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Article type: Clinical Trial

Effects of intermittent very-low calorie diet on glycemic control and cardiovascular risk factors in obese patients with type 2 diabetes mellitus: a randomized controlled trial

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Abbreviated title: Intermittent very-low calorie diet in obese subjects with diabetes

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/JDI.13619

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**Keywords:** Intermittent very-low calorie diet; Caloric restriction; Obesity; Weight loss; Diabetes; Quality of life

**Abstract**

**Aim/Hypothesis:** Very few studies assess the effectiveness of different protocols of intermittent very-low calorie diet (VLCD) in patients with diabetes. This study was designed to compare the effects of 2 days/week and 4 days/week of intermittent VLCD on glycemic control, diabetes remission, metabolic parameters, and quality of life (QoL) in patients with type 2 diabetes and obesity.

**Methods:** Participants with obesity and type 2 diabetes were recruited and randomly assigned to 3 groups, consisting of control, 2 days/week, and 4 days/week of intermittent VLCD. In the intermittent VLCD groups, participants received a 600-kcal diet per day on restricted days and *ad libitum* food consumption on non-restricted days. Glycemic control, rate of diabetes remission, metabolic parameters and QoL were evaluated at baseline, weeks 2, 10 and 20.

**Results:** Forty participants were enrolled. The mean body mass index (BMI) was 30.1 ± 5.9 kg/m² and the mean HbA₁c was 7.4 ± 1.2%. At week 20, there was an improvement in glycemic control in both intermittent VLCD groups with significant decreases in HbA₁c levels and insulin resistance index throughout the study periods. Diabetes remission without needs for medications was equally found in 29% of subjects in both intermittent VLCD groups. Serum triglyceride, body weight, BMI, and fat mass were also significantly decreased in both VLCD groups. No serious adverse events were encountered.

**Conclusion:** Intermittent VLCD was highly effective in achieving optimal glycemic control. The effects of 2 days/week and 4 days/week of intermittent VLCD on diabetes remission were relatively similar.

**ClinicalTrials.gov Identifier:** 20160118001

1. **Introduction**

Type 2 diabetes is a progressive disease with a gradual decrease in beta cell function over time. Recent studies, however, have shown that inducing negative energy balance can reverse the
underlying defects of type 2 diabetes (1). Very-low calorie diet (VLCD) has been reported to rapidly improve glycemic control within 1-2 weeks, resulting in diabetes remission (2-5). Nevertheless, maintaining the beneficial effects of continuous VLCD is quite challenging and long-term diabetes remission is closely related to the ability to maintain long-term weight loss. Unfortunately, weight regain following discontinuation of VLCD is common and is detrimental to glycemic and other metabolic effects that have previously been achieved (3, 6-8). From the DiRECT trial, diabetes remission was closely related to the degree of weight loss maintained at 12 months with the achievement rate of 86% in participants with at least 15 kg weight loss and only 7% of participants who maintained 0-5 kg weight loss (7). Continuous VLCD also requires careful management of oral hypoglycemic agents to prevent hypoglycemia and carries a risk of long-term complications such as micronutrient deficiency (9).

Intermittent VLCD is one of the modalities proposed to achieve weight loss in overweight and obese patients (10-12). Theoretically, it provides more flexibility to optimize individual results; however, data are scarce on the effectiveness of intermittent VLCD in patients with type 2 diabetes (2, 13-15). In addition, there is no standard definition of “intermittent” VLCD and no data are available to directly compare different protocols of intermittent VLCD in achieving glycemic control and diabetes remission.

This study was designed to compare the effects of 2 intermittent VLCD protocols (2 days/week and 4 days/week) with those of the control group on glycemic control, rate of diabetes remission, metabolic parameters, and quality of life, in patients with type 2 diabetes and obesity.

2. Methods

2.1 Study design

This randomized controlled trial utilized an allocation ratio of 1:1:1 to 1 of the 3 groups (2 days per week, 4 days per week of intermittent VLCD and the control group). Randomization was used to generate an online random number allocation and was not blinded. The study was approved by our institutional research ethics committee. This clinical trial was registered under the Thai Clinical Trials Registry (TCTR) number 20160118001. Reporting has been described in details with
CONSORT guideline standard. The trial was conducted at the Diabetes, Hormone, and Metabolism Excellence Center of King Chulalongkorn Memorial Hospital between January 2016 – June 2018.

2.2 Subjects

Participants were recruited using advertisement posted in the Hospital. Inclusion criteria were patients aged between 30-60 years and diagnosed with type 2 diabetes within the previous 10 years with a body mass index (BMI) ≥23 kg/m² and a glycated hemoglobin (HbA₁C) level between 6.5-10%. Type 2 diabetes was defined as a fasting plasma glucose (FPG) level ≥126 mg/dL or a 2-hr plasma glucose level after a 75-gram oral glucose tolerance test (OGTT) ≥200 mg/dL or use of glucose-lowering medication(s). Exclusion criteria were fasting C-peptide level <1 ng/mL, previous use of insulin, previous treatment with a thiazolidinedione or a glucagon-like peptide-1 receptor agonist in the past 3 months, serum creatinine more than 1.5 mg/dL, and serum alanine aminotransferase (ALT) more than 2.5-fold above the upper limit of reference range.

2.3 Interventions

The study protocol was composed of 2 periods: a 2-week run-in period and an 18-week intermittent caloric restriction period. In the 2-week run-in period, participants were tried on VLCD (total calorie intake of 600 kcal/day) for 10 days to assess compliance. In the 18-week intermittent caloric restriction period, participants received 2 or 4 non-consecutive days/week of intermittent VLCD. Ad libitum food consumption was allowed on non-restricted days. A calorie-restricted diet protocol in our study consisted of 55% carbohydrate, 15% protein, and 30% fat. The calories in our study were divided evenly among the three meals. In some cases, 200 mL of Once-pro® (Thai Otsuka Pharmaceutical®, Thailand) was provided to replace one meal. Non-starchy vegetables and other energy-free beverages were allowed on restricted days. Subjects were encouraged to consume a minimum of 2,500 ml of water daily. One daily tablet of multivitamin was provided throughout the study. In the control group, participants received a normal diet of 1,500-2,000 kcal/day throughout the study period and continued to receive usual standard diabetes care. All participants were encouraged to continue their usual physical activities and were in close contact with an endocrinologist using smartphones to ensure compliance and safety throughout the study periods. Appointments were made...
with an endocrinologist and a dietitian every 2 weeks for 20 weeks. Blood chemistries, metabolic parameters, body weight, body composition and quality of life were evaluated during each study period. Dietary record was used to assess dietary compliance.

2.4 Medication protocol

All participants were required to self-monitor their blood glucose levels by a fingerstick at least twice per week and when necessary to prevent hypoglycemia or hyperglycemia. The records of blood glucose levels were reviewed at each clinical visit. The medical management protocol was developed under Thai national clinical guideline and consulted with an endocrinologist. At the commencement of VLCD, the dosages of glucose-lowering medications were reduced by 50%. During the ensuing run-in period, glucose-lowering medications were either decreased or discontinued by an endocrinologist based on the glycemic control. The protocol required discontinuation of a sulfonylurea if the baseline HbA$_1C$ level was $\leq$6.5%. If the HbA$_1C$ level was >6.5% but <9%, a sulfonylurea was discontinued on the energy restriction days only. During the intervention period, if the mean of all two-week blood glucose readings was $\leq$140 mg/dL, a sulfonylurea was either decreased or discontinued first, followed by an alpha-glucosidase inhibitor and lastly metformin. Medications were reinitiated if the mean of all two-week blood glucose readings was >140 mg/dL. If the mean level was >200 mg/dL, medications were increased in a reverse order following the Thai national clinical guideline. Medication effect score (MES) was used to quantify diabetes medication changes (13). The MES was calculated as the percentage of maximum daily dose for each medication multiplied by an adjustment factor. An adjustment factor was the reported median absolute decrease in HbA$_1C$ for each medication (25). A higher score reflects a high use of the medication.

2.5 Outcomes and measurements

The primary outcomes were changes in glycemic control (plasma glucose and HbA$_1C$ levels) and the rate of diabetes remission, defined as a FPG level <126 mg/dL and a HbA$_1C$ level <6.5% in the absence of pharmacologic therapy for diabetes, at the end of the study. The secondary outcomes
were changes in insulin secretion, insulin sensitivity, anthropometric parameters, cardiovascular risk factors, and quality of life.

All outcome data were collected on all participants at baseline, weeks 2, 10 and 20. The OGTT-based measurement of insulin secretion, insulin sensitivity and insulin resistance were performed, in which blood was sampled at 0, 30, 60, 90 and 120 minutes after a 75-g OGTT to measure glucose, C-peptide and insulin concentrations. Homeostasis model assessment-insulin resistance (HOMA-IR) was calculated using the original equation \[(\text{fasting plasma insulin (mU/L}) \times \text{fasting plasma glucose (mmol/L)})/22.5\]. Matsuda index was derived to represent both hepatic and peripheral insulin sensitivity \[\left[\frac{10,000}{\sqrt{\text{fasting glucose} \times \text{fasting insulin}}}\right] \text{(mean glucose x mean insulin)}\], whereas insulinogenic index indicated insulin response to a glucose challenge \[\Delta \text{insulin (0-30 min)}/\Delta \text{glucose (0-30 min)}\]. Lastly, oral disposition index, a composite measure of both insulin secretion and insulin sensitivity, was also determined \[\left(1/\text{fasting insulin}\right) \times \left(\Delta \text{insulin (0-30 min)}/\Delta \text{glucose (0-30 min)}\right)\]. Samples for insulin and C-peptide measurements were frozen at -20° celsius for subsequent analysis using a solid phase two-site chemiluminescence immunoassay kit (SIEMENS, Erlangen, Germany) with an IMMULITE 1000 analyzer.

Safety parameters including complete blood count (CBC), liver function, renal function, electrolyte, and lipid levels were determined in the central laboratory. Anthropometric measurement was collected by use of body composition analysis (TANITA model, BC-418). Quality of life (QoL) was assessed using the SF-36 questionnaire, which measured eight health concepts: (1) physical functioning, (2) role limitations due to physical health problems, (3) bodily pain, (4) general health perceptions, (5) vitality, energy or fatigue, (6) social functioning, (7) role limitations due to emotional problems, and (8) general mental health. The eight scaled scores were the weighted sums of the questions in their section. Each scale was directly transformed into a 0-100 scale on the assumption that each question carried equal weight and a higher score indicated a better health status.

2.6 Statistical analysis
Power analysis was used to calculate the sample size based on data by Williams et al. (13). Forty-two subjects (14 subjects in each group) were needed to provide 90% statistical significance to detect differences in an expected proportion of 0.95.

Statistical analyses were performed using SPSS 17.0 software. All data were presented as mean ± standard error of the mean (SEM). Chi-square ($\chi^2$) test was used to analyze differences between groups at baseline. Analysis of variance (ANOVA) with repeated measure was used to detect changes in metabolic parameters over time during the study periods. Post hoc analysis was performed using the Bonferroni correction. The primary analysis was done according to the intention to treat analysis protocol. Sensitivity analysis using the last observation carried forward (LOCF) method assumption was performed to impute missing data. Analysis was also performed using a linear mix model to adjust the effects of diabetes medications. Logistic regression analysis was used to determine independent factors associated with the primary outcomes at week 20. A $p$-value <0.05 was considered statistically significant.

3. Results

3.1 Subject Characteristics

A total of 42 subjects with obesity and type 2 diabetes were recruited but 2 were excluded due to meeting the exclusion criteria (Figure 1). A total of 40 participants (29 women and 11 men) entered the study with 14 participants in the 2 days/week intermittent VLCD group, 14 participants in the 4 days/week intermittent VLCD group and the remaining 12 participants in the control group. All participants completed the study with no drop-outs. Baseline subjects’ characteristics are shown in Table 1. The mean age ($\pm$ SEM) was 49.6 ± 7.9 years and the mean BMI ($\pm$ SEM) was 30.1 ± 5.9 kg/m$^2$. The mean duration of diabetes ($\pm$ SEM) was 4.9 ± 3.1 years and the mean HbA$_{1C}$ level ($\pm$ SEM) was 7.4 ± 1.1%. More than half of the study participants had a history of hypertension and dyslipidemia but none had established cardiovascular diseases. The differences among the 3 groups were not statistically significant. The majority of participants were prescribed glucose-lowering medications as monotherapy or dual therapy. A number of glucose-lowering medications prescribed at baseline were comparable. Metformin was most commonly prescribed (100% in the control group,
79% in the 2 days/week intermittent VLCD group and 93% in the 4 days/week intermittent VLCD group, \( p=0.174 \). The use of sulfonylurea was also not significantly different among the three groups (50% in the control group, 29% in the 2 days/week intermittent VLCD group and 57% in the 4 days/week intermittent VLCD group, \( p=0.289 \)). The overall compliance to intermittent VLCD by self-report dietary records in both groups was excellent (more than 95%).

### 3.2 Changes in glycemic control and rate of diabetes remission

After VLCD, rapid improvements in FPG and 2-hour plasma glucose levels after an OGTT were observed at week 2 in both of the intermittent VLCD groups compared to those of the control group and were sustained until week 20 as shown in Figure 2 and Table 2.

The 3 groups did not differ in FPG levels at the end of the study. However, subjects in the 4 days/week group were more likely to attain lower FPG, 2-hour plasma glucose and HbA\(_1c\) levels compared to those in the 2 days/week and control groups (Table 2).

At week 20, the change from baseline in the mean (± SEM) FPG level was -39.7 (± 12.5) mg/dL in the 4 days/week group (\( p=0.003 \)), -25.1 (± 12.5) mg/dL in the 2 days/week group (\( p=0.051 \)) as compared with -7.9 (± 13.5) mg/dL in the control group (\( p=0.56 \)), with a mean difference (each of the intermittent VLCD groups vs. placebo) of 17.3 (± 14.6) and 6.3 (± 14.6) mg/dL (\( p= 0.244 \) and 0.669, respectively). The mean difference in the change in the mean FPG level between the 2 days/week and the 4 days/week intermittent VLCD groups was 10.7 mg/dL (95% CI -10.3 to 33.0, \( p=0.439 \)). Similarly, greater improvements in glucose tolerance after an OGTT were observed in both of the intermittent VLCD groups than that in the control group (Table 2).

At week 20, the mean HbA\(_1c\) (± SEM) fell by 1.2 ± 0.3% in the 4 days/week group (\( p <0.001 \)), 0.7 ± 0.3% in the 2 days/week group (\( p=0.042 \)), and by 0.1 ± 0.3% in the control group (\( p=0.862 \)). In addition, the 3 groups differed in the percentage of patients who attained a HbA\(_1c\) level of <6.5% at week 20, i.e. 10 participants (64%) in the 4 days/week group achieved a HbA\(_1c\) level of <6.5%, whereas only 5 patients (29%) in the 2 days/week group and 2 patients (25%) in the control group although the difference did not reach statistical significance (\( p=0.07 \)).
At the end of week 20, diabetes remission without need for glucose-lowering medications was found in 29% of participants in both the 2 days/week and the 4 days/week of intermittent VLCD groups compared with none of the participants in the control group (p=0.117, Table 3, Figure 3). Glucose-lowering medications were successfully withdrawn in 58% in the control group, 64% in the 2 days/week group, and 86% in the 4 days/week group (p=0.267, Table 3, Figure 3). The total mean (± SEM) MES of sulfonylurea and metformin decreased significantly over time and were relatively similar in all 3 groups (Table 4), suggesting the lower use of the medications.

After adjusting for different medication use and dosage changes among different subjects with a linear mix model analysis, similar results in plasma glucose levels were obtained. In a stepwise linear regression, no significant effects of age, duration of diabetes, HbA1C level or changes in body weight and body composition were observed on diabetes remission.

3.3 Changes in insulin resistance/insulin sensitivity and insulin secretion indices

In both intermittent VLCD groups, there were significant improvements in insulin resistance as reflected in HOMA-IR at week 20 (Table 2), and the mean difference in changes in HOMA-IR between the 2 days/week group and the 4 days/week group at week 20 was not significantly different (mean difference 0.1 (95% CI -1.9 to 2.0, p=0.924). An improvement in Matsuda index, an index of insulin sensitivity, was seen only in the 4 days/week group at week 10, but not at week 20. Changes in the insulinogenic index, an index of insulin secretion, indicated a significant improvement in the 4 days/week group only at week 20. Lastly, significant changes in the disposition index, a composite measure of insulin secretion and insulin sensitivity, were also observed in the 4 days/week group only at week 20 (Table 3).

3.4 Changes in body weight and body composition

All 3 groups had significant decreases in weight and BMI at weeks 10 and 20 (Table 2). The average weight loss (± SEM) at week 20 was 8.6 ± 1.3 kg (equivalent to 10.4% of participants’ initial body weight) in the 4 days/week intermittent VLCD group, 5.5 ± 1.3 kg (equivalent to 7.1% of their initial body weight) in the 2 days/week group, and 4.9 ± 1.4 kg (equivalent to 6.7% of their initial body weight) in the control group. We found no significance differences in changes in body weight
among the 3 groups. Similarly, the mean BMI (± SEM) decreased by 3.6 ± 0.5 kg/m² in the 4
days/week group, 2.1 ± 0.5 kg/m² in the 2 days/week group and 2.0 ± 0.6 kg/m² in the control group
with no significant differences among the 3 groups.

Weight loss was predominantly due to fat loss. There were marked decreases in the percentage
of fat and fat mass in all groups, and there were no significant differences among the 3 groups at
weeks 10 and 20 (Table 2).

3.5 Changes in metabolic parameters

At weeks 10 and 20, the mean serum triglyceride levels were significantly decreased in both
the 4 days/week and the 2 days/week groups (Table 2). Changes in serum levels of total cholesterol,
LDL-cholesterol, and HDL-cholesterol were, however, not statistically significant when compared
with their baseline values.

Participants in the 4 days/week intermittent VLCD group also had significant decreases in
AST and ALT levels and systolic blood pressure at weeks 10 and 20 (Table 2). There were no
significant differences among the 3 groups in terms of changes in serum albumin,
hemoglobin/hematocrit, or creatinine at week 20 (data not shown).

3.6 Changes in quality of life

There was a significant improvement in quality of life scores in both intervention groups at
week 10 and only in the 4 days/week at week 20 (Table 2), which was primarily due to a significantly
higher scores in certain domains, such as role limitations due to physical health and health change
domains (data not shown).

3.7 Safety/side effects

During the 20-week period, no serious adverse events were observed. No severe hypoglycemia
was found.
4. Discussion

To our knowledge, this is the first randomized controlled trial comparing 2 days/week of intermittent VLCD with 4 days/week and the control group in patients with obesity and type 2 diabetes. Our current study demonstrated that either 2 days/week or 4 days/week of intermittent caloric restriction was relatively comparable and highly effective in improving glycemic control. Glucose-lowering medications could be successfully withdrawn in 64-86% in the intermittent VLCD groups. At the end of the study, diabetes remission was found in almost one-third of the subjects in both of the VLCD groups.

VLCD has been shown to improve glycemic control, resulting in diabetes remission. We and others have previously reported that continuous VLCD is highly effective in inducing short-term remission of diabetes (6-8), however, our long-term result has shown that only one-third of subjects remain in optimal glycemic control without restarting diabetes medications 12 months after VLCD has ended (6). The beneficial effects of VLCD seem to diminish after the recurrence of weight increase (3, 6, 7). In this regard, the use of intermittent VLCD might be an interesting option for obese patients who find it difficult to adhere to continuous VLCD to maintain weight loss (16), since intermittent VLCD provides more flexibility than continuous VLCD (17-24).

So far, there have been only a few of intermittent VLCD studies performed in obese patients with type 2 diabetes (2, 13-15). The majority of studies have shown that intermittent VLCD could improve glycemic control with the reduction of HbA\textsubscript{1C} of approximately 0.3-1.5%. The change in HbA\textsubscript{1C} level in our study (0.7-1.2%) is comparable to the changes seen in the previous trials. Changes in body composition such as body weight, fat mass, and fat free mass are also similar to what has been reported in the previous trials of obese subjects without type 2 diabetes (15, 20, 25-28).

Currently, it should be noted that there is no standard definition of “intermittent” caloric restriction/VLCD, and it is extremely difficult to compare various methods of intermittent VLCD among various studies because of the differences in the study populations, the duration of studies and the types of VLCD. Nevertheless, the main result of our study showed that the beneficial effects of intermittent VLCD could be achieved using only 2 days/week of VLCD and the rate of diabetes remission was comparable to that of 4 days/week, although the beneficial effects in several metabolic parameters were more pronounced in the 4 days/week group.
A recent study comparing intermittent energy restriction (2 days/week of 500-600 kcal/d diet) with continuous energy restriction (1,200-1,500 kcal/d diet, 7 days/week) in patients with type 2 diabetes has shown that glycemic improvement is comparable (25). At 12 months, the reductions in the mean HbA_1c level, weight change, BMI, fat mass, and fat-free-mass were relatively similar between the intermittent and the continuous energy restriction groups (15).

The mechanism by which intermittent energy restriction modulates diabetes remission is not well understood. In our study, we found a significant reduction in HOMA-IR, a marker of insulin resistance, but we did not observe a significant change in Matsuda index, which represented whole body insulin sensitivity. In the 4 days/week intermittent VLCD group, we observed improvements in insulinogenic index and disposition index, suggesting that intermittent VLCD may exert beneficial effects on insulin secretion or beta cell function. These results are similar to those of our previous study using continuous VLCD for 8 weeks, which has shown improvement in both insulin resistance and beta cell function (6).

Our study has certain limitations. First, the sample size was small and was restricted to an Asian population not on insulin therapy only. Second, the slight improvement in the control group might be due to minor differences in baseline data or it could be attributed to some contamination in subjects with intention to lose weight. We observed deliberate weight loss in the control group, which could have affected the outcomes and statistical comparisons between groups. Third, although we provided VLCD and recorded caloric intake on restricted days, we allowed ad libitum intake on non-restricted days and did not record caloric intake on those days. Therefore, participants might consume less caloric intake on non-restricted days. Lastly, our study was limited to 20 weeks, and longer-term follow-up data are needed to evaluate the durability of diabetes remission.

5. Conclusion

Our study demonstrated that intermittent caloric restriction for 2 days/week and 4 days/week were highly effective in achieving glycemic control without serious adverse events. Improvement in glycemic control was associated with a reduction in insulin resistance and improvements in insulin secretion, body weight, BMI, body composition, cardiovascular risk factors and quality of life. The rate of diabetes remission in subjects using VLCD 2 days/week was comparable to that of 4
days/week, suggesting that this modality of treatment may have great clinical implications for patients with type 2 diabetes and obesity.

Acknowledgements

This work was supported by National Research Council of Thailand and Heath Systems Research Institute (HRSI). Once-pro® was provided by Thai Otsuka Pharmaceutical®, Thailand and glucometer machines were provided by Roche®. The funding sources/sponsors have no role in the study design, collection, analysis and interpretation of data, writing of the manuscript, and decision to submit the article for publication. The authors acknowledge contribution made by all participants in the study and wish to express our utmost appreciation to their efforts and dedications.

Disclosure

The study protocol was ethically reviewed and approved by our institutional research ethic committee (Chulalongkorn University) on 17th November 2016. The certificate of approval number 046/2016.

MU, PR, SL, WS, KB and WK declare that they have no conflict of interest. MU and WK coauthored a Thai pocketbook with copyright on low calorie menus

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Figure legends

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Fig. 1 CONSORT flow diagram.

Fig. 2 (A) Changes in fasting plasma glucose (FPG), (B) 2-hr plasma glucose after an OGTT (2-hr PPG), and (C) HbA\textsubscript{1c} during the study periods. *: $P<0.01$, **: $P<0.001$ compared to values at week 0.

Fig. 3 The percentage of diabetes remission at week 20, defined as a fasting plasma glucose (FPG) level <126 mg/dL and HbA\textsubscript{1c} <6.5% without the use of glucose-lowering medications (left panel) and the percentage of subjects with no glucose-lowering medications at week 20 (right panel). VLCD: very-low calorie diet
### Table 1. Baseline characteristics of the subjects

| Variable                              | Control (n=12) | 2 days/wk intermittent VLCD (n=14) | 4 days/wk intermittent VLCD (n=14) |
|---------------------------------------|----------------|-----------------------------------|-----------------------------------|
| **Baseline demographics**             |                |                                   |                                   |
| Age (y)                               | 52.0 ± 6.0     | 49.5 ± 7.2                        | 47.6 ± 7.9                        |
| Female sex (%)                        | 83.3           | 85.7                              | 50.0                              |
| Duration of diabetes (y)              | 5.2 ± 3.2      | 5.5 ± 3.0                         | 3.1 ± 2.8                         |
| **Number of oral diabetes medication (%)** |                |                                   |                                   |
| Diet alone                            | 0              | 21                                | 7                                 |
| 1                                     | 42             | 50                                | 36                                |
| ≥2                                    | 58             | 29                                | 57                                |
| **Types of oral diabetes medication (%)** |                |                                   |                                   |
| Metformin                             | 100            | 79                                | 93                                |
| Sulfonylureas                         | 50             | 29                                | 57                                |
| Hypertension (%)                      | 45.5           | 64.3                              | 66.7                              |
| Dyslipidemia (%)                      | 72.7           | 71.4                              | 75.0                              |
| **Glycemic control and indices**      |                |                                   |                                   |
| FPG (mg/dL)                           | 145.1 ± 14.0   | 156.0 ± 13.0                      | 159.6 ± 12.8                      |
| 2-hr glucose after an OGTT (mg/dL)   | 306.7 ± 26.4   | 318.2 ± 24.4                      | 349.2 ± 24.4                      |
| HbA1c (%)                             | 6.9 ± 0.3      | 7.5 ± 0.3                         | 7.7 ± 0.3                         |
| HOMA-IR                               | 3.66 ± 1.14    | 4.31 ± 1.06                       | 4.52 ± 1.06                       |
| Matsuda index                         | 5.24 ± 0.96    | 4.94 ± 0.89                       | 4.71 ± 0.89                       |
| Insulinogenic index                   | 0.12 ± 0.04    | 0.10 ± 0.03                       | 0.14 ± 0.03                       |
| Disposition index                     | 0.44 ± 0.11    | 0.16 ± 0.14                       | 0.36 ± 0.10                       |
| **Metabolic parameters/cardiovascular risk factors** | | | |
| Total cholesterol (mg/dL)             | 188.8 ± 12.5   | 181.1 ± 11.5                      | 201.5 ± 11.5                      |
| Triglyceride (mg/dL)                  | 148.2 ± 18.2   | 170.4 ± 16.9                      | 139.3 ± 16.9                      |
| HDL-cholesterol (mg/dL)               | 50.3 ± 2.4     | 51.4 ± 2.3                        | 43.7 ± 2.2                        |
| LDL-cholesterol (mg/dL) | AST (U/L) | ALT (U/L) | ALP (IU/L) | Albumin (g/dL) | Creatinine (mg/dL) | Systolic BP (mmHg) | Diastolic BP (mmHg) |
|------------------------|-----------|-----------|------------|----------------|------------------|------------------|------------------|
| 118.1 ± 11.8           | 21.7 ± 3.0 | 24.5 ± 3.9 | 72.0 ± 6.5 | 4.4 ± 0.1      | 0.6 ± 0.1        | 140.4 ± 5.5      | 80.3 ± 4.3       |
| 104.6 ± 10.9           | 19.6 ± 2.8 | 19.5 ± 3.6 | 67.4 ± 6.0 | 4.3 ± 0.1      | 0.7 ± 0.04       | 122.9 ± 5.1      | 74.9 ± 4.0       |
| 135.2 ± 10.9           | 31.1 ± 2.8 | 32.9 ± 3.6 | 71.6 ± 6.0 | 4.3 ± 0.1      | 0.7 ± 0.1        | 140.9 ± 5.1      | 85.6 ± 4.0       |

**Anthropometric parameters**

| Body weight (kg) | BMI (kg/m²) | Waist circumference (cm) | %Fat (%) | Fat mass (kg) | Fat free mass (kg) | Muscle mass (kg) | Total body water (kg) |
|------------------|-------------|--------------------------|----------|---------------|-------------------|------------------|----------------------|
| 73.6 ± 6.0       | 29.1 ± 1.7  | 93.3 ± 3.9               | 36.0 ± 2.2 | 26.4 ± 3.3    | 47.2 ± 3.8        | 44.9 ± 3.6        | 46.9 ± 2.0           |
| 77.2 ± 5.5       | 29.9 ± 1.6  | 94.8 ± 3.6               | 37.7 ± 2.0 | 29.7 ± 3.1    | 45.7 ± 3.5        | 45.5 ± 3.4        | 45.6 ± 1.8           |
| 82.9 ± 5.5       | 31.0 ± 1.6  | 96.2 ± 3.8               | 32.1 ± 2.0 | 27.9 ± 3.1    | 55.1 ± 3.5        | 52.4 ± 3.4        | 47.8 ± 1.8           |

**Quality of life**

| SF-36 (point) | |
|---------------|------------------|
| 2,563 ± 163   | 2,444 ± 151      | 2,081 ± 151      |

Data are mean ± standard error of the mean, unless otherwise specified.

Abbreviations: VLCD, very-low calorie diet; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; HbA₁c, hemoglobin A₁c; HOMA-IR, homeostasis model assessment-insulin resistance; HDL, high-density lipoprotein; LDL, low-density lipoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; BP, blood pressure; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); SF-36, short form 36 items (measuring eight health concepts: (1) physical functioning,(2) role limitations due to physical health problems, (3)bodily pain, (4) general health perceptions, (5) vitality, energy or fatigue, (6) social functioning, (7) role limitations due to emotional problems, and (8) general mental health). It consisted of eight scaled scores, which were the weighted sums of the questions in their section. Each scale was directly transformed into a 0-100 scale on the assumption that each question carried equal weight; a higher score indicated a better health status.
Table 2. Effects of intermittent VLCD on various parameters and mean changes at weeks 10 and 20

| Variable                   | Week 10                                      | Week 20                                      |
|----------------------------|----------------------------------------------|----------------------------------------------|
|                            | Control (n=12) | 2 days/wk intermittent VLCD (n=14) | 4 days/wk intermittent VLCD (n=14) | Control (n=12) | 2 days/wk intermittent VLCD (n=14) | 4 days/wk intermittent VLCD (n=14) |
|                            | Mean ± SEM     | Mean ± SEM     | Mean ± SEM     | Mean ± SEM     | Mean ± SEM     | Mean ± SEM     |
| Mean difference ± SEM      |                |                |                |                |                |                |
| p-value by time            |                |                |                |                |                |                |
| Glycemic control and indices | FPG (mg/dL)     | 140.6 ± 9.2 | 134.3 ± 8.5 | 107.9 ± 8.5 | 137.2 ± 10.7 | 130.9 ± 9.9 | 119.9 ± 9.9 |
|                           | -4.5 ± 12.8 | 0.728           | -21.7 ± 11.9 | 0.075           | -51.7 ± 11.9 | <0.001         | -7.9 ± 13.5 | 0.560           | -25.1 ± 12.5 | 0.051           | -39.7 ± 12.5 | 0.003           |
|                           | 2-hr glucose after OGTT (mg/dL)               | 291.0 ± 24.8 | 266.4 ± 23.0 | 225.3 ± 23.0 | 317.3 ± 22.5 | 256.3 ± 20.8 | 235.9 ± 20.8 |
|                           | -15.7 ± 25.4 | 0.541           | -51.9 ± 23.5 | 0.033           | -123.9 ± 23.5 | <0.001         | 10.7 ± 23.3 | 0.650           | -61.9 ± 21.6 | 0.007           | -113.4 ± 21.6 | <0.001         |
|                           | HbA1c (%)     | 6.7 ± 0.3      | 6.7 ± 0.2      | 6.4 ± 0.2      | 6.9 ± 0.3      | 6.8 ± 0.2      | 6.4 ± 0.3     |
|                           | -0.2 ± 0.3    | 0.497           | -0.8 ± 0.3    | 0.010           | -1.2 ± 0.3    | <0.001         | -0.1 ± 0.3 | 0.862           | -0.7± 0.3    | 0.042           | -1.2 ± 0.3    | <0.001         |
|                            | HOMA-IR       | 3.05 ± 0.77    | 2.57 ± 0.71    | 2.54 ± 0.71    | 3.47 ± 0.74    | 2.48 ± 0.68    | 2.39 ± 0.68   |
|                           | -0.61 ± 1.00  | 0.546           | -1.74 ± 0.93  | 0.069           | -1.98 ± 0.93  | 0.040           | -0.19 ± 0.94 | 0.837           | -1.83 ± 0.86  | 0.041           | -2.14 ± 0.87  | 0.018           |
|                            | Matsuda index | 5.39 ± 1.48    | 5.37 ± 1.37    | 7.83 ± 1.37    | 6.22 ± 1.40    | 6.24 ± 1.30    | 6.46 ± 1.30   |
|                           | 0.15 ± 1.18   | 0.899           | 0.43 ± 1.09   | 0.694           | 3.11 ± 1.09   | 0.007           | 0.98 ± 1.17 | 0.406           | 1.30 ± 1.08  | 0.237           | 1.74 ± 1.08  | 0.115           |
|                            | Insulinogenic index | 0.16± 0.05 | 0.10 ± 0.05    | 0.23± 0.05    | 0.15± 0.06    | 0.13± 0.06    | 0.28 ± 0.06   |
|                           | 0.04± 0.05    | 0.408           | -0.01 ± 0.04  | 0.860           | 0.08± 0.04    | 0.067           | 0.04± 0.06 | 0.552           | 0.03± 0.06  | 0.625           | 0.14± 0.06  | 0.019           |
| Disposition index          | 0.47 ± 0.35   | 0.48 ± 0.33    | 1.03 ± 0.33    | 0.51 ± 0.23    | 0.33 ± 0.21    | 1.00± 0.21     |
|                           | 0.03 ± 0.37   | 0.938           | 0.33± 0.35   | 0.352           | 0.67± 0.35    | 0.060           | 0.07± 0.24 | 0.765           | 0.17± 0.22  | 0.434           | 0.64± 0.22  | 0.006           |
| **Metabolic parameters/cardiovascular risk factors** | **Total cholesterol (mg/dL)** | **Triglyceride (mg/dL)** | **HDL-cholesterol (mg/dL)** | **LDL-cholesterol (mg/dL)** | **AST (U/L)** | **ALT (U/L)** | **Systolic BP (mmHg)** | **Diastolic BP (mmHg)** | **Anthropometric parameters** |
|--------------------------------------------------|-----------------------------|-------------------------|----------------------------|-----------------------------|--------------|--------------|-----------------------|--------------------------|--------------------------|
| **Total cholesterol (mg/dL)**                      | 187.6 ± 11.0                | 184.9 ± 10.2            | 195.2 ± 10.2                | 200.0 ± 12.4                |              |              |                       |                          |                          |
| **Triglyceride (mg/dL)**                           | -1.3 ± 12.1                 | -38.9 ± 17.1            | 0.29                       | -37.4 ± 17.1                | 0.035        | -1.3 ± 15.1  | 0.241                 | 0.857                    | 0.191                    |
| **HDL-cholesterol (mg/dL)**                        | 115.0 ± 11.0                | 111.6 ± 10.7            | 127.1 ± 11.6                | 120.2 ± 10.7                |              |              |                       |                          |                          |
| **LDL-cholesterol (mg/dL)**                        | -3.1 ± 11.5                 | 7.0 ± 10.6              | 0.514                      | -1.6 ± 10.6                 | 0.883        | 9.0 ± 12.7   | 9.0 ± 12.7            | 0.483                    | 0.191                    |
| **AST (U/L)**                                     | 19.4 ± 2.6                  | 16.4 ± 2.5              | 22.3 ± 2.5                 | 19.1 ± 2.7                  | 18.8 ± 2.5   | 21.8 ± 2.5   |                       |                          |                          |
| **ALT (U/L)**                                     | 19.0 ± 2.3                  | 15.1 ± 2.1              | 23.5 ± 2.1                 | 20.3 ± 2.2                  | 13.7 ± 2.1   | 24.6 ± 2.1   |                       |                          |                          |
| **Systolic BP (mmHg)**                             | 133.4 ± 5.0                 | 128.3 ± 4.6             | 127.4 ± 4.6                | 125.5 ± 4.0                 | -14.9 ± 5.0  | 0.005        | -12.4 ± 6.6          | 0.794                    | -9.7 ± 4.6               |
| **Diastolic BP (mmHg)**                            | 78.0 ± 3.4                  | 79.2 ± 3.2              | 74.7 ± 3.2                 | 73.8 ± 3.3                  | -2.3 ± 4.9   | 0.042        |                       |                          |                          |
| **Anthropometric parameters**                      |                            |                          |                            |                            |              |              |                       |                          |                          |
| **Weight (kg)**                                   | 68.7 ± 5.6                  | 71.7 ± 5.1              | 76.1 ± 5.1                 | 68.7 ± 5.7                  | 71.7 ± 5.2   | 74.3 ± 5.2   |                       |                          |                          |
| **BMI (kg/m²)**                                   | -4.9 ± 1.1                  | -5.5 ± 1.0              | -6.8 ± 1.0                 | -4.9 ± 1.4                  | 0.002        | -5.5 ± 1.3   | -8.6 ± 1.3           | -0.001                   | -8.6 ± 1.3               |
| **Fat mass (kg)**                                 | 23.0 ± 3.2                  | 25.7 ± 3.0              | 23.4 ± 3.0                 | 22.6 ± 3.2                  | 25.2 ± 3.0   | 22.4 ± 3.0   |                       |                          | -0.001                   |
| **Fat free mass (kg)**                            | 45.7 ± 3.5                  | 46.0 ± 3.3              | 52.7 ± 3.3                 | 46.1 ± 4.0                  | 46.5 ± 3.7   | 49.8 ± 3.7   |                       |                          |                          |
| Quality of life | SF-36 (point) | 2730 ± 116 | 2785 ± 107 | 2866 ± 107 | 2684 ± 127 | 2757 ± 118 | 2697 ± 118 |
|----------------|----------------|-------------|-------------|-------------|-------------|-------------|-------------|
|                |                | 166 ± 158   | 341 ± 146   | 784 ± 146   | 120 ± 171   | 313 ± 158   | 615 ± 158   |
|                |                | 0.299       | 0.025       | <0.001      | 0.485       | 0.055       | <0.001      |

Abbreviations: VLCD, very-low calorie diet; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; HbA1c, hemoglobin A1c; HOMA-IR, homeostasis model assessment-insulin resistance; HDL, high-density lipoprotein; LDL, low-density lipoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BP, blood pressure; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); SF-36, short form 36 items
Table 3. The rate of diabetes remission and discontinuation of diabetes medications at weeks 10 and 20

| Variable                        | Time         | Group                            | Total  |
|---------------------------------|--------------|----------------------------------|--------|
|                                 |              | Control (n=12)                   |        |
|                                 |              | 2 days/wk intermittent VLCD (n=14)|        |
|                                 |              | 4 days/wk intermittent VLCD (n=14)|        |
| Diabetes remission<sup>a</sup>  | Week 10      | 2 (17%)                          | 9 (23%)|
|                                 | Week 20      | 0 (0%)                           | 8 (20%)|
| Discontinuation of diabetes medications<sup>b</sup> | Week 10      | 7 (58%)                          | 31 (78%)|
|                                 | Week 20      | 7 (58%)                          | 28 (70%)|

Abbreviations: VLCD, very-low calorie diet.

<sup>a</sup> Diabetes remission was defined as a fasting plasma glucose level <126 mg/dL and HbA<sub>1c</sub> level <6.5% in the absence of pharmacologic therapy for diabetes, at the end of the study.

<sup>b</sup> Diabetes medication protocol:

During run-in period, a sulfonylurea was discontinued if the baseline HbA<sub>1c</sub> level was ≤6.5%. If the HbA<sub>1c</sub> level was >6.5% but <9%, a sulfonylurea was discontinued on the energy restriction days only.

During the intervention period, if the mean of all two-week blood glucose readings was ≤140 mg/dL, a sulfonylurea was either decreased or discontinued first, followed by an alpha-glucosidase inhibitor and lastly metformin.

Medications were reinitiated if the mean of all two-week blood glucose readings was >140 mg/dL. If the mean level was >200 mg/dL, medications were increased in a reverse order.
### Table 4. Medication effect score (MES) of sulfonylurea and metformin at various time points

| Variable                  | Groups                             | Week 0                      | Week 10                      | Week 20                      |
|---------------------------|------------------------------------|-----------------------------|-----------------------------|-----------------------------|
|                           |                                    | Mean ± SEM | p-value | Mean ± SEM | p-value | Mean ± SEM | p-value |
| Medication effect score   | Control (n=12)                      | 0.45 ± 0.15 | -       | 3.469E-10±0.02 | 0.003       | 3.469E-10±0.02 | 0.003       |
| (MES) sulfonylurea        | 2 days/wk intermittent VLCD (n=14) | 0.23 ± 0.13 | -       | 0.05 ± 0.02 | 0.202       | 0.05 ± 0.02 | 0.202       |
|                           | 4 days/wk intermittent VLCD (n=14) | 0.41 ± 0.13 | -       | -3.966E-10±0.02 | 0.004       | -3.966E-10±0.02 | 0.004       |
| Medication effect score   | Control (n=12)                      | 0.64 ± 0.10 | -       | 0.32 ± 0.10 | 0.003       | 0.21 ± 0.07 | <0.001      |
| (MES) metformin           | 2 days/wk intermittent VLCD (n=14) | 0.48 ± 0.10 | -       | 0.22 ± 0.10 | 0.07        | 0.18 ± 0.07 | 0.006        |
|                           | 4 days/wk intermittent VLCD (n=14) | 0.52 ± 0.10 | -       | 2.780E-10±0.10 | <0.001      | 0.02 ± 0.07 | <0.001      |

Abbreviations: VLCD, very-low calorie diet.

Medication effect score (MES = [actual drug dose/maximum drug dose] x drug mean adjustment factor). The MES was calculated as the percentage of maximum daily dose for each medication multiplied by an adjustment factor. An adjustment factor was the reported median absolute decrease in HbA1c for each medication. It was used to quantify diabetes medication changes and a higher score reflected a high use of the medication.

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42 Patients assessed for eligibility

40 Randomized

2 Excluded (meeting exclusion criteria)

Run-in period

2 weeks

12 control group

14 intermittent VLCD 2 days/week

14 intermittent VLCD 4 days/week

18 weeks

18 weeks

18 weeks

12 completed

14 completed

14 completed

Accepted Article

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Fig. 2 (A)

FPG

Fig. 2 (B)

2-hr PPG
Fig. 2 (C)

HbA$_{1C}$

- **Control**
- **Intermittent VLCD 2 day/week**
- **Intermittent VLCD 4 day/week**

Run-in period

Intervention period

mg/dL

Week
Fig. 3

| Control | Diabetes remission | No glucose-lowering medication |
|---------|-------------------|-------------------------------|
|         | 58.3%             |                               |

| Intermittent VLCD 2 days/week | Diabetes remission | No glucose-lowering medication |
|-------------------------------|-------------------|-------------------------------|
|                               | 28.6%             | 64.3%                         |

| Intermittent VLCD 4 days/week | Diabetes remission | No glucose-lowering medication |
|-------------------------------|-------------------|-------------------------------|
|                               | 28.6%             | 85.7%                         |

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