4 ± 11.0, CR 39.1 ± 9.0	n-35 18 IF and 17 CR. Completed the protocol W-22 M-6	IF fasted for 3 non-consecutive days of partial fasting per week compared to CR	12 weeks	Visual analogue scale	No statistically significant differences between groups assessing hunger. Two dropped out due to hard to adhere to the diet protocol (one from each group).
Harvie et al. (2013)	Obese Adult women mean BMI IECR 29.6, IER+PF 31.0, DER 32.2 31.1± 5.3 IECR mean age 45.6, IECR+PF mean age 48.6, DER mean age 47.9	n-115	Random assignment to either one of three groups IECR, IECR+PF, or DER	17.39 weeks	Visual analogue scale	Overall, no differences in their hunger satiety ratings among groups. The DER group seemed marginally less healthy compared to the other groups at one month hunger and desire to eat were marginally greater after the first restricted day of IECR compared to IECR+PF.

Hoddy et al. (2016)	Obese Adults mean BMI 34 ± 1 mean age 46 ± 1	n-59 50/F 9/M	Experimental design to examine the effect of ADF on postprandial hunger ratings and gut peptides.	8 weeks	Visual analogue scale	There was a decrease in subjective feeling of hunger during the study. There was no increase in subjective hunger by the end of the study. There were no differences between males and females for subjective hunger ratings
Johnstone et al. (2008)	Obese men Mean BMI 35.1± 3.8 Mean age 38± 10	n-17	Randomized to a within-subject, cross- over design to a 4-wk period—then to a LC (4% carbohydrate) ketogenic diet and then to MC ketogenic diet (35% carbohydrate).	8 weeks	Three-Factor Eating Inventory	The researchers did seem to see differences in hunger, but only approached significance for prospective feeding and desire to eat.
Kalam et al. (2021)	Obese Adults mean BMI 31.4 ± 2.8 mean age 48 ±2	n-52, W-44, M-8	No control groups. Examining the effects of 6-months of ADF combined with a low carbohydrate diet on fasting and postprandial hunger ratings.	26 weeks	Visual analogue Scale	Six participants dropped out of the study due to disliking the dietary protocol. In response to a test meal hunger remained unchanged from baseline (month 0) to month 3 (weight loss period) and from month 3 to month 6 (weight maintenance period).
Klempel et al. (2010)	Obese adults Mean BMI 34 ± 1 kg/m Mean age 46 ± 3	n-16 12/F 4/M	Single cohort study consisting of three consecutive dietary intervention phases: (1) 2-week pre-loss control phase, (2) 4-week weight loss/ADMF controlled feeding phase, and (3) 4-week weight loss/ADMF self-selected feeding phase.	10 weeks	Visual analogue Scale	During the first week of ADMF, hunger scores were elevated. Hunger on the fast day decreased ($P < 0.05$) by week 2 and remained low.

Kroeger et al. (2018) secondary analysis from Trepanowski et al. (2017)	Obese adult men mean BMI 37±1 Mean age 37±1	n-34	Random assignment to a alternate-day fasting group, daily calorie restriction group, or no-intervention control group	52 weeks	Three-Factor Eating Inventory & Visual Analogue Scale	Hunger decreased (ADF high-weight-loss group from baseline to post-treatment but remained unchanged in the ADF low-weight-loss group. Hunger values did not differ between CR group.
Nymo et al. (2017)	Obese adult men 37 ± 4.5 kg m – 2 age 43±10 years.	n-31	Longitudinal intervention study	13 weeks	Visual analogue scale	A significant increase in fasting hunger was observed by day 3 and wk. 13. Additionally, hunger feelings and AG concentrations increase significantly from baseline once refeeding occurs.
Saslow et al. (2014)	Obese mean BMI 36.2 LCK Mean age 64.8 (7.7) MCCR Mean age 55.1 (13.5)	n-34 W-25 M-9	Random assignment either a low carbohydrate ketogenic diet (LCK), or a medium carbohydrate, low fat, calorie-restricted, carbohydrate counting diet (MCCR).	13.04 weeks	Food Craving Inventory, Three-Factor Eating Questionnaire	Participants within both groups reported significantly reduced carbohydrate and sweet cravings, emotional eating, hunger, and eating disinhibition but increased dietary restraint. When the two groups were compared there were no statistically significant differences in changes in these measures between groups.
Sundfør et al. (2018)	Obese Adults mean BMI 35.1 Mean age IF-49.9 CR-47.5	n-112 W-54 M-58	Randomized to intermittent or continuous energy restriction 6-month weight-loss phase followed by a 6-month maintenance phase	52 weeks	Visual Analog Scale	Intermittent restriction participants reported higher hunger scores than continuous restriction participants on a subjective numeric rating scale.
Teong et al. (2021) secondary analysis from Hutchison et al. (2019)	Obese women BMI 32.9 ± 4.4 Mean 50	n-88	Randomized to one of 4 groups CR group, IF group, IF100 group, control group.	8 weeks	Three Factor Eating Questionnaire	CR and IF increased dietary restraint and decreased susceptibility to hunger, while disinhibition was reduced solely in CR

Appendix 3
BMI Ranges

Adult BMI RANGES

Weight status	Body mass index (BMI), kg/m^2
underweight	<18.50
normal range	18.50-24.99
Overweight	≥25.00
Pre-obese	25.00-29.99
Obese	≥30.00
Obese class I	30.00-34.99
Obese class II	35.00-39.99
Obese class III	≥40.00

BMI values are age-independent and the same for both sexes.
The table is adapted from WHO 2000 report. "Obesity: preventing and managing the global epidemic: report of a WHO consultation"

Obesity: preventing and managing the global epidemic. Report of a WHO consultation. (2000). *World Health Organ Tech Rep Ser*, *894*, i-xii, 1-253.

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