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Intermittent Fasting in Weight Loss and Cardiometabolic Risk Reduction: A Randomized Controlled Trial

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ABSTRACT

Background: Intermittent fasting is an effective approach to promote weight loss. The optimal model of intermittent fasting in achieving weight management and cardiometabolic risk reduction is an underexplored but important issue.

Purpose: This study was designed to examine the effects of alternate-day fasting (ADF) and 16/8 time-restricted fasting (16/8 TRF) on weight loss, blood glucose, and lipid profile in overweight and obese adults with prediabetes.

Methods: A randomized controlled trial was conducted on a sample of 101 overweight and obese adults with prediabetes. The participants were randomized into the ADF group (n = 34), 16/8 TRF group (n = 33), and control group (n = 34). The intervention lasted for 3 weeks. Data on body weight, body mass index, waist circumference, blood glucose, and lipid profile were collected at baseline, at the end of the intervention, and at the 3-month follow-up.

Results: The reductions in body weight, body mass index, and waist circumference in the ADF and 16/8 TRF groups were more significant than those in the control group across the study period (all ps < .05). Moreover, significant reductions on blood glucose and triglycerides were observed in the two intervention groups as well. Furthermore, the reductions in body weight and body mass index in the ADF group were more significant than those in the 16/8 TRF group (all ps < .001). However, differences on the changes in blood glucose, waist circumference, and low-density lipoprotein cholesterol between the two intervention groups were not significant.

Conclusions/Implications for Practice: The benefits of ADF and 16/8 TRF in promoting weight loss in overweight/obese adults with prediabetes were shown in this study. ADF was shown to have more-significant reduction effects on body weight and body mass index than 16/8 TRF. These findings indicate the potential benefit of integrating intermittent fasting regimens into normal dietary patterns to reduce the risk of diabetes and cardiovascular disease in this population.

Key Words:
alternate-day fasting, 16/8 time-restricted fasting, intermittent fasting, weight loss, prediabetes.

Introduction

Type 2 diabetes has become a public health problem worldwide, with an estimated 462 million people (6.28% of the world's population) having this disease (Khan et al., 2020). China has the largest number of patients with Type 2 diabetes (129.8 million; Li et al., 2020). Prediabetes is an impairment in fasting plasma glucose (Brannick & Dagogo-Jack, 2018). In a survey of 170,287 adults in China, 35.7% were found to have prediabetes (Wang et al., 2017). Prediabetes is not only a risk factor for Type 2 diabetes but also associated with an increased risk for cardiovascular diseases (Brannick & Dagogo-Jack, 2018). Therefore, managing prediabetes is crucial to preventing the onset of Type 2 diabetes. In individuals with prediabetes, controlling body weight has been shown to reduce the incidence of Type 2 diabetes significantly, especially in overweight and obese individuals with prediabetic conditions (Guess, 2018; Pal & Nanda, 2017).

Continuous calorie restriction is commonly used in body weight control and in interventions to prevent cardiometabolic diseases in obese and overweight populations (Rynders et al., 2019). However, people find it difficult to follow this diet pattern as it requires the consistent reduction of daily calorie intake (Golbidi et al., 2017). Furthermore, continuous calorie restriction may enable adaptive responses (e.g., increased appetite, reduced physical activity, deactivated hypothalamic–pituitary–thyroid axis), which results in weight

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regain (Seimon et al., 2015) and increases the risk of adverse effects such as hypoglycemia and malnutrition (Corley et al., 2018). Recently, intermittent fasting has been proposed as an alternative to continuous calorie restriction. Intermittent fasting typically involves restricting calorie consumption during a controlled period and then engaging in *ad libitum* calorie consumption during nonfasting times (Muñoz-Hernández et al., 2020). Therefore, individuals are more likely to adhere to this dietary plan than plans that mandate continuous calorie restriction. Alternate-day fasting (ADF) and time-restricted fasting (TRF) are the two most commonly used dietary interventions in intermittent fasting studies. ADF involves calorie restriction on the fasting day and eating *ad libitum* on "feed" days, whereas TRF allows individuals to eat during a specific, time-limited period each day and fast for the remaining time (e.g., an 8-hour eating window followed by fasting for the remaining 16 hours of the day; Muñoz-Hernández et al., 2020).

The effects of intermittent fasting on weight and blood glucose control in people with metabolic risks have been evaluated in several prior studies (Cho et al., 2019). A systematic review that synthesized the findings of 40 intermittent-fasting studies revealed significant reductions in body weight and fat mass and improvements in glucose homeostasis with intermittent fasting (Seimon et al., 2015). Similarly, the effects of intermittent fasting identified in prior interventional studies of overweight and obese adults were summarized in two recent meta-analyses, with findings supporting the effectiveness of this approach on weight loss (Cho et al., 2019; Harris et al., 2018). However, the intermittent fasting interventions differed across these studies, and no direct comparisons were made among the intermittent fasting interventions, making it difficult to determine the optimal intermittent fasting regimen. In addition, most previous studies focused on people who were overweight or obese, while excluding those with comorbid conditions such as prediabetes (Harris et al., 2018), which may put them at a higher risk of developing cardiometabolic diseases.

Thus, an evaluation of the effects of different, intermittent fasting regimens on weight control and the management of cardiometabolic outcomes in high-risk populations is urgently needed. Thus, this study was developed to examine the effects of ADF and 16/8 TRF on body weight, blood glucose, body mass index (BMI), waist circumference, and lipid profile in overweight and obese individuals with prediabetes.

Methods

Study Design

This was a randomized controlled trial (RCT) study that used convenience sampling. Participants were randomized to the ADF group (n = 34), the 16/8 daily TRF group (n = 33), and the usual care group (n = 34) using a computer-generated randomization list created by an offsite research staff who was not involved in the practical conduct of this study. Random numbers with allocation codes were kept in opaque sealed envelopes that were sequentially numbered and distributed to participants by a research assistant according to participants' enrolment sequence.

Participants and Setting

The participants were recruited from a weight management clinic in Hunan Provincial People's Hospital, Changsha, China, from August 2018 to April 2019. The inclusion criteria were as follows: (a) age of 18–65 years, (b) having a diagnosis of prediabetes (blood glucose level: 100–125 mg/dl; American Diabetes Association, 2020), (c) being overweight or obese (BMI: ≥ 23 kg/m^2; WHO Expert Consultation, 2004), and (d) being able to give written informed consent. Patients were excluded from the study if they (a) were pregnant or planning to become pregnant; (b) had an eating disorder, a serious cognitive impairment, a psychiatric disease, or a gastrointestinal disorder; (c) were being treated with insulin, glyburide, or other antiobesity drugs; or (d) had been involved in a diary-related program during the previous 12-month period.

Sample Size Estimation

The sample size was determined as adequate for detecting a 5% difference in the reduction of body weight between the two intervention groups (Seimon et al., 2015). The power analysis software PASS 14.0 (NCSS, Kaysville, UT, USA) was used to estimate the power when regression analysis was applied. Thus, it was estimated that a sample size of 29 participants per arm was needed to give 80% power at a 5% level of significance (two sided). Allowing for a 10% attrition rate, 33 participants were recruited for each arm.

Dietary Interventions

The intervention lasted for 3 weeks. The participants in both of the intervention groups received an individual education session on healthy diet provided by a nurse in the weight management clinic. This session covered topics including diet and health, benefits of energy control, and skills to maintain a healthy diet. The participants in the ADF group were instructed by a dietitian to consume 600 kcal on fasting days and to consume a usual diet on eating days. The fasting days alternated with eating days throughout the intervention period. The ADF group participants were free to divide up the calories into different meals during fasting days. The 16/8 TRF group was asked to consume their daily calorie intake during an 8-hour window during the daytime and then fast for the remaining 16 hours each day throughout the intervention period. Participants were free to arrange the 8-hour eating window based on personal preferences. The daily calorie requirement was determined according to Chinese Dietary Reference Intakes in which daily calorie requirements are estimated based on level of physical activity and gender (Chinese Nutrition Society, 2016). This flexibility was expected to help the participants adapt to their individual lifestyles and to facilitate compliance with the dietary intervention. In addition, both the ADF and 16/8 TRF groups received individualized menus tailored to their dietary interventions and individual counseling provided by a dietitian. Weekly telephone calls were conducted by a research nurse to facilitate participants' adherence to their dietary intervention. Furthermore, the participants were asked to record and report adverse effects experienced during the study period.

To minimize potential attention bias, the participants in the control group also received the same individual educational session. All of the participants were asked to maintain their usual physical activity throughout the study period.

Outcome Measures

Primary outcome

The primary outcome of this study was the change in body weight. Body weight was measured using a calibrated digital scale with light clothing and without shoes or jewelry.

Secondary outcomes

Secondary outcomes included blood glucose, BMI, waist circumference, and a lipid profile that included total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglyceride. Blood glucose was measured via blood testing in the laboratory of the study hospital. The blood sample was drawn by a trained research nurse via venepuncture after 8 hours of overnight fasting. BMI was calculated using the formula: body weight (kg) / body height^2 (m^2). Waist circumference was measured using a tape at midway between the bottom of the rib cage and the top of the iliac crest at the end of normal exhalation. Lipid profile was measured via blood testing in the laboratory of the studied hospital using the same blood sample for blood glucose testing.

Participants' physical activity may confound the intervention effects. Participants were asked to complete the physical activity subscale of the Chinese version of the Health Promoting Lifestyle Profile II to track changes in physical activity level. The Chinese version of the Health Promoting Lifestyle Profile II is a reliable and valid questionnaire, with a satisfactory Cronbach's alpha of .95 for the whole scale and .91 for the physical activity subscale in a Chinese sample (Meihan & Chung-Ngok, 2011).

Ethical Considerations

Ethical approval was obtained from the Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee (No. CRE-2017.704). Participants were informed about their right to withdraw from the study at any time without penalty to their present or future care. Furthermore, the study conformed to the principles outlined in the Helsinki Declaration.

Data Collection

Patients who were admitted for weight management were screened for eligibility based on the inclusion and exclusion criteria by a research nurse. The research nurse explained the study purposes, procedures, and benefits/risks to eligible patients and invited them to participate. After obtaining written informed consent, the participants were randomized to one of the three groups. Data collection was conducted at three time points: baseline (T0), end of the intervention (T1), and 3-month follow-up (T2).

Data Analysis

Data analyses were performed using SPSS Statistics 22.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics, including mean (*SD*), median (interquartile range), frequency, and percentage, were used as appropriate to present the data. Continuous data were examined for normal distribution using Q-Q plots. For comparisons among the three groups, one-way analysis of variance, Kruskal–Wallis test, and chi-square test were used as appropriate. The generalized estimating equation (GEE) model was performed to assess differences in the changes between groups in each outcome across the time points. The linear link function was applied for data that were normally distributed. For nonnormal distributed continuous data, the data were natural log-transformed before being subjected to GEE analysis. The autoregressive model (AR-1) was used for the working matrix. As the GEE is able to use partial observation data to estimate the regression parameters (Ziegler & Vens, 2010), the missing data were not particularly handled in the data analysis in this study. Adverse events during the duration of the study were recorded. The intention-to-treat principle was followed unless indicated otherwise. The level of significance was set at < .05 (two sided).

Results

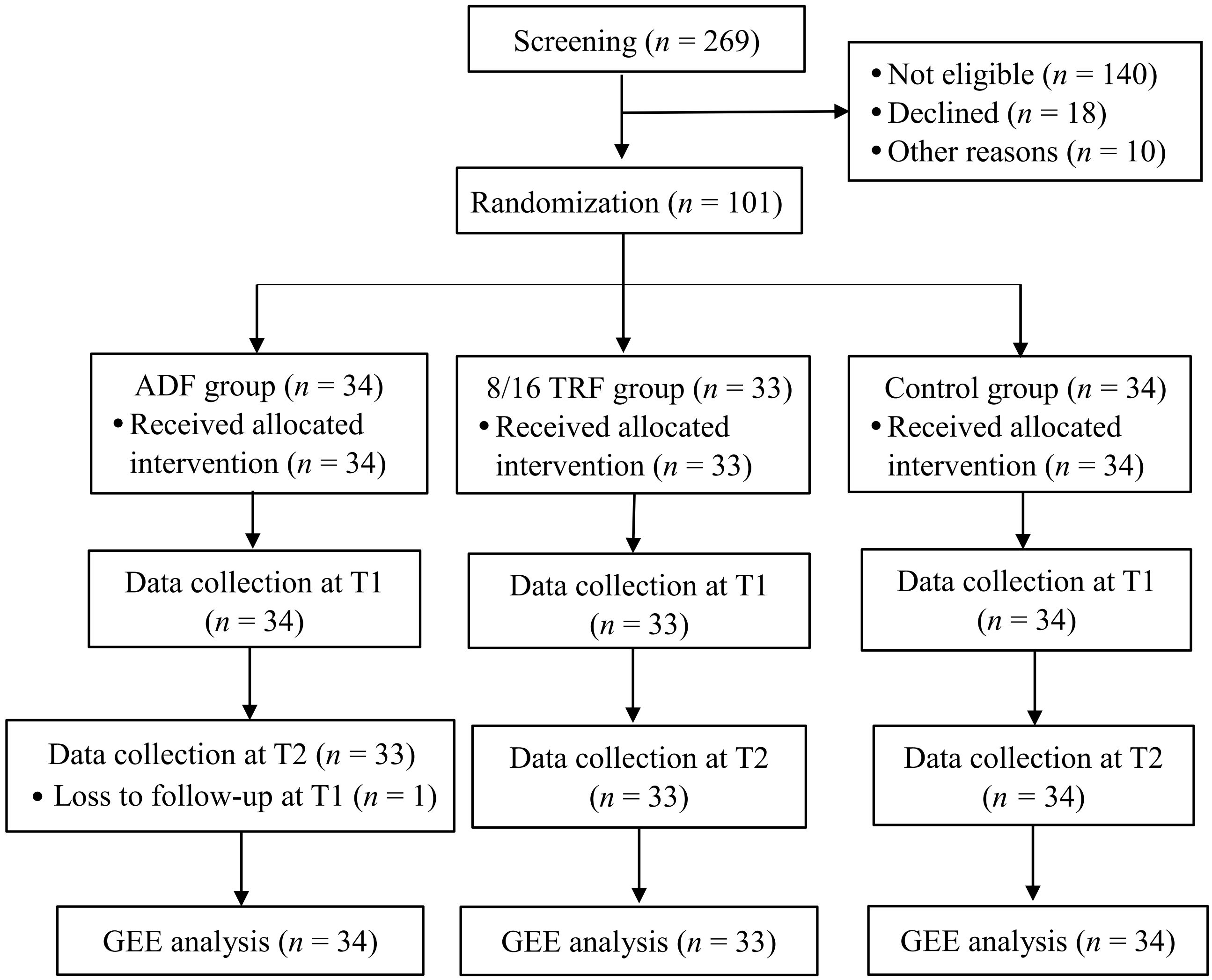
Two hundred sixty-nine patients were screened and 168 were excluded, mainly because of ineligibility or lack of interest. One hundred one patients were included in the final sample and randomized, with 34 in the ADF group, 33 in the 16/8 TRF group, and 34 in the control group. There was one dropout in the ADF intervention group and no dropouts in the other two study groups. Three participants (all in the 16/8 TRF group) reported occasional feelings of hunger during fasting hours. No severe, adverse events were reported. The Consolidated Standards of Reporting Trials flowchart of this study is illustrated in Figure 1.

Characteristics of Participants

The characteristics of the participants are presented in Table 1. Mean age was 35.23 (*SD* = 6.19) years, with more women (63.4%) than men (36.6%); most (80.2%) held a bachelor's degree and were married (86.1%). The average BMI was 26.56 (*SD* = 1.95) kg/m^2, and the mean waist circumference was 90.77 (*SD* = 8.80) cm.

Figure 1

Consolidated Standards of Reporting Trials Flowchart of the Study and Length, Width, and Size Similar



Note. ADF = alternate-day fasting; TRF = time-restricted fasting; GEE = generalized estimating equations.

T1 = end of the intervention; T2 = 3-month follow-up.

No significant differences in most of the baseline variables were observed among the three study groups, with the exception of gender (p = .013), marital status (p = .025), HDL-C (p = .027), total cholesterol (p = .006), and physical activity level (p = .003). These variables were then considered as confounding factors and adjusted in the GEE analysis.

Body Weight

The results of the GEE analysis are presented in Tables 2 and 3. Compared with the control group, both of the intervention groups showed significant body weight reductions at T1 and T2 (all ps < .001; Table 2). Compared with the 16/8 TRF group, the ADF group showed more significant weight reductions across the study period (all ps < .001; Table 3).

Body Mass Index

More significant decreases in BMI were observed in both of the intervention groups across the study period (all ps < .001, Table 2) than in the control group. In comparing the two intervention groups, the ADF group showed more significant reductions in BMI at both T1 and T2 than the 16/8 TRF group (all ps < .001; Table 3).

Waist Circumference

Both of the intervention groups showed more significant reductions in waist circumferences at T1 and T2 than the control group (Table 2; all ps < .001). The 16/8 TRF group showed significant reductions in waist circumference at T1

Table 1
Baseline Characteristics of the Participants (N = 101)

Characteristic	Total		Control (*n* = 34)		ADF (*n* = 34)		16/8 TRF (*n* = 33)		*p*
	n	%	*n*	%	*n*	%	*n*	%	
Gender									.013 [b]
Female	64	63.33	20	58.88	28	82.35	16	48.48	
Male	37	36.67	14	41.12	6	17.65	17	51.52	
Educational attainment									.301 [b]
Associate degree or below	11	10.89	2	5.88	4	11.76	5	15.15	
Bachelor's degree	81	80.20	29	85.29	29	85.29	23	69.70	
Master's degree or above	9	9.01	3	8.83	1	2.95	5	15.15	
Income level (RMB)									.737 [b]
< 6,000	44	43.56	13	38.24	16	47.06	15	45.45	
≥ 6,000	57	56.44	21	61.76	18	52.94	18	54.55	
Marital status (*n* = 99)									.025 [b]
Single	12	12.12	3	8.82	1	3.03	8	25.00	
Married	87	87.88	31	91.18	32	96.97	24	75.00	
Living alone									.926 [b]
No	90	89.11	30	88.24	31	91.18	29	87.88	
Yes	11	10.89	4	11.76	3	8.82	4	12.12	
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*p*
Age (years)	35.23	6.19	34.97	6.23	34.68	4.37	36.06	7.67	.634 [a]
Body weight (kg)	74.30	8.39	72.15	8.47	75.78	8.46	74.98	8.02	.173 [a]
Body height (cm)	167.13	7.78	164.94	8.36	169.15	6.97	167.30	7.58	.081 [a]
Body mass index (kg/m^2)	26.56	1.95	26.47	1.84	26.46	2.36	26.74	1.58	.809 [a]
Waist circumference (cm)	90.77	8.80	90.65	9.35	92.03	9.27	89.61	7.73	.531 [a]
HDL-C (mmol/L)	1.14	0.36	1.26	0.42	1.02	0.24	1.15	0.37	.027 [a]
LDL-C (mmol/L)	2.94	0.79	3.05	0.78	2.94	0.73	1.14	0.37	.492 [a]
Total cholesterol (mmol/L)	4.63	1.32	4.89	1.32	4.94	1.16	4.04	1.30	.006 [a]
TG (mmol/L; median and interquartile range)	2.16	1.70–2.79	1.97	1.37–2.52	2.36	1.77–2.66	2.26	1.93–3.21	.307 [c]
Blood glucose (mmol/L; median and interquartile range)	5.13	4.72–5.64	4.92	4.67–5.69	5.14	4.82–5.65	5.30	4.80–5.52	.574 [c]
Physical activity score (range: 8–32)	16.40	4.53	16.03	5.02	18.38	4.16	14.73	3.59	.003 [a]

Note. ADF = alternate-day fasting; TRF = time-restricted fasting; RMB = renminbi; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglyceride.
[a] One-way analysis of variance. [b] Chi-square test. [c] Kruskal–Wallis analysis.

(β = −5.69, $p < .001$) and T2 (β = −5.84, $p < .001$) compared with baseline. The ADF group reported less significant reductions in waist circumference than the 16/8 TRF group across the study period (Table 3).

Blood Glucose

Compared with the control group, the ADF group showed more significant reductions in fasting blood glucose at both T1 (β = −0.13, $p = .027$) and T2 (β = −0.13, $p = .02$; Table 2), whereas the 16/8 TRF group showed more significant reductions in fasting blood glucose only at T2 (T1: β = −0.16, $p = .014$; T2: β = −0.25, $p < .001$). However, when compared with the control group, the 16/8 TRF group showed significant reductions in fasting blood glucose at T2 only (β = −0.19, $p = .003$). Furthermore, no statistically significant difference in fasting blood glucose reductions over the study period was identified between the two intervention groups (Table 3).

Lipid Profile

Compared with the control group, the ADF group exhibited more significant improvements in HDL-C across the study period (all *p*s < .05), whereas the 16/8 TRF group showed

Table 2

Generalized Estimating Equation (GEE) Models for the Comparison of Cardiometabolic Outcomes Across Time Between the Control Group and the Two Intervention Groups (With the Control Group as Reference)

Variable [a]	Body Weight (kg)			Body Mass Index (kg/m²)			Waist Circumference (cm)			HDL Cholesterol (mmol/L)		
	β	95% CI	*p*	β	95% CI	*p*	β	95% CI	*p*	β	95% CI	*p*
T1	−0.06	[−0.14, 0.02]	.145	−0.02	[−0.05, 0.01]	.145	−0.15	[−0.49, 0.20]	.406	0.13	[−0.03, 0.29]	.101
T2	−0.24	[−0.49, 0.02]	.074	−0.09	[−0.19, 0.01]	.082	−0.18	[−0.46, 0.11]	.230	−0.05	[−0.20, 0.11]	.565
ADF	4.85	[0.89, 8.80]	.016	0.00	[−1.06, 1.06]	.998	1.66	[−2.57, 5.88]	.442	−0.27	[−0.43, −0.11]	.001
16/8 TRF	2.73	[−0.91, 6.37]	.141	0.45	[−0.37, 1.26]	.285	−0.22	[−4.11, 3.66]	.910	−0.06	[−0.25, 0.12]	.505
ADF × T1	−14.72	[−18.92, −10.52]	< .001	−3.69	[−4.80, −2.57]	< .001	−8.16	[−11.98, −4.34]	< .001	0.28	[0.02, 0.53]	.032
ADF × T2	−14.80	[−19.02, −10.58]	< .001	−3.69	[−4.81, −2.57]	< .001	−8.34	[−12.14, −4.54]	< .001	0.34	[0.08, 0.60]	.009
16/8 TRF × T1	−4.55	[−5.65, −3.45]	< .001	−1.59	[−1.96, −1.22]	< .001	−5.54	[−7.22, −3.86]	< .001	−0.08	[−0.32, 0.16]	.517
16/8 TRF × T2	−4.44	[−5.52, −3.35]	< .001	−1.55	[−1.91, −1.18]	< .001	−5.67	[−7.23, −4.11]	< .001	0.45	[0.14, 0.75]	.004

Note. Only the model estimates of regression coefficients of the dummy variables for group (ADF: 0 = control [reference], 1 = ADF group; 16/8 TRF: 0 = control [reference], 1 = 16/8 TRF group), time points (T1 and T2 with the baseline [T0] as reference), time points, and group interaction terms (ADF × T1, ADF × T2, 16/8 TRF × T1, and 16/8 TRF × T2) are shown for the GEE models. HDL = high-density lipoprotein; LDL = low-density lipoprotein; ADF = alternate-day fasting; TRF = time-restricted fasting; T1 = end of the intervention; T2 = 3-month follow-up.

[a] Gender, marital status, baseline levels of HDL-C, total cholesterol, and physical activity were adjusted. [b] Natural log-transformed before being subjected to GEE analysis.

significant improvements in HDL-C at T2 only (β = 0.45, *p* = .004). Comparing the two intervention groups, the ADF group showed more significant improvements in HDL-C at T1 (β = 0.35, *p* = .009).

In terms of LDL-C, the 16/8 TRF group reported a significant decreased LDL-C at T2 compared with its baseline level (β = −0.68, *p* < .001). No significant differences in LDL-C reduction were observed between the two intervention groups (Table 3).

In terms of total cholesterol, the ADF group reported a more significant reduction in total cholesterol at T1 than either the control group (β = −0.79, *p* = .032) or the 16/8 TRF group (β = −0.80, *p* = .029).

In terms of triglycerides, the 16/8 TRF group exhibited significant reductions at both T1 and T2 (all *p*s < .001; Table 3) from baseline. Compared with the control group, the 16/8 TRF group showed more significant reductions in triglycerides across time (T1: β = −0.34, *p* = .015; T2: β = −0.66, *p* < .001). A more significant increase in triglycerides was found in the ADF group compared with the 16/8 TRF group across time (T1: β = 0.32, *p* = .041; T2: β = 0.46, *p* = .010), indicating that ADF is less effective than 16/8 TRF in reducing triglyceride level (Table 3).

Discussion

This study was designed to examine the effects of two intermittent fasting interventions (ADF and 16/8 TRF) on weight loss, blood glucose, and lipid profile in overweight and obese patients with prediabetes. The findings indicated that both intervention groups achieved significantly better results in terms of reducing body weight, BMI, and waist circumference across the study period than the control group. The ADF group achieved more significant reductions in body weight and BMI over time than the 16/8 TRF group. However, no significant differences between the two intervention groups were observed in terms of reductions in blood glucose or LDL-C.

Alternate-Day Fasting vs. Control

Consistent with previous studies (Trepanowski et al., 2017; Varady et al., 2016), the findings of this study revealed that ADF achieved more-significant reductions in body weight, BMI, and waist circumference than following a usual diet, suggesting that ADF may be a potentially effective weight-loss strategy. A possible mechanism for its effectiveness may be that the intense calorie restriction (e.g., over 24-hour intervals) used in ADF triggers a lipolysis response, which is especially influential in mobilizing fat adipocytes, and thus promotes adipose tissue reduction (Golbidi et al., 2017). Regarding the fasting blood glucose and lipid profile, the results of this study showed that ADF significantly reduced fasting blood glucose and improved HDL-C across time in comparison with a usual diet. Unfortunately, no effects on LDL-C or triglycerides were observed in this study for ADF across time. Different from this study, Kessler et al.'s (2018) study of healthy individuals found no significant reduction in blood glucose or improvement in lipid profile (including HDL-C, LDL-C, total cholesterol, triglycerides) in the ADF group or difference compared with the usual diet group. In another RCT study on obese individuals, ADF did not exhibit any significant within-group effects in terms

LDL Cholesterol (mmol/L)			Total Cholesterol (mmol/L)			Triglycerides (mmol/L)[b]			Blood Glucose (mmol/L)[b]		
β	95% CI	*p*	β	95% CI	*p*	β	95% CI	*p*	β	95% CI	*p*
−0.11	[−0.47, 0.25]	.536	0.08	[−0.51, 0.68]	.788	0.17	[−0.07, 0.41]	.171	0.03	[−0.06, 0.12]	.509
−0.22	[−0.61, 0.18]	.286	−0.84	[−1.45, −0.23]	.007	0.03	[−0.30, 0.36]	.850	−0.01	[−0.08, 0.07]	.896
−0.10	[−0.38, 0.17]	.464	0.16	[−0.34, 0.67]	.528	−0.21	[−0.37, −0.05]	.012	−0.02	[−0.08, 0.03]	.392
−0.40	[−0.67, −0.12]	.005	−0.27	[−0.71, 0.18]	.244	−0.09	[−0.29, 0.10]	.354	−0.06	[−0.13, 0.01]	.088
−0.07	[−0.54, 0.40]	.771	−0.79	[−1.52, −0.07]	.032	−0.02	[−0.29, 0.25]	.892	−0.13	[−0.24, −0.02]	.027
−0.04	[−0.49, 0.42]	.875	−0.62	[−1.31, 0.07]	.076	−0.20	[−0.50, 0.09]	.178	−0.13	[−0.24, −0.02]	.020
−0.25	[−0.71, 0.22]	.298	0.05	[−0.68, 0.77]	.898	−0.34	[−0.61, −0.07]	.015	−0.14	[−0.28, 0.00]	.052
−0.29	[−0.72, 0.15]	.199	0.13	[−0.62, 0.88]	.737	−0.66	[−0.99, −0.33]	< .001	−0.19	[−0.31, −0.06]	.003

of blood glucose or lipid profile reductions during the 3-month intervention period but did exhibit a significant within-group improvement in HDL-C and a significant within-group decrease in triglycerides at 12 months (Sundfør et al., 2018).

The above-noted discrepancies in blood glucose and lipid profile may be attributed to differences in the interval of fasting and calorie restriction policies in ADF interventions among studies. For example, in Trepanowski et al. (2017), caloric consumption was divided between 25% (about 500 kcal) and 125% of calorie needs with a 24-hour interval, which is similar to this study. However, in Sundfør et al. (2018), a 5:2 model was adopted that restricted calories (with 400 kcal for women and 600 kcal for men) on each of two nonconsecutive days in a week and allowed participants to consume a usual diet during the remaining 5 days of that week, whereas in Kessler et al. (2018), the intermittent fasting intervention consisted of one fasting day per week with a maximum calorie intake of 300 kcal on each fasting day. Variations in intervention durations in the above studies may also help explain the conflicting results in blood glucose and lipid profile. In addition, the high dropout rates (38%; Sundfør et al., 2018) and adverse cases (e.g., dizziness, headache, or nausea; Trepanowski et al., 2017) reported with other ADF formats in previous studies may limit their potential in practice. Conversely, in this study, a low dropout rate (only one dropout) and no adverse cases were reported in the ADF group, which may indicate that this ADF format is superior to the ADF formats used in prior studies. Unfortunately, limited comparison studies of different ADF formats have been done, which hinders the identification of the most optimal ADF format.

16/8 Time-Restricted Fasting vs. Control

To date, few studies have been published investigating the effects of TRF. The several pilot studies conducted to examine the effect of TRF reported inconsistent results on weight loss and cardiometabolic risk reduction (Gabel et al., 2018; Moro et al., 2016; Tinsley et al., 2017). Moro et al. compared the effects of an 8-week TRF with those of a normal diet in healthy men, finding an effect of the intervention on weight loss but not on lipid profile. Similar results have also been reported in obese adults by Gabel et al.'s study, which adopted a 12-week-long, 8-hour time-restricted feeding intervention. However, Tinsley et al.'s study failed to observe any in-group or between-group effects of a TRF intervention on fat mass and body fat loss. In this study, an 8-hour feeding window was used, and significant effects for the TRF intervention were found on weight loss and blood glucose reduction (only at T2), as well as on improvements in some lipid profile categories (HDL-C at T2 and triglycerides at both T1 and T2). The fasting hours (e.g., 20 or 16 hours) and eating windows varied across the abovementioned studies, which may explain the discrepancies in findings. A clinical trial compared two TRF regimens, namely, the 6-hour feeding period with dinner before 3 p.m. (early TRF, intervention group) and the 12-hour feeding period with dinner around 10 p.m. (TRF control group), in men with prediabetes (Sutton et al., 2018). Both treatments lasted for 5 weeks. The results showed no significant difference between the two TRF regimens in reducing blood glucose, but the early TRF group reported more significant increases in triglyceride and total cholesterol levels than those in the control group (Sutton

Table 3

Generalized Estimating Equation (GEE) Models for the Comparison of Cardiometabolic Outcomes Across Time Between the Two Intervention Groups (With 16/8 TRF as Reference)

Variable [a]	Body Weight (kg)			Body Mass Index (kg/m²)			Waist Circumference (cm)			HDL Cholesterol (mmol/L)		
	β	95% CI	*p*	β	95% CI	*p*	β	95% CI	*p*	β	95% CI	*p*
T1	−4.61	[−5.71, −3.51]	< .001	−1.61	[−1.98, −1.24]	< .001	−5.69	[−7.38, −4.31]	< .001	0.05	[−0.13, 0.23]	.554
T2	−4.67	[−5.73, −3.62]	< .001	−1.63	[−1.98, −1.28]	< .001	−5.84	[−7.38, −4.31]	< .001	0.40	[0.14, 0.67]	.003
ADF × T1	−10.16	[−14.50, −5.82]	< .001	−2.10	[−3.27, −0.93]	< .001	−2.60	[−6.75, 1.54]	.216	0.35	[0.09, 0.62]	.009
ADF × T2	−10.34	[−14.67, −6.00]	< .001	−2.15	[−3.32, −0.97]	< .001	−2.65	[−6.74, 1.44]	.199	−0.11	[−0.44, 0.23]	.527

Note. Only the model estimates of regression coefficients of the dummy variables for group (0 = 16/8 TRF group [reference], 1 = ADF group; time points [T1 and T2 with the baseline [T0] as reference), time points, and group interaction terms (ADF × T1, ADF × T2) are shown for the GEE models. HDL = high-density lipoprotein; LDL = low-density lipoprotein; ADF = alternate-day fasting; TRF = time-restricted fasting; T1 = end of the intervention; T2 = 3-month follow-up.
[a] Gender, marital status, baseline levels of HDL-C, total cholesterol, and physical activity were adjusted. [b] Natural log-transformed before subjected to GEE analysis.

et al., 2018). The longer fasting hours before blood testing in the TRF group than in the control group may have contributed to the elevated levels of triglycerides and total cholesterol because of the triglyceride reesterification resulting from the lipolysis process during fasting (Soeters et al., 2012), suggesting that different fasting hours preceding blood test may have affected the test results for blood glucose and lipid profiles in the TRF literature. Finally, caution should be used when practicing 16/8 TRF because of the cases of mild dizziness reported in our study.

Alternate-Day Fasting vs. 16/8 Time-Restricted Fasting

Intermittent calorie restriction interventions currently employ a diverse range of dietary strategies because of the lack of a clear definition for this intervention (Sutton et al., 2018). Most previous studies have compared ADF and daily calorie restriction with usual diet in terms of weight loss and cardiometabolic risk factor control (Alhamdan et al., 2016; Headland et al., 2016). Few studies in the literature have compared the effects of ADF and TRF directly. In this study, an ADF with a 24-hour interval was compared with 16/8 TRF, with results showing that ADF had a more significant effect on weight loss in terms of body weight and BMI reduction than 16/8 TRF. Alhamdan et al. synthesized the respective effects of ADF and very-low-calorie dieting (a model of TFR) in meta-analyses, finding ADF to be superior in terms of weight loss in terms of fat mass loss and fat-free mass loss but not in terms of body weight reduction. However, Alhamdan et al.'s study included non-RCT studies, indicating the need of RCTs to verify the findings.

In this study, 16/8 TRF was found to have a more significant effect than ADF in reducing triglycerides. However, no significant difference in either blood glucose or LDL-C reduction effect was observed between the two intervention groups. Because of the limited number of studies comparing the different types of intermittent fasting interventions, it is difficult to compare findings from this study with others. More trials comparing different intermittent fasting interventions are necessary. With regard to the potential adverse effects of these two interventions, three cases of dizziness were reported in the 16/8 TRF group, but no cases of dizziness were reported in the ADF group. This is consistent with Alhamdan et al.'s (2016) study, which reported an increased risk of headache, dizziness, and fatigue with very-low-calorie diet. The occurrence of adverse effects may result in lower adherence to 16/8 TRF than ADF, which may help explain the superiority of ADF in weight loss. In addition, the adverse effects associated with 16/8 TRF may raise concerns when practicing this pattern of dieting.

Limitations

This study was affected by several limitations. First, a relatively short period of follow-up was used, which prevents the observation of the longer-term effects of the interventions. Second, the small sample size in this study may decrease the power to detect significant intergroup differences in some outcomes. Thus, studies using large sample populations are needed to confirm the findings. Third, changes in physical activity during the study period may confound the intervention effects, although the participants were asked to maintain their usual physical activity habits and the changes in physical activity were adjusted in the data analysis. In addition, although strategies were taken to facilitate participant compliance with the calorie restriction requirements, information on actual daily calorie intake was not collected in this study. The actual compliance of participants with the intervention should be tracked in future studies.

Conclusions

The effects of two intermittent fasting interventions (ADF and 16/8 TRF) on weight reduction, blood glucose, and lipids control in overweight or obese adults with prediabetes were investigated in this study. The results provide evidence that the two intermittent fasting interventions examined in this study facilitate reductions in body weight, BMI, and

LDL Cholesterol (mmol/L)			Total Cholesterol (mmol/L)			Triglycerides (mmol/L)[b]			Blood Glucose (mmol/L)[b]		
β	95% CI	*p*	β	95% CI	*p*	β	95% CI	*p*	β	95% CI	*p*
−0.35	[−0.72, 0.03]	.068	0.21	[−0.31, 0.73]	.424	−0.55	[−0.77, −0.33]	< .001	−0.16	[−0.29, −0.03]	.014
−0.68	[−1.02, −0.34]	< .001	−0.14	[−0.74, 0.46]	.655	−0.75	[−1.02, −0.49]	< .001	−0.25	[−0.35, −0.14]	< .001
0.18	[−0.35, 0.72]	.502	−0.80	[−1.52, −0.08]	.029	0.32	[0.01, 0.63]	.041	0.01	[−0.15, 0.18]	.869
0.26	[−0.24, 0.76]	.305	−0.70	[−1.47, 0.08]	.077	0.46	[0.11, 0.81]	.010	0.06	[−0.08, 0.19]	.389

waist circumference that significantly exceed those achieved by following a usual diet. Compared with the usual diet approach, ADF more significantly improved HDL-C and reduced blood glucose over time, whereas 16/8 TRF showed similarly positive effects in reducing triglyceride levels. In terms of the two intervention groups, ADF was superior to 16/8 TRF in reducing body weight and BMI but inferior in reducing triglycerides. These two interventions were comparable in their effects on reducing blood glucose and LDL-C. Intermittent fasting dietary interventions may be recommended for overweight or obese adults with prediabetes to reduce their risk of developing cardiovascular disease. However, attention should be taken when practicing 16/8 TRF because of the identified risk of dizziness. Considering the limitations of this study, future trials using a more rigorous methodology and a long-term follow-up are recommended to verify the findings and to further explore the underlying mechanisms to elucidate the intervention effects.

Implications for Practice

Nurses, who have the most contact with patients of all healthcare professionals, are in a good position to use evidence-based information to inform their practice to provide quality care and benefit patients. Therefore, nurses may incorporate an evidence-based, collaborative intermittent fasting intervention (e.g., ADF) in their practice for overweight or obese patients with prediabetes to prevent the development of diabetes and other cardiovascular diseases.

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Author Contributions

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