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ARTICLE

Effects of 16/8 Intermittent Fasting on Type 2 Diabetes

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This research aims to investigate the effect of 16/8 intermittent fasting on type 2 diabetes. When people eat during an eight-hour period and fast for the remaining sixteen hours of a 24-hour day it is identified as 16/8 intermittent fasting (IF); water and black coffee are generally allowed. Adult type 2 diabetes is one of the most common global metabolic disorders with a global prevalence that increased by almost 4% from 1980 to 2014. In this meta-analysis, nine qualified studies were collected from the PubMed website and the University of New Brunswick online library. The calorie intake of control and treatment groups was collected to evaluate the difference between 16/8 IF and a normal diet. The differences in fasting blood glucose levels before and after the IF intervention reflect the severity of type 2 diabetes.

The results of the meta-analysis show that fasting blood glucose decreased among people with type 2 diabetes who followed 16/8 IF. Thus, IF could be considered as an intervention to slow down the progression of type 2 diabetes without the use of medication.

INTRODUCTION

Intermittent fasting (IF) is an eating pattern where people do not eat during certain periods of a day or days in a week (Gunnars, 2017). In Michael Mosley's 2012 study, he conceptualized 16/8 IF, in which people consume carbohydrates, proteins, and fats that contain energy in a consecutive eight-hour period, and fast for the remaining sixteen hours of a day. In addition, he proposed introducing IF into clinical trials. Intermittent fasting is primarily different from a normal diet routine in eating time and the amount of calorie intake. Recent studies have shown that IF can reduce body weight and the risk of metabolic syndrome --- a group of chronic diseases including type 2 diabetes mellitus (T2DM), hypertension, and obesity (Cho et al., 2019; Eckel et al., 2005; Hameed et al., 2015)
Currently, T2DM is one of the most common global metabolic syndromes, which is increasing rapidly. Between 1980 and 2014, its global prevalence increased from 4.7% to 8.5%, with a total of 314 million people having been diagnosed in 2014 (Wang et al. 2021). T2DM is characterized by insulin resistance, a scenario in which human body cells cannot respond to insulin normally, and thus glucose cannot be transferred into cells and used as energy (Taylor 2012). A high fasting blood glucose level is referred to glucose intolerance (Olatunbosun, 2022) (Goyal et al. 2021). The more glucose-intolerant a person is, the more severe that T2DM is, and the more likely that diabetic patients will develop some cardiovascular disease (Reaven 2006). For instance, glucose intolerance may increase blood viscosity and decrease blood mobility, thus, increasing the risk of blood clot formation (Mushtaq et al., 2019). The formation of a blood clot may lead to serious consequences, even death. Therefore, it is necessary to prevent the further progression of T2DM. This research is aimed to explore how 16/8 IF slows down the progression of T2DM.

Some research suggests that IF induces changes in gut microbiota that can activate the phosphorylation of insulin receptors and thus, interfere with the metabolic pathway to increase the absorption of insulin (Caricilli & Saad, 2013, Zhang et al., 2014). The gut microbiota includes bacteria and archaea which are living in a mammal's digestive system (Moszak et al. 2020). In a 4-week crossover mouse study, 16/8 IF induced protective changes in gut microbiome metabolic pathways, when compared to a usual dietary pattern; the richness of Lactobacillaceae and Bacteroidaceae increased (Cignarella et al., 2018). In particular, the presence of Lactoacillaceae in the small intestine increased insulin secretion due to augmented incretin release, which is a group of hormones simulating a decrease in blood glucose level (Simon et al., 2015). Bacteroidaceae inhibits the expression of fast-induced adipokine (Fiaf), which acts as a powerful signal to prevent the formation of glycogen and fat storage and enhance glucose intolerance (Mandard et al., 2006).

In Bäckhed's study, six germ-free adult C57BL/ mice were subjected to a 14-day crossover IF experiment. The group of mice were evenly distributed into one control group with normal diet and one treatment group with IF. At the end of the experiment, mice from the treatment group experienced a 60% increase in body fat content of the distal intestines. In the meantime, fasting blood glucose and insulin levels increased as well (Bäckhed et al., 2004). Despite reduced energy intake, the absence of Bacteroidaceae led to the increase of body fat and fasting blood glucose levels. In Mitev and Taleski's experiment, they utilized obese adult mice to detect if the presence of Bacteroidaceae may reduce the content of body weight and lower fasting blood glucose level (Mitev & Taleski, 2019). The mice with the Bacteroidetes diet had decreased body weight and lowered fasting blood glucose levels more than the control group mice without the Bacteroidaceae diet. Therefore, Bacteroidaceae has the potential to improve insulin resistance in mice. Thus, IF could improve insulin resistance by influencing gut microbiota, especially Bacteroidaceae.
However, most current studies were focusing on the effect of 16/8

IF within 4 weeks. Long-term investigations lasting beyond 8 weeks are lacking (Cao et al. 2019, Le Chaterlier et al. 2013). Therefore, the approach of this study was to investigate the long-term effect of 16/8 IF on type 2 diabetes.

Pathogenesis of type 2 diabetes

After a healthy person eats, the pancreas secretes insulin, then the body's cells respond by absorbing glucose into cells. Glucose is used as fuel for cells to maintain cellular activity, and excess glucose is converted into glycogen by the liver for storage. For people with type 2 diabetes, insulin is normally secreted, but cells do not respond to it, therefore glucose is left in the bloodstream instead of being transferred into cells (Taylor 2012). High blood glucose level is one of the symptoms of type 2 diabetes. The lack of glucose absorption often leads to hunger for people with type 2 diabetes, which makes them intake more calories. Therefore, obesity is usually affiliated with type 2 diabetes, which is an independent risk factor for type 2 diabetes (Stanaway et al., 2018). The fasting blood glucose is measured before people eat and is used as an index to determine the severity of type 2 diabetes. Healthy fasting blood glucose is below or equal to 100mg/dL (World Health Organization, 2021). As the magnitude of fasting blood glucose increases, the severity of type 2 diabetes increases. To understand and treat type 2 diabetes, researchers have manipulated several factors that could influence glucose intolerance or insulin resistance (He et al. 2018, Gao et al. 2019).

The positive effect of gut microbiota on type 2 diabetes

Observational studies concluded that people with type 2 diabetes have lower numbers of beneficial gut microbiota than healthy people, such as Lactobacillus and Bacteroides (Gurung et al. 2020). Gurung utilized 42 human studies to investigate the effect of Lactobacillus on the human body in clinical trials by meta-analysis method. The studies he collected show that there was an improvement in glucose metabolism after feeding genetically diabetic mice with an extra Lactobacillus diet. Also, four clinical trials show Lactobacillus exerted the effect on reducing type 2 diabetes symptoms. Lactobacillus helps itself and other probiotics co-exist in the human gut by secreting mucins, the chemical substance helps probiotics stick firmly to host cells and colonize local tissues (Zhang et al. 2019). Fåk's experiment validates Gurung's conclusion that Lactobacillus can reduce body weight and decrease blood glucose level (Fåk & Bäckhed, 2012). Fak distributed 8-week-aged Apoe-/- mice into treatment groups with feeding Lactobacillus in a normal daily diet cycle, and a control group without bacteria feeding. Twelve weeks later, mice receiving bacterial feeding gained less body weight than the control group mice. Gurung also used six db/db mice in another experiment and found that the Bacteroides could effectively lower blood glucose level and decrease the level of insulin resistance. Therefore, the amount of Lactobacillus is directly related to the adjustment of insulin resistance, which can further lead to type 2 diabetes treatment. A symbiotic relationship also exists between Lactobacillus and Bacteroides. Yang's research concludes that as the amount of Lactobacillus microbiota increases to a certain level, the Bacteroides will be more active since they can adhere to the intestinal wall (Yang et al. 2016). This research suggests that type 2 diabetes can be improved by adjusting gut microbiota. Even though this research was not aimed to investigate the effect of gut microbiota on type 2 diabetes specifically, the background information of gut microbiota provided information of its mechanism on manipulating type 2 diabetes. Since IF could positively impact gut microbiota in the following paragraph, the effect of IF on type 2 diabetes was interconnected via microbiota.

Intermittent fasting diet on gut microbiota

As the pathogenesis and factors that could affect type 2 diabetes are identified, how to treat it becomes a new problem. In Cignarella's study, he found that the db/db mice in 2-week 16/8 IF had greater amounts of active gut microbiota than mice that do not proceed with IF. Since gut microbiota plays a role in nutrient absorption, metabolism, and storage in animal's body, IF could affect the human body by regulating the antioxidant signalling pathways of the gut microbiota by controlling energy intake (Cignarella et al., 2018). Human participants performed in the experiment also confirmed the benefit of 16/8 IF on gut microbiota. Halberg's study involved eight healthy young men whose body mass index was 25.7± 0.4 kg/m2. The participants were subjected to 16/8 IF every second day for 15 days (Halberg et al. 2005). This experiment was the first to show the effect of intermittent fasting diet on human in decreasing insulin resistance and increasing cellular glucose intake. These studies have demonstrated that IF indirectly improved type 2 diabetes by altering the amount of gut microbiota, but they were done in animal studies or short-term human studies. therefore, this research study is aimed to investigate the effect of long-term 16/8 IF which duration is longer than 12 weeks on treating type 2 diabetes.

Gap and Research Purpose

Several systematic reviews and meta-analyses have shown that there are effects of a short-term 16/8 intermittent fasting diet on weight loss and insulin resistance in participants with type 2 diabetes (Barnosky et al., 2014, Seimon et al. 2019, de Cabo et al. 2019). However, the effect of IF on glycemic control in patients with type 2 diabetes remains inconclusive, with little data regarding long-term effects in senior patients in a typical area (Harris et al., 2018, Huseinovic et al., 2016). Therefore, this research systematically reviewed how would long-term 16/8 intermittent fasting diet impact type 2 diabetes.

METHOD

This meta-analysis aims to answer the research question: "Can long-term 16/8 intermittent fasting benefit type 2 diabetes?" Meta-analysis is a statistical method to approach an unknown result when multiple academic studies address the same question. Each study provided some degree of error, meta-analysis derived an overall estimate close to the unknown result according to these errors (Herrera Ortiz et al., 2021).

ALIGNMENT

Meta-analysis was strictly performed according to the Preferred Reporting Items for Systematic Review and Meta-analysis statement (Moher et al., 2009). To find the most appropriate method to perform, other frequently used methods such as experiments, randomized noninferiority trials, and sampling were considered as well. However, animal models, large sample groups and lab experiments could not be achieved. Therefore, meta-analysis was considered as the aligned method. Meta-analysis was a trustworthy method to investigate medical health related questions since the collected studies were academically credible. In this research study, meta-analysis was used as a non-experimental, quantitative method. The null hypothesis was that the long-term IF did not impact type 2 diabetes. The alternative hypothesis was that the long-term IF exerted a rule of improving type 2 diabetes.

VARIABLES

The amount of calorie intake became the independent quantitative variable. The unit of calorie intake was kcal.

Fasting blood glucose level was the dependent variable so that the severity of type 2 diabetes could be evaluated quantitatively. Due to the various eating time among selected studies, measuring participants' blood glucose level before they eat could minimize the environmental impact. The unit of fasting blood glucose level is mg/dL.

Every qualified study contained one treatment group with proceeding 16/8 IF, and one control group proceeding normal three-meal routine instead of 16/8 IF. The calorie intake before the treatment group proceeded with IF was recorded as "baseline" in both treatment and control groups. The average calorie intake during treatment groups proceeded IF was recorded as "after" in both treatment and control groups. The fasting blood glucose was recorded as a "baseline" value before treatment groups proceeded with IF. The fasting blood glucose was recorded as an "after" value after treatment groups completed IF.

PARTICIPANT

The total number of participants was 525 of which 318 participants were in the treatment groups and 207 participants were in the control groups. 149 males and 147 females were involved in this study; 229 participants were not specified gender. All general characteristics were included in Table 1.

DATA COLLECTION INSTRUMENTS

Studies published between January 1st, 2017, to November 30th, 2021, were gathered from English language academic websites including PubMed and the UNB Library website. Other databases such as EMBASE was accessed via UNB Library. In addition to this, reference lists of selected articles were also screened.

Keywords used for searching included "intermittent fasting", "16/8 intermittent fasting diet", "prediabetes", "type 2 diabetes", "obesity", "cardiovascular disease", and "fasting blood glucose".

Review Manager (RevMan) is a meta-analysis software from Cochrane. This program can graphically show the overall effect for all selected studies and the individual effect from each study respectively.

PROCEDURE

All peer-reviewed studies were found in PubMed and UNB Library website by typing key words "intermittent fasting diet", "type 2 diabetes", "obesity", and "blood glucose level". Meta-analysis was based on study selection that fit specific criteria. The selected studies had to meet all following criteria: all participants included were adult patients between 45 to 65 years old who had been diagnosed with type 2 diabetes; the treatment group only proceeded 16/8 intermittent fasting diet; the study designs were a noninferiority randomized trial or control experiment; the change in calorie intake and fasting blood glucose level were included, and the duration of the study was between 12 to 52 weeks. North America was the only region included in this research. The region of participants was assumed to be the same as the authors of the study.

If studies included these conditions, they were excluded: animal study, non-randomized trial, observational study, review, or pilot study; the treatment group continued a very-low calorie restriction diet, 5:2 intermittent fasting diet (the pattern of normal three-meal routine for 5 consecutive days per week and no calorie intake for remaining two days), 12/12 intermittent fasting diet (the pattern of taking calorie for randomly consecutive 12 hours per

Figure 1. The distribution of meta-analysis studies on the North America map

Note. The red location icons illustrated the city of the first author's institution.

Table 1. Characteristics of nine crossover studies included in the meta-analysis
Note. M=male, F=female, P=participant who did not specify gender, y.o=average year old around nearest integer.

Study #	Author	Year	Duration	Experimental group	Control group
1	**Arnason et al.**	2017	12 weeks	10M, 54 y.o	10M, 56 y.o (7.1)
2	**Gabel et al.**	2018	12 weeks	20 females, 3 males, 50±2 20 F, 3M; 50 y.o	21F, 2 M; 48 y.o
3	**Kraus et al.**	2019	24 weeks	143 P; 43 y.o	75 P; 45 y.o
4	**Lowe et al.**	2020	12 weeks	24F, 35M; 47 y.o	22F, 35 M, 46 y.o
5	**Saslow et al.**	2020	32 weeks	6F, 6M, 53 y.o	4F, 9M, 46 y.o
6	**Sutton et al.**	2018	12 weeks	8M; 56 y.o	8M, 56 y.o
7	**Trepanowski et al.**	2018	24 weeks	23F, 6M; 44 y.o	21 F, 4M, 44 y.o
8	**Wei et al.**	2017	16 weeks	39P, 50 y.o	43 P, 48 y.o
9	**Wilkinson et al.**	2020	16 weeks	6F, 13M, 59 y.o	19P, 57 y.o

day and no calorie intake for the remaining 12 hours); the duration of intervention was shorter than 12 weeks; the region of authors was not in North America; the fasting blood glucose levels before and after the experiment were not specified; the published date of the paper was not in the range of 1st January 2017 to 30th November 2021, or the age of participants was not specified.

A total of 3284 peer-reviewed studies were screened according to the search engine. 1120 duplicate documents were eliminated, 1and 609 documents were not selected due to improper time range. Finally, 323 studies were selected by reviewing titles and abstracts, 116 studies were not using a 16/8 intermittent fasting diet, 48 studies were not in the 45-65 age range, 137 studies lasted shorter than 12 weeks, and 13 studies were not in North America. A total of 9 studies were left that met all criteria as shown in Table 1. The distribution of locations was shown in Figure 1.

The locations of meta-analysis studies by study number order included Saskatoon, SK Canada; Chicago, IL, USA; Durham, NC, USA; San Francisco, CA, USA; Ann Arbor, MI, USA; Baton Rouge, LA, USA; Stanford, CA, USA; Los Angeles, CA, USA; and San Diego, CA, USA.

The comparison of calorie intake between treatment groups and control groups was utilized to quantitatively demonstrate the effect of 16/8 IF. The change in fasting blood glucose level could evaluate whether the type 2 diabetes improved or not. The difference between calorie intake and change in blood glucose level before and after intermittent fasting diet were analysed to explain the effect of intermittent fasting diet on type 2 diabetes.

The difference of fasting blood glucose level between baseline and after-IF in treatment group and control group in every study was utilized in RevMan. The result was shown graphically in Figure 4.

The effect of the difference of fasting blood glucose level in individual study and overall effect among nine studies would show whether the result favours the control group or treatment group. The result could evaluate the effectiveness of long-term 16/8 IF. The p-value in this meta-analysis would be calculated and compare with the critical p value, 0.05. If the experimental p value was less than 0.05, the null hypothesis would be rejected. If the experimental p value was greater than 0.05, the null hypothesis would not be rejected.

The x-axis represents the study number, complementary to Table 1. The y-axis represents calorie intake during IF in kcal. Blue and green bars represent treatment group and control group respectively. As the graph shows, there is not a large difference between treatment group and control group in calorie intake among nine studies. This phenomenon demonstrates that the treatment groups consume approximate the same amount of calorie as control groups.

The x-axis represents the study number, complementary to Table 1. The y-axis represents baseline of fasting blood glucose level in mg/dL. Blue and green bars represent treatment group and control group respectively. There is not a large difference between treatment and control group for baseline of fasting blood glucose level of any of 9 studies. The fasting blood glucose level in study #1 and study #5 are relatively higher than other 7 studies.

The x-axis represents the study number, complementary to Table 1. The difference in fasting blood glucose is calculated by subtracting the mean value of baseline of fasting blood glucose

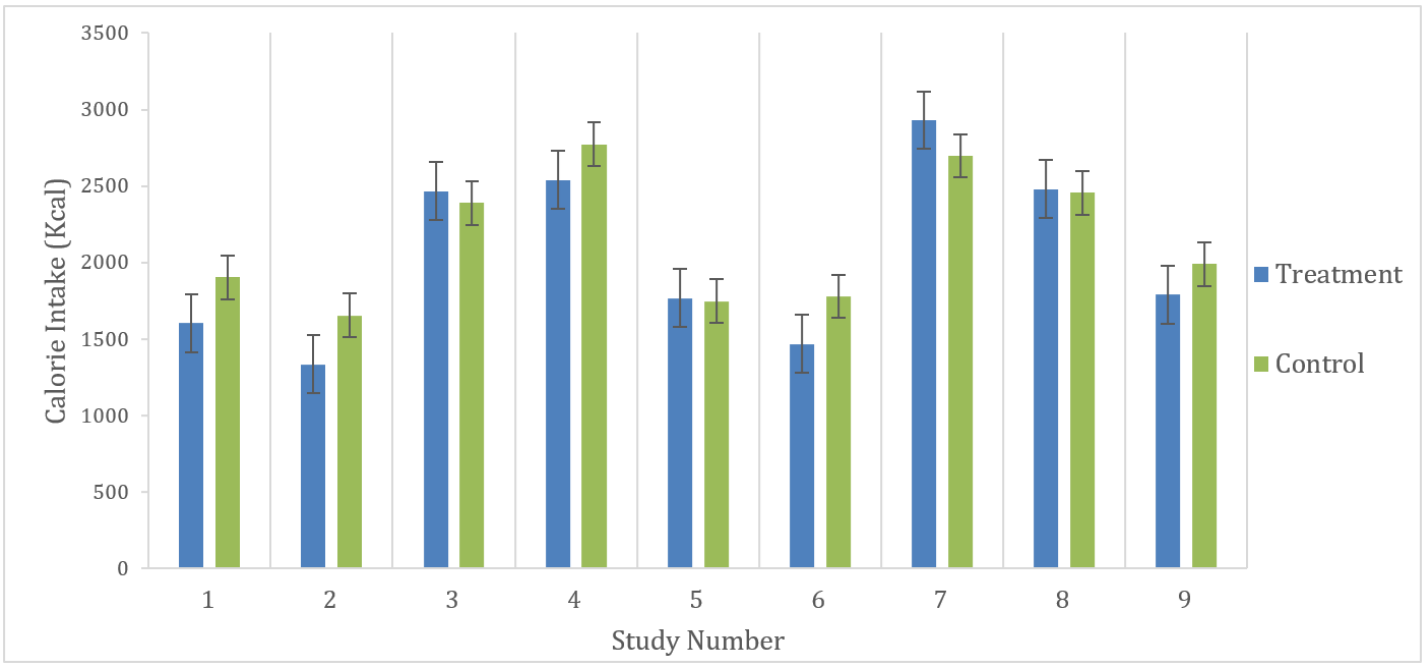

Figure 2. Comparison of calorie intake during intermittent fasting diet in treatment groups and control groups.
Note. The error bars show standard errors, and they were illustrated in the following graphs.

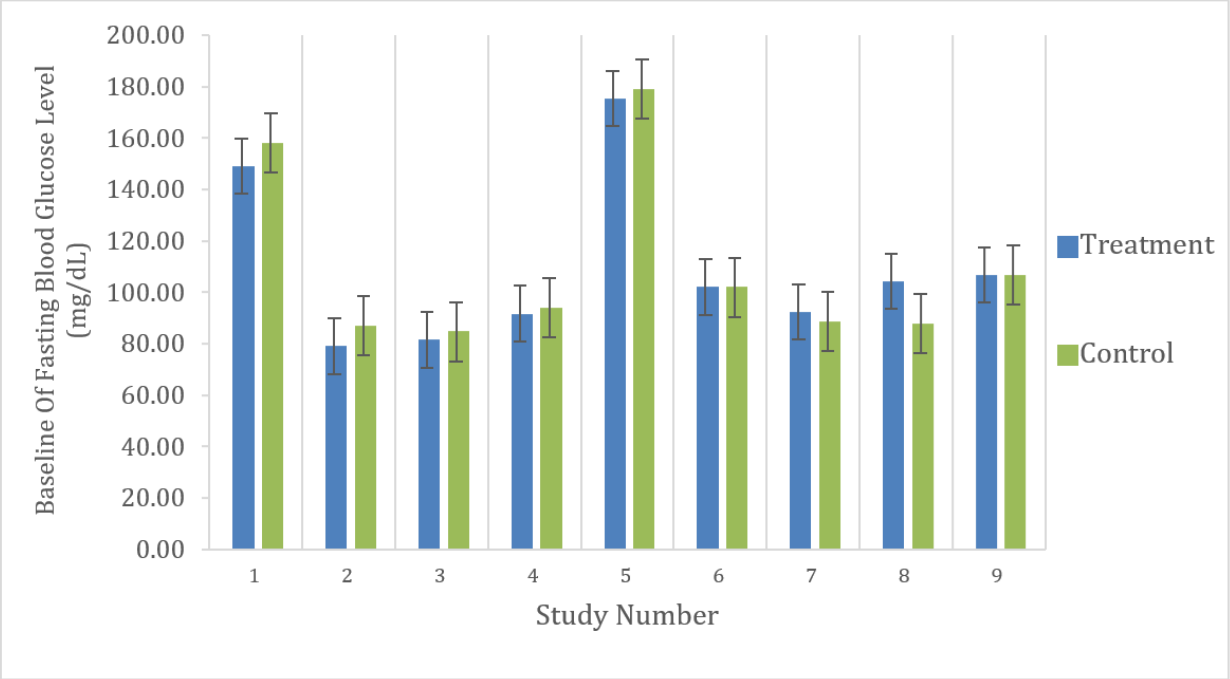

Figure 3. Baseline of fasting blood glucose in treatment groups and control groups

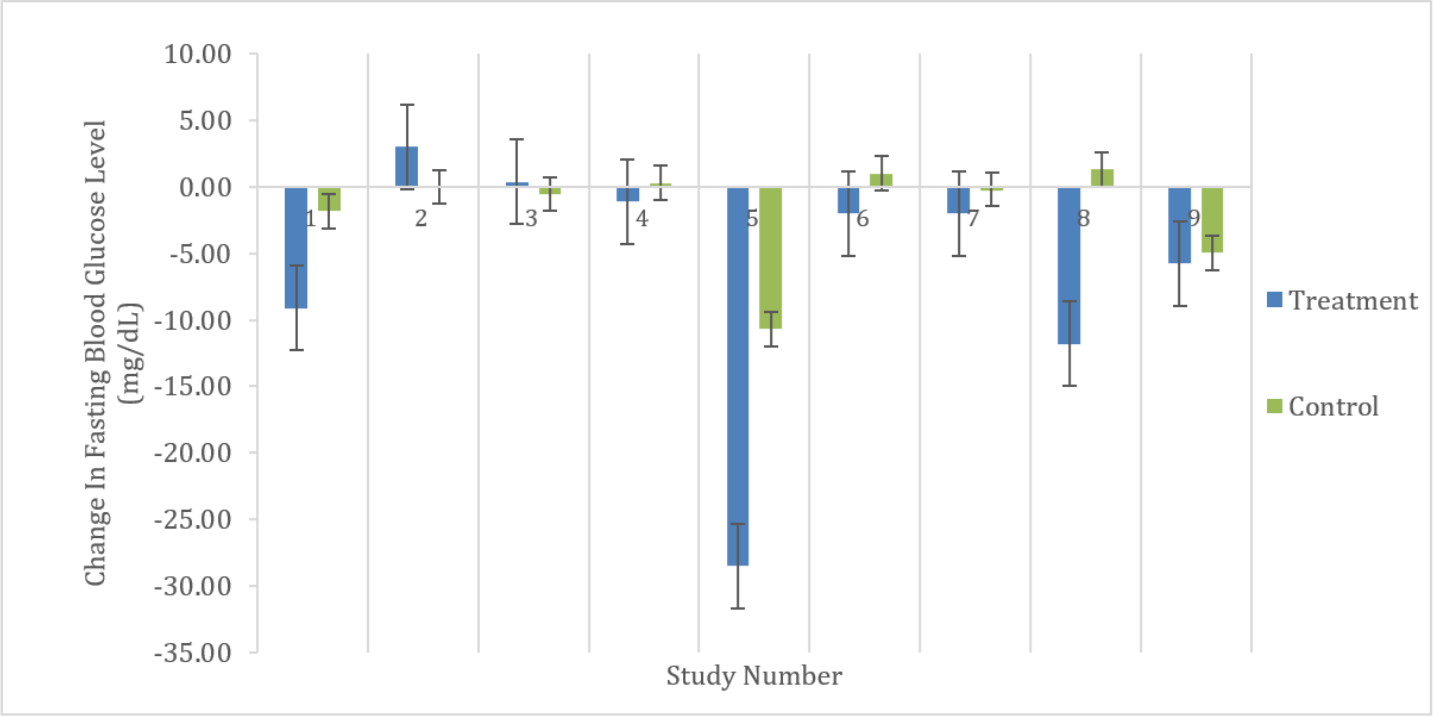

Figure 4. Changes of blood glucose level between treatment group and control group

from the mean value after the experiment. The y-axis represented difference of fasting blood glucose level (after-baseline) in mg/dL. Blue and green bars represented treatment group and control group respectively. The bars above 0-axis represented the fasting blood glucose level after experiment was higher than before. The bars below 0-axis represented the fasting blood glucose level after experiment was lower than before. The difference in fasting blood glucose level was considerably large between treatment and control group in all 9 studies. However, study #2 and study #3 had a positive difference in treatment groups, and study #4, study #6, and study #8 had a positive difference in control groups. Study #5 had the greatest magnitude of change in fasting blood glucose level in treatment group and control groups.

The magnitudes of difference and standard errors of in fasting blood glucose level from treatment groups and control groups were from Figure 4. Since standard deviation (SD) was required for the RevMan analysis, they were not shown in Figure 2, 3, and 4. Standard deviation was converted by taking standard error and multiplying the square root of the number of participants in each group. The vertical line of zero represents no effect. The right side of vertical line indicates results favoured to control groups, without proceeding IF. The left side vertical line indicates results favoured to treatment groups, with proceeding of IF. The diamond at the bottom indicated the overall effect, and the horizontal whisker lines indicated 95% confidence interval of individual studies by study number order from top to bottom. The squares in the middle of lines indicated effect estimate for each study. On the bottom of diagram, the p value was 0.003 and heterogeneity value was 94%.

DISCUSSION

Few studies had investigated the effect of long-term 16/8 intermittent fasting diet on type 2 diabetes among a certain aged patients in particular area. This meta-analysis evaluated the effect of 12 to 52 weeks 16/8 intermittent fasting diet randomized trials studies that targeted to 45-65 aged people in North America.

Based on Figure 2, the difference in calorie intake during experiment between control groups and treatment groups was not significant. Since each trial was conducted at a different time, eating time was not able to be an independent variable to quantify the effect of 16/8 IF on type 2 diabetes. According to the National Health Service, the recommended calorie intake for an adult is 1600-2500 calories a day. In this research study, the treatment group consumed an average of 2043 kcal a day, while the control group consumed an average of 2155 kcal a day, both within healthy levels of 2000-2500 kcal per day. Therefore, calorie intake during 16/8 IF was not much different from daily intake. The factor that could reduce diabetes may not be calorie intake, eating time could be considered as the influential factor.

The baseline of fasting blood glucose demonstrated the severity of type 2 diabetes in each group before IF as shown in Figure 3. This was compared with fasting blood glucose levels after IF so that whether fasting improves diabetes could be demonstrated. Figure 4 illustrated that decreases in fasting blood glucose existed in seven out of nine experimental groups, group 1, 4, 5, 6, 7, 8, 9 respectively. The average decrease in treatment group was 4.65% as compared to baseline. The average decrease in control group was 1.58% as compared to baseline. By comparing the baseline decreases in treatment groups with control groups, the treatment groups applied a more noticeable decrease on reducing fasting blood glucose level than control groups. Additionally, after the experiment, the average fasting blood glucose in treatment groups was 102.69mg/dL, which was close to the normal blood glucose level of 100.00mg/dL. The magnitudes of the change in fasting blood glucose level were adopted in RevMan meta-analysis program, so that the results could be demonstrated more accurately and precisely.

The RevMan program analysis demonstrated the impact of IF on the overall population through the differences in fasting blood glucose of control and treatment groups. In eight of the nine studies, the treatment groups had a greater effect on improving fasting

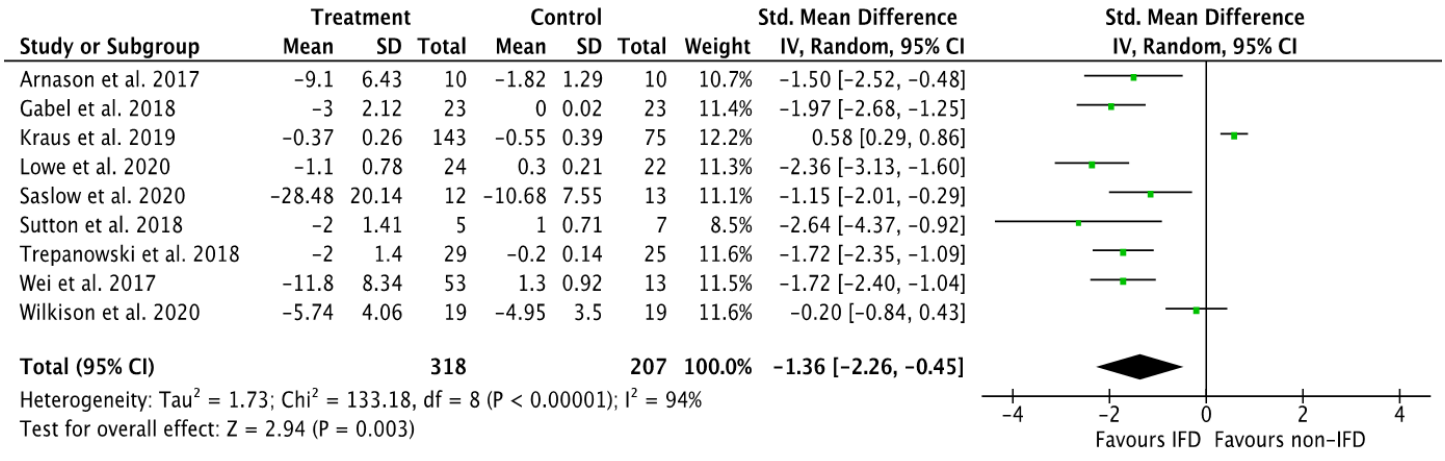

Figure 5. RevMan analysis for the standard mean difference

blood glucose level than the control groups. The bottom diamond is on the left of the "no-effect" line, which means the treatment groups have a more significant effect on decreasing blood glucose level than control groups. This meta-analysis illustrated that IF had the effect on reducing fasting blood glucose and thus improving type 2 diabetes. The p value was 0.003, which was less than the critical p value 0.05. The experimental p value rejected null hypothesis, which is the long-term IF did not impact type 2 diabetes. The RevMan meta-analysis results suggest that long-term 16/8 intermittent fasting diet contributed to reduce type 2 diabetes patients' fasting blood glucose level and improve type 2 diabetes.

The result of this meta-analysis research was compared with Lichtash's study, which was utilizing a case-study with proceeding 14 months 16/8 intermittent fasting diet for a woman with type 2 diabetes (Lichtash et al. 2020). The screening conditions set up in this research were the same as those of the subjects studied in Lichtash's paper, such as participant with type 2 diabetes, the same age and region restriction, and both utilized long-term 16/8 intermittent fasting diet. The only difference was that this research covered more participants, and her paper only included one participant. Lichtash's study concluded that after 14-month observation, the participant's haemoglobin A1c (HbA1c) was reduced from 9.3% to 5.8%. Based on Centers for Disease Control and Prevention, the reduced magnitude 5.8% was in prediabetes range (CDC, 2018). Linchatah's study and this meta-analysis research both validated that the long-term 16/8 intermittent fasting diet existed a positive impact on improving type 2 diabetes.

The current clinical trials confirmed that the medicine such as sulfonylureas and insulin were beneficial to treat type 2 diabetes. The short-term of 16/8 intermittent fasting diet was already introduced to clinical trials (Pfeiffer & Klein, 2014). As the benefit of long-term intermittent fasting diet on treating type 2 diabetes was shown by this research, doctors should recommend long-term 16/8 intermittent fasting diet for clinical use. During intermittent fasting diet, the calorie intake for treatment groups was 2043 kcal per day, which was within the healthy range of energy for a healthy adult should consume in a day. Therefore, the nine studies included in this research did not negatively affect the health of the participants. Thus, long-term 16/8 IF would be considered as an option.

LIMITATIONS AND FUTURE DIRECTIONS

The heterogeneity value (I2) refers to the variation of study outcomes between studies included in the meta-analysis. I2 values were interpreted as follows: 0% to 40%, no important heterogeneity; 30% to 60%, moderate; 50% to 90%, substantial; and 75% to 100%, considerable heterogeneity (Cho et al. 2019). 94% heterogeneity was in this meta-analysis. This might be caused by a large age range and location variation. As Figure 1 shows, the easternmost city Durham, is 4,542 kilometers away from the westernmost city, San Francisco. The northernmost city Regina is 2489 kilometers away from the southernmost city, Baton Rouge (Google Map). The heterogeneity value could be decreased by narrowing down the scope of age range and location distribution. This limitation provided advice for future researchers.

The effect of 16/8 intermittent fasting diet could be various between females and males. However, in this research, participants' gender was not specified in every study. Study #3 and study #8 remained inconclusive on participants' gender. Therefore, the effect of long-term 16/8 IF between different genders could be an alternative question for future researchers.

Currently, intermittent fasting diet is primarily utilized as religious behavior, the medical use of intermittent fasting diet as a type 2 diabetes treatment was not widely utilized yet. Developing people's recognition that 16/8 intermittent fasting diet can improve type 2 diabetes and being able to consider 16/8 IF as an alternative lifestyle is inconclusive yet. Therefore, how to encourage people to adopt 16/8 intermittent fasting diet as a lifestyle is a worthy direction from a human behavioral standpoint (Adafer et al., 2020).

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