Obesity Research & Clinical Practice (2013) 7, e43—e54

ORIGINAL ARTICLE

The effects of partial use of formula diet on weight reduction and metabolic variables in obese type 2 diabetic patients—Multicenter trial

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Received 18 November 2011; received in revised form 28 March 2012; accepted 30 March 2012

KEYWORDS
Weight reduction;
Visceral fat;
Obesity;
Formula diet;
Diabetes mellitus;

Summary
Aims: To clarify the usefulness of protein-sparing modified formula diet in obese type 2 diabetic patients, the effects of partial use of formula diet on weight reduction and changes in related metabolic variables, and the improving rates of risk factors per 1% body weight reduction, were compared with those of conventional subcaloric diet.

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1871-403X/$ — see front matter
http://dx.doi.org/10.1016/j.orcp.2012.03.002

Subjects and methods: Obese patients [BMI >25 kg/m^2] with diabetic mellitus were randomly assigned to a low-caloric diet with partial use of formula diet group (FD, $n = 119$) and a conventional low-caloric diet group (CD, $n = 110$). Subjects in FD took one pack of formula diet (MicroDiet®, 240 kcal/pack) in place of one of three daily low-caloric meals for 24 weeks. Total daily calorie prescribed was same.
Result: Weight reduction was greater in FD than in CD (week 24: −3.5 vs −1.4 kg; all $p < 0.001$). Systolic blood pressure decreased significantly only in FD. HbA_{1c} reduction was greater in FD than in CD. HDL-cholesterol increased significantly more in FD than in CD (week 24: +2.8 vs. +0.6 mg/dl, $p < 0.001$). Among several improving rates (%) of risk factors/1% body weight reduction, those of HbA_{1c} at weeks 16 and 24, triglyceride at week 8 and HDL-cholesterol at week 24, were significantly higher in FD than CD. Doses of sulfonylurea and thiazolidinedione were significantly decreased in FD than in CD.
Conclusion: Partial use of formula diet was much more effective in reducing body weight, and also in improving coronary risk factors than conventional diet in part due to reduced body weight through decreased energy diet intake and due to dietary composition of the formula diet.

Introduction

Obesity, particularly visceral adiposity, contributes to the clustering of many coronary risk factors such as hypertension, insulin resistance or type 2 diabetes and dyslipidemia in individuals [1—3]. And, these risk factors contribute to the development of cerebro-cardiovascular diseases [4,5] and also chronic renal disease [6]. Furthermore, obesity provokes sleep apnea syndrome and fatty liver, and worsens knee joint pain and lumbago [7,8]. Recently, a cluster of multiple risk factors has been called metabolic syndrome [9,10]. The core of this syndrome is visceral fat accumulation [3]. Obesity is apparently a modifiable risk factor for coronary heart disease, and weight reduction is known to confer great benefit in the improvement of several co-morbidities [11,12].

The treatments of obesity are composed of diet, exercise, drugs and behavior modification. However, obese persons are generally resistant to these treatments [13]. A considerable number of obese patients do not successfully reduce weight with low caloric conventional diet. There were many reasons for the failure in achieving weight reduction or maintaining weight loss. The individuals may have some difficulties in cocking or selecting the complicated low-calorie menus, in which various factors such as energy, protein, vitamins and minerals are involved.

A protein-sparing modified fasting therapy, in which 1.2—1.4 g protein per kg ideal body weight, fluid ad libitum, and vitamin and mineral supplementation are taken, is effective in achieving weight reduction [14,15]. This therapy can be possible by using formula diet, which is composed of high protein, low carbohydrate, low fat and enough vitamins and minerals. There were several papers reporting the usefulness and the safety of this formula diet [14—16]. But, low compliance and rebound of body weight were frequently observed. We hypothesize that partial use of formula diet to replace one meal a day could be beneficial for the treatment of obese diabetic patients in the long term, even though the body weight reduction would be less than total use. Cheskin et al. [17] reported that the efficacy of a portion-controlled meal replacement diet to a standard diet in achieving and maintaining weight loss among obese participants with type 2 diabetes for 34 weeks.

Furthermore, the roles of a high dietary protein to carbohydrate ratio in enhancing weight loss and decreasing risks have been discussed [18—20]. Layman et al. [21] reported that diets with a high protein to carbohydrate ratio have positive effects on markers of cardiovascular disease risks and these benefits may be mediated by a lower glycemic load. Gannon and Nuttall [22] also reported the beneficial effect of a high-protein, low-carbohydrate diet on blood glucose control in people with type 2 diabetes. On the other hand, some researchers reported that an energy-restricted, high-protein, low-fat diet provides nutritional and metabolic benefits more than a low-carbohydrate diet [23,24]. Therefore, the significance of high-protein and low-carbohydrate diet remains controversial, especially in Asian peoples. One of the reasons for the inconsistent result is compliance with the prescribed diet in the long term. Formula diet is a high-protein, low-carbohydrate and low-fat diet, and is easy to be administered.

Therefore, we attempted to clarify the usefulness of a 24-week dietary regimen using formula diet once a day in combination with conventional low-caloric diet in obese patients with type 2 diabetes mellitus. The formula diet used was MicroDiet®. The reduction in body weight and visceral fat, and the improvements of related metabolic variables were compared with those of conventional low-caloric diet alone. The changes in adiponectin [25,26] and lipoprotein lipase mass [27,28], which are considered to be markers of insulin sensitivity, were also studied. In

Table 1 Clinical backgrounds of conventional group and formula diet group.

Clinical backgrounds	Conventional diet group (CD) $n = 110$	Formula diet group (FD) $n = 119$	p-Value
Age (years)	51.7 ± 10.9	50.5 ± 11.8	0.594 (NS)
Sex males:females (%)	36:64	38:62	0.891 (NS)
Height (cm)	160.8 ± 8.5	160.8 ± 9.0	0.761 (NS)
Weight (kg)	77.9 ± 14.9	79.9 ± 17.8	0.793 (NS)
Body mass index (kg/m^2)	30.0 ± 4.6	30.8 ± 5.8	0.514 (NS)
Visceral fat area (cm^2)	166.5 ± 59.4	165.2 ± 63.2	0.855 (NS)
Subcutaneous fat area (cm^2)	272.8 ± 97.7	285.0 ± 124.3	0.862 (NS)
V/S ratio	0.707 ± 0.416	0.666 ± 0.320	0.839 (NS)
Systolic blood pressure (mmHg)	138.9 ± 19.7	138.8 ± 17.5	0.651 (NS)
Diastolic blood pressure (mmHg)	83.3 ± 12.2	81.3 ± 9.5	0.238 (NS)
Fasting blood glucose (mg/dl)	153.5 ± 52.6	148.1 ± 49.2	0.409 (NS)
HbA_{1c} (%)	7.7 ± 1.3	7.7 ± 1.4	0.994 (NS)
HOMA-IR	7.0 ± 7.9	7.5 ± 7.6	0.701 (NS)
Non HDL-cholesterol (mg/dl)	156.0 ± 33.7	154.8 ± 39.9	0.702 (NS)
LDL-cholesterol (mg/dl)	131.3 ± 29.1	131.0 ± 32.9	0.654 (NS)
HDL-cholesterol (mg/dl)	52.7 ± 12.5	51.5 ± 12.5	0.355 (NS)
Triglyceride (mg/dl)	158.3 ± 107.3	152.5 ± 102.4	0.584 (NS)
Leptin (ng/ml)	9.9 ± 5.8	11.9 ± 11.2	0.248 (NS)
Adiponectin (mg/ml)	6.4 ± 4.0	6.4 ± 3.5	0.810 (NS)
Lipoprotein lipase (ng/ml)	51.2 ± 18.8	51.1 ± 17.0	0.903 (NS)

V/S, visceral fat area/subcutaneous fat area; HbA_{1c}, hemoglobin A_{1C}; HOMA:-IR, homeostasis model assessment of insulin resistance. Values are expressed as mean $\pm$ S.D. NS, not significant.

addition, improvement rates of metabolic variables per 1% body weight reduction were compared between two groups.

Subjects and methods

Subjects

A total of 11 hospitals in Japan participated in the present study. Patients with type 2 diabetes mellitus (HbA_{1c}(JDS) $\geq$ 6.0%): this value is Japanese diabetes society standard. Usually, HbA_{1c} (JDS) is lower by 0.4% comparing to international standard value (NGSP), and body mass index (BMI) over 25 kg/m^2 were recruited. Participants were excluded if they had massive proteinurea; had malignancy; had a history of hepatitis, cardiovascular events, respiratory or gastrointestinal diseases; had uncontrolled hypertension; were pregnant or breast feeding. A total of 240 patients aged from 20 to 69 years entered the study. Mean BMI was 30.4 kg/m^2. Before entry to this study, most patients came the clinics over 6 months, and had undertaken a course of diet therapy with conventional diet menu (25—30 kcal/kg/day), but overweight and glucose metabolic disorders were not improved sufficiently. They were randomly assigned to a conventional diet group (CD; $n = 120$) or a formula diet group (FD; $n = 120$). Eleven patients withdrew from the study before completion; 10 in CD and 1 in FD. Subject characteristics were not significantly different between two groups at baseline (Table 1).

Dose of injected insulin just before taking formula diet was reduced to half. Sulfonylurea just before taking formula diet was stopped. Thiazolidinedione were changed depending on the levels of blood glucose and HbA_{1c}. Sulfonylurea was discontinued or the dose was decreased in subjects with fasting plasma glucose (FPG) less than 90 mg/dl (12 in FD and 6 in CD) with a fear of hypoglycemic attack. Subjects on antihypertensive and/or lipid-lowering medications were essentially asked to maintain the same medications and dosages throughout the study.

The study was approved by the ethnical committee of each hospital. Informed consent was obtained from all subjects before participation in the study. We declare that all these studies were conducted in accordance with the declaration of Helsinki http://www.wma.net/ and that all procedures were carried out with the adequate understanding and written consent of the subjects.

Study design

The subjects were randomly assigned to one of two isocaloric dietary interventions; 20 kcal/kg times standard body weight (kg), for 24 weeks. Standard body weight was assumed to be equivalent to a BMI of 22 kg/m^2. Conventional diet was composed of classical

Table 2 Composition of one pack of formula diet (Microdiet®).

Nutrient	Contents	Nutrient	Contents
Energy	240 kcal	Vitamin B_1	0.9 mg
Protein	21.5 g	Vitamin B_2	0.9 mg
Fat	2.4 g	Niacin	6.0 mg
Carbohydrate	16.5 g	Pantothenic acid	3.3 mg
Dietary fiber	5.5 g	Vitamin B_6	1.3 mg
		Vitamin B_{12}	2.2 mg
Sodium	320 mg	Vitamin C	43.3 mg
Calcium	380 mg	Folic acid	163 mg
Magnesium	116 mg	Biotin	13.3 mg
Potassium	700 mg	Vitamin A	350 mg
Phosphorus	268 mg	Vitamin D	4.2 mg
Iron	6.7 mg	Vitamin E	4.4 mg

Japanese low-caloric meals 3 times a day. Formula diet was composed of one pack of MicroDiet® (240 kcal/meal) in the morning and two conventional Japanese low-caloric meals at noon and in the evening. MicroDiet® was provided by Sunny Health Co. Ltd (Tokyo, Japan) and the compositions are shown in Table 2. Proteins were composed of egg white, casein and soybean proteins. One pack of Microdiet® was dissolved in 450 ml cold water, and was drunken.

The same total calorie intake was prescribed to the two groups as described above. The protein:fat:carbohydrate ratio prescribed at the beginning was 15:25:60 in CD and 18:30:52 in FD.

All patients visited the clinic every 4 weeks. At each visit, the patients received guidance on lifestyle improvement conducted by dieticians and/or nurses. A food diary was recorded by each patient, and energy intake was calculated by the dieticians.

Serum adiponectin and lipoprotein lipase mass were measured using ELISA kits (Daiichi Pure Chemical, Co. Ltd., Tokyo, Japan). Imunoreactive insulin was measured by immunoassay. Visceral and subcutaneous fat areas in the abdomen were measured using computed tomography at the umbilical level [1]. Other chemical analyses were performed at integrated central laboratories.

Dietary composition was assessed by a qualified dietician using a computerized database, based on the analysis of the semi-quantitative food record of 3 consecutive days for each 2-week period.

The basal doses of used drugs were essentially not changed during intervention term, except the cases in which the glucose levels were remarkably improved well by enough weight reduction, and concerns about hypoglycemic attack were occurred. The reduction dose of sulfonylurea was mostly reduced into half, in case of blood glucose control improved (HbA_{1c} (JSD) < 6.0%). Furthermore, in cases of hypotension attack or enough lowered LDL-cholesterol levels (LDL-cholesterol < 80 mg/dl), the affecting drugs were withdrawn.

Statistical analysis

Dietary composition data were analyzed using raw, unadjusted means. Between-group differences in dietary intake at each time point were tested by analysis of variance (ANOVA).

Results

Body weight and visceral fat outcomes

One hundred and ten patients in CD and 119 in FD completed the study and were analyzed. The reason for drop-out was mainly inconvenience to the patients. Baseline data of the patients are shown in Table 1. Mean body mass index (BMI) was 30.0 kg/m^2 in CD and 30.8 kg/m^2 in FD, with no significant difference between two groups. Age, male/female ratio, blood pressure, hemoglobin $(Hb)A_{1c}$, LDL-cholesterol, HDL-cholesterol and triglycerides were also not significantly different between two groups.

Body weight started to decrease from week 4 and significant decreases relative to baseline were maintained until week 24 in both groups (Fig. 1A). However, the weight flattened from week 12 in CD, but continued to decline gradually until week 24 in FD. Mean weight reduction relative to baseline was greater in FD than in CD (Table 3.1) (week 8: −2.9 vs −0.7 kg; week 16: −3.3 vs −1.4 kg; week 24: −3.5 vs −1.4 kg; all $p < 0.001$). BMI showed the same trend of decrease.

Visceral fat area decreased significantly ($p < 0.01$) in FD, but not in CD (Table 3.1). Subcutaneous fat area also decreased significantly ($p < 0.01$) in FD but not in CD. The decreases in visceral fat and subcutaneous fat were significantly ($p = 0.001$ and 0.049, respectively) greater in FD compared to CD.

Blood pressure outcome

Significant decreases in systolic blood pressure were observed from weeks 4 to 24 in FD, but only on week 20 in CD (Fig. 1B).

Significant decreases in diastolic blood pressure were observed only in FD from weeks 4 to 20 (Fig. 1C). When the magnitudes of decrease were compared between CD and FD (Table 3.1), decreases in systolic blood pressure

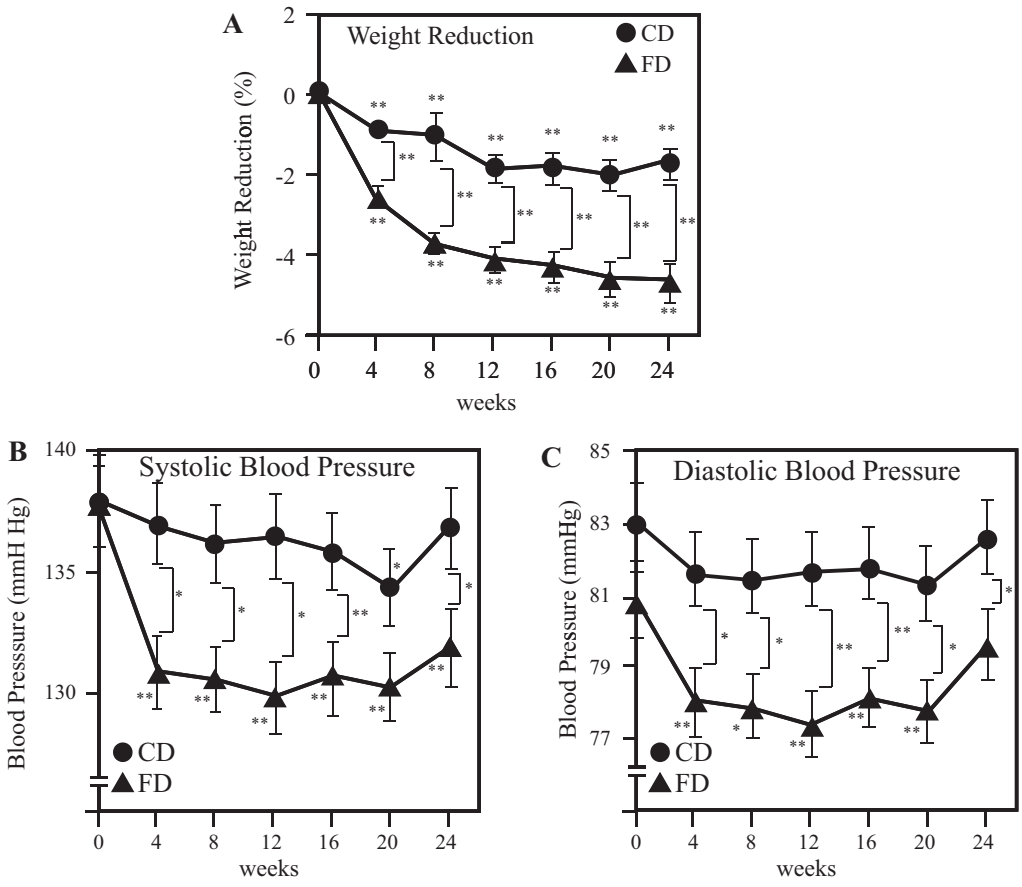

Figure 1 (A) Percent weight reduction in formula diet group and conventional diet group. (B) and (C) Comparison of changes in blood pressures between formula diet group and conventional diet group. (B) Changes in systolic blood pressure and (C) changes in diastolic blood pressure. Values are expressed as mean ± S.D. *$p < 0.05$ and **$p < 0.005$ compared with baseline. Abbreviations: FD, formula diet group; CD, conventional diet group.

were significantly greater in FD compared to CD at weeks 8, 16 and 24 ($p = 0.009$, 0.015 and 0.0256, respectively).

Glucose, HbA_{1c} and insulin

Fasting blood glucose decreased from week 4 in both groups, and a significant decrease was maintained until week 20 in FD and week 12 in CD (Fig. 2A). The decreases were apparently greater in FD than in CD at weeks 12, 16 and 20, but did not reach statistical significance (Table 3.1).

HbA_{1c} started to decrease in both groups at week 4 and significant decreases were maintained until week 24 in both groups (Fig. 2B). In CD, HbA_{1c} decreased from week 4 to week 12, but reversed gradually from week 16 to week 24. In FD, HbA_{1c} decreased from week 4, reached a trough at week 16, and stabilized thereafter. The decreases were significantly greater in FD compared to CD at weeks 8, 16 and 24 ($p = 0.024$, 0.016 and 0.002, respectively) (Table 3.1).

Insulin decreased significantly in FD only at week 24, and did not decrease in CD (Fig. 2C). The decreased amounts of insulin at weeks 8, 16 and 24 were tended to be greater in FD than in CD, but not significantly (Table 3.1).

HOMA index were significantly lower than baseline at weeks 8, 12, 20 and 24 in FD, but did not change in CD (Fig. 2D). The decreases in HOMA tended to be greater in FD compared to CD at weeks 8 and 24, but not significantly.

Lipid outcomes

LDL-cholesterol decreased in both groups from week 4, and the decreases were maintained until week 16. Thereafter, gradual increases were observed after week 20 in both groups (data not shown). The decreases in LDL-cholesterol were not different between FD and CD (Table 3.2).

In FD, triglyceride decreased significantly from week 4 and this tendency was maintained until week 24. In CD, triglyceride also decreased significantly on week 4, but rebounded thereafter (data not shown). The changes in triglyceride were significantly greater different between FD and CD at weeks 16 and 24 ($p = 0.037$ and 0.025) (Table 3.2).

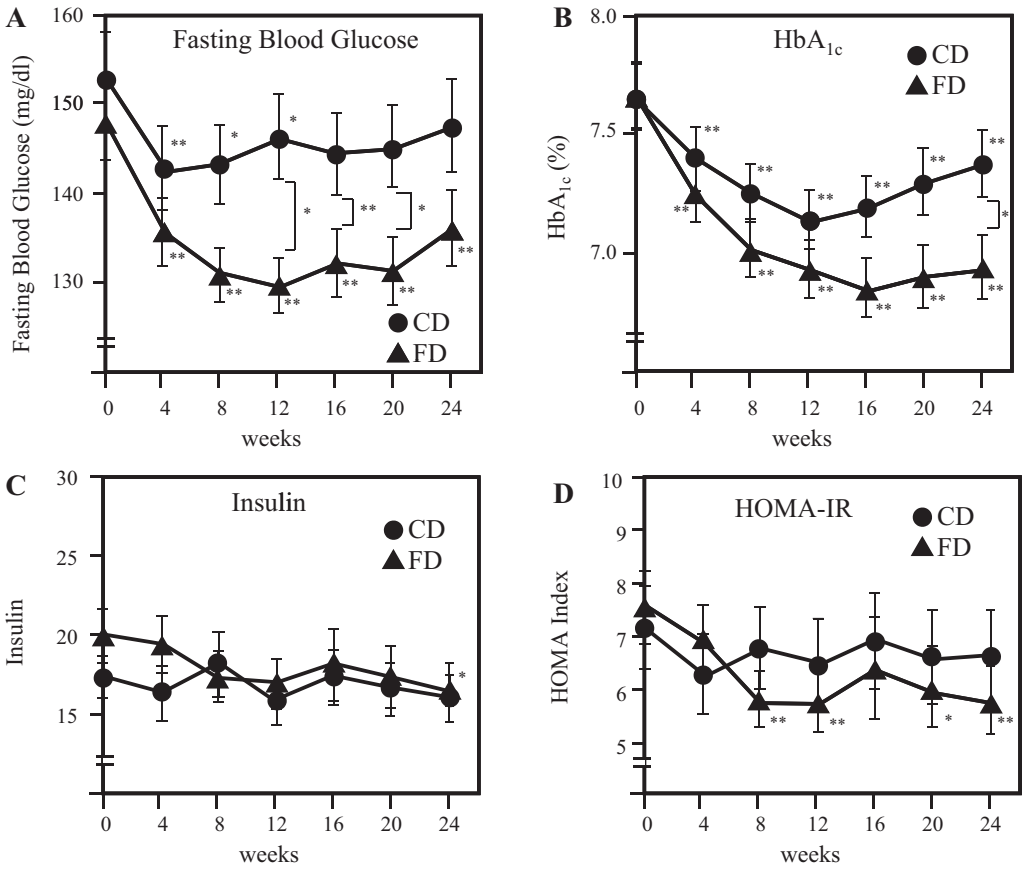

Figure 2 Comparison of changes in glucose metabolism parameters between formula diet group and conventional diet group. (A) Changes in fasting blood glucose, (B) changes in HbA_{1c}, (C) changes in insulin level and (D) changes in HOMA index. Values are expressed as mean ± S.D. *$p < 0.05$ and **$p < 0.005$ compared with baseline. Abbreviations: FD, formula diet group; CD, conventional diet group.

HDL-cholesterol decreased initially and remained significantly lower than baseline until week 12 in FD and week 20 in CD. The level started to increase after week 16 in FD and reached significantly higher level at week 24 (data not shown). The change in HDL-cholesterol in FD (increase) was significantly different from that in CD (decrease) at week 24 (Table 3.2). Non-HDL-cholesterol decreased at week 4 in both FD and CD, and the low levels were maintained stably during 24 weeks (data not shown). The decreases in non-HDL-cholesterol were not significantly different between FD and CD at weeks 8, 16 and 24 (Table 3.2).

Changes in leptin, adiponectin and lipoprotein lipase mass

In FD, leptin decreased from week 4 to week 12 and increased at weeks 20 and 24. In CD, leptin did not decrease but increased from week 16 to week 24 (Fig. 6). The changes in leptin in FD (decreases) were significantly different from those in CD (increases) at weeks 8, 16 and 24 (Table 3.2).

Adiponectin increased gradually in both groups (Fig. 6). After week 16, adiponectin tended to increase more in FD than in CD, but the difference between two groups were not significant (Table 3.2).

LPL mass increased gradually and significantly from week 8 in both groups (Fig. 6). After week 16, LPL mass tended to increase more in FD than in CD, but without significant (Table 3.2).

Comparisons of improving rates of coronary risk factors per 1% body weight reduction (ΔBW) between CD and FD (Table 4)

Coronary risk improving rate was obtained from the % change in measurement of risk marker divided by % body weight reduction, and were compared at weeks 8, 16 and 24 among patients with each risk factor at baseline. The subjects whose risk factor values were higher than following each values, were selected for this analysis: visceral fat area > 100 m^2, systolic pressure >140 mmHg, diastolic pressure > 100 mmHg, HbA_{1c} > 7.0%, non HDL-cholesterol > 160 mmHg, triglyceride > 150 mg/dl, HDL-cholesterol < 50 mg/dl.

Table 4 shows % improvement of coronary risks per % body weight reduction (risk improvement rate/ΔBW). Improvement rate was expressed as positive when the values decreased except HDL-cholesterol.

Table 3.1 The changes of BW and coronary risk factors.

Characteristics	Conventional diet group (CD) $n = 110$	Formula diet group (FD) $n = 119$	p-Value
Weight (kg)			
8 W	−0.7 ± 6.3**	−2.9 ± 2.3**	0.000
16 W	−1.4 ± 3.0**	−3.3 ± 3.4**	0.000
24 W	−1.4 ± 3.4**	−3.5 ± 4.0**	0.000
Body mass index (kg/m^2)			
8 W	−0.3 ± 2.1	−1.1 ± 0.8**	0.000
16 W	−0.6 ± 1.2**	−1.3 ± 1.3**	0.000
24 W	−0.6 ± 1.3**	−1.4 ± 1.5**	0.000
Visceral fat area (cm^2)			
24 W	−5.3 ± 34.7	−23.6 ± 27.5**	0.001
Subcutaneous fat area (cm^2)			
24 W	−12.3 ± 50.3	−31.6 ± 61.9**	0.049
Systolic blood pressure (mmHg)			
8 W	−1.7 ± 15.4	−7.2 ± 15.5**	0.009
16 W	−2.1 ± 14.4	−7.1 ± 15.8**	0.015
24 W	−1.1 ± 15.5	−5.9 ± 16.2**	0.026
Diastolic blood pressure (mmHg)			
8 W	−1.5 ± 9.7	−2.9 ± 9.3**	0.302 (NS)
16 W	−1.2 ± 10.4	−2.6 ± 8.9**	0.273 (NS)
24 W	−0.3 ± 11.3	−1.1 ± 9.0	0.582 (NS)
Fasting blood glucose (mg/dl)			
8 W	−9.4 ± 39.7*	−17.3 ± 37.3**	0.127 (NS)
16 W	−8.2 ± 37.6*	−15.9 ± 39.6**	0.138 (NS)
24 W	−5.2 ± 37.6	−12.1 ± 37.6**	0.171 (NS)
HbA_{1c} (%)			
8 W	−0.3 ± 0.7**	−0.5 ± 0.7**	0.024
16 W	−0.4 ± 0.8**	−0.7 ± 0.9**	0.016
24 W	−0.2 ± 0.8**	−0.6 ± 1.1**	0.002
Insulin (μu/ml)			
8 W	0.8 ± 15.2	−2.6 ± 17.2	0.117 (NS)
16 W	0.0 ± 11.1	−1.8 ± 18.6	0.378 (NS)
24 W	−1.3 ± 9.8	−3.6 ± 18.1*	0.254 (NS)
HOMA-IR			
8 W	−0.4 ± 6.5	−1.8 ± 6.2**	0.107 (NS)
16 W	−0.2 ± 5.5	−1.2 ± 7.7	0.317 (NS)
24 W	−0.5 ± 5.7	−1.8 ± 7.3**	0.152 (NS)

HbA_{1c}, hemoglobin A_{1C}; HOMA-IR, homeostasis model assessment of insulin resistance. Values are expressed as mean ± S.D.
* $p < 0.05$ compared with baseline.
** $p < 0.005$ compared with baseline. NS, not significant.

Visceral fat area improvement rate/ΔBW at week 24 was significantly higher in FD than in CD (2.37 vs 1.34%, $p = 0.029$).

HbA_{1c} improvement rate/ΔBW were significantly higher in FD than in CD at weeks 16 and 24 (week 16: 2.74 vs 1.63%, $p = 0.030$; week 24: 2.2 vs 1.10%, $p = 0.032$).

Among the lipid components (Table 4), non-HDL cholesterol improvement rates/ΔBW were not significantly different between FD and CD at weeks 8, 16 and 24. Triglyceride improvement rate/ΔBW was significantly greater in FD than in CD at week 8. HDL-cholesterol improvement rate/ΔBW was higher in FD than in CD at week 24.

Analysis of diet components at week 16

Table 5 shows the analysis of food records at week 16 in 44 subjects (22 in FD, 22 in CD) in one institution. Mean total calorie intake was significantly lower in FD than CD (1574 vs 1386 kcal/day, $p = 0.037$). Mean protein intake was higher in FD than in CD (73.4 vs 62.3 g, $p = 0.019$). Fat was not different between two groups (53.1 vs 48.5, $p = 0.23$). Carbohydrate was significantly lower in FD than in CD (164 vs 212 g, $p = 0.032$). Mean protein:fat:carbohydrate ratio (PFC ratio) was 21 ± 3.2:31 ± 6.4:47 ± 8.2 in FD, and 16 ± 4.1:33 ± 4.1:54 ± 12 in CD.

Table 3.2 The changes of coronary risk factors.

Characteristics	Conventional diet group (CD) $n = 110$	Formula diet group (FD) $n = 119$	p-Value
LDL-cholesterol (mg/dl)			
8 W	−5.2 ± 17.3**	−6.2 ± 21.9**	0.701 (NS)
16 W	−7.8 ± 19.5**	−7.0 ± 25.7**	0.798 (NS)
24 W	−2.7 ± 22.1	−3.2 ± 26.3	0.881 (NS)
Triglyceride (mg/dl)			
8 W	−9.2 ± 71.6	−19.7 ± 54.2**	0.212 (NS)
16 W	12.3 ± 117.1	−16.2 ± 85.5*	0.037
24 W	−1.1 ± 81.9	−22.6 ± 60.4**	0.025
HDL-cholesterol (mg/dl)			
8 W	−2.7 ± 5.8**	−1.0 ± 5.8	0.033
16 W	−1.7 ± 6.0**	−0.2 ± 6.8	0.023
24 W	−0.6 ± 6.8	−2.8 ± 7.3**	0.0001
Non HDL-cholesterol (mg/dl)			
8 W	−5.3 ± 18.4**	−10.3 ± 25.1**	0.092 (NS)
16 W	−5.5 ± 25.2*	−9.6 ± 30.8**	0.272 (NS)
24 W	−2.5 ± 22.0	−6.6 ± 30.7*	0.256 (NS)
Leptin (ng/ml)			
8 W	0.1 ± 4.2	−2.1 ± 9.2*	0.023
16 W	1.2 ± 4.6*	−1.1 ± 9.7	0.025
24 W	1.6 ± 4.4**	−0.7 ± 9.6	0.020
Adiponectin (mg/ml)			
8 W	0.0 ± 1.2	0.0 ± 1.4	0.934 (NS)
16 W	0.2 ± 1.5	0.2 ± 2.0	0.770 (NS)
24 W	0.4 ± 1.7*	0.5 ± 2.2*	0.761 (NS)
Lipoprotein lipase mass (ng/ml)			
8 W	2.0 ± 10.1*	2.0 ± 10.4*	0.979 (NS)
16 W	3.5 ± 11.6**	3.9 ± 12.0**	0.790 (NS)
24 W	5.1 ± 12.7**	5.6 ± 12.8**	0.756 (NS)

Values are expressed as mean ± S.D.
* $p < 0.05$ compared with baseline.
** $p < 0.005$ compared with baseline. NS, not significant.

Changes in medications (Table 6)

The changes of medicines after this intervention study are shown in Table 6. As for Insulin therapy, insulin dose was reduced in 9/26 patients in CD and 17/20 patients in FD, not significant. As for sulfonylureas, discontinued persons were 3/51 in CD, and 20/57 in FD ($p < 0.02$). Reduced persons were 3/51 in CD, and 11/51 in FD ($p < 0.05$). As for thiazolizine, discontinued persons were 4/24 in CD, and 12/27 in FD ($p < 0.01$).

As for statins, ceased case was 4/11 in CD, and 4/13 in CD, 45 in FD.

As for angiotensin 2 receptor blockers, discontinued case was 3/12 in CD, and 4/20 in FD. As for calcium channel blockers, discontinued case was 2/21 in CD, and 4/21 in FD.

Clinical laboratory data and absence of adverse effect (Table 7)

Serum total protein did not change in CD and FD during 24 weeks. Liver function tests such as aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyl transpeptidase did not change. Uric acid, blood urea nitrogen and creatinine also did not change in both groups.

Red blood cell and white blood cell counts remained unchanged in both groups. No subject showed elevated AST or ALT to higher than normal levels during this study in both FD and CD. Abnormal clinical sign and symptom were not observed. Especially, mental problems were not observed.

Discussion

Body weight reduction was achieved with both FD and CD, but the magnitude of reduction was greater in FD than in CD throughout the intervention period up to week 24. Significant visceral fat area reduction was only observed in FD, and subcutaneous fat area also decreased significantly only in FD (Table 3.1).

Fasting glucose was reduced in both FD and CD, but the reduction tended to be greater in FD, although not significantly (Fig. 2A). HbA_{1c} reduction was observed in both FD and CD, and the decrease was significantly greater in FD

Table 4 Improvement rates (%) of cardiovascular risk markers per 1% body weight reduction.

Cardiovascular risk markers	Improvement rates (%) of per 1% body weight reduction				
	Conventional diet group (CD)		Formula diet group (FD)		*p*-Value
Visceral fat area high group (>100 cm^2)					
24 W	1.342	(*n* = 50)	2.373	(*n* = 64)	0.029
Systolic blood pressure high group (>140 mmHg)					
8 W	0.591		1.988		0.093
16 W	0.845	(*n* = 44)	1.470	(*n* = 47)	0.142
24 W	0.633		0.713		0.834
Diastolic blood pressure high group (>90 mmHg)					
8 W	1.203		1.432		0.810
16 W	0.883	(*n* = 28)	1.212	(*n* = 22)	0.654
24 W	1.185		0.200		0.161
HbA_{1c} high group (>7%)					
8 W	1.872		2.249		0.503
16 W	1.626	(*n* = 56)	2.742	(*n* = 58)	0.030
24 W	1.096		2.187		0.032
Non HDL-cholesterol high group (>160 mg/dl)					
8 W	−0.354		−0.855		0.643
16 W	−0.122	(*n* = 43)	−0.197	(*n* = 51)	0.854
24 W	0.000		0.168		0.720
Triglyceride high group (>150 mg/dl)					
8 W	1.133		5.304		0.031
16 W	−0.306	(*n* = 44)	3.667	(*n* = 44)	0.229
24 W	2.337		3.349		0.534
HDL-cholesterol low group (<50 mg/dl)					
8 W	0.957		−0.050		0.266
16 W	−0.270	(*n* = 48)	−0.662	(*n* = 58)	0.417
24 W	−0.016		−1.251		0.013

Table 5 Comparison of dietary compositions between conventional diet group and formula diet group at 16 weeks.

Compositions	Conventional diet group at 16 W (*n* = 22)	Formula diet group at 16 W (*n* = 22)	*p*-Value
Total energy (kcal)	1574 ± 299	1386 ± 210	0.037
Protein (g)	62.3 ± 14 (15.8 ± 4.1%)	73.4 ± 8.6 (21 ± 3.2%)	0.019
Fat (g)	53.1 ± 8.3 (32.9 ± 4.1%)	48.5 ± 12.9 (31 ± 6.4%)	0.132
Carbohydrate (g)	212 ± 46.7 (54 ± 12%)	164 ± 26.8 (47 ± 8.2%)	0.032

Values are expressed as mean ± S.D.

than in CD (Fig. 2B). As for coronary risk markers, systolic blood pressure decreased significantly only in FD (Fig. 1B and C). Triglycerides decreased to a greater extent in FD compared with CD at weeks 16 and 24. HDL-cholesterol was significantly increased only in FD on week 24 from base line (Table 3.2).

Several factors may account for why FD was more effective than CD in achieving body weight reduction. First, the actual calorie intake was probably lower in FD than in CD (Table 5), although the prescribed total calorie intake was the same. Actually, the calorie intake calculated from the food records was almost 200 kcal/day less in FD. Future research is needed to investigate the reduced energy intake in recipients of FD. These participants may have restricted intake energy because of limited food choice, or the low-carbohydrate diet may have an appetite suppressing effect [29]. Second, the compositional difference between FD and CD may affect weight reduction. The ratios of protein to carbohydrate and to fat were high in FD than in CD. Several reports [19—22] have shown that a high-protein and low-carbohydrate diet achieves greater weight loss and more favorable metabolic effects in 6—12 months.

The third factor might be motivation. The greatest weight loss was observed during the first 1—2 months, and the resulting sense of achievement might have motivated the subjects to continue diet therapy using formula diet. However, precise data is not available.

Generally, FD improved coronary risk markers more than CD did. A greater body weight reduction achieved with FD than CD might contribute to these improvements. However, other possibilities should also be examined.

Table 6 The changes of administered drugs after intervention of diets.

Used drugs	Conventional diet group ($n = 110$)			Formula diet group ($n = 119$)		
	Administered case	Reduced case	Discontinued case	Administered case	Reduced case	Discontinue case
Insulin	19	9	0	20	17	0
Sulfonylureas	51	3	3	57	11*	20**
Thiazolizine	24	0	4	27	0	12**
Biganides	31	0	0	33	4	4
Glinides	9	0	0	9	0	4
Alfa glucosidase inhibitors	15	0	0	13	0	0
Statins	11	0	4	13	0	4
Fibrates	6	0	0	5	0	0
Eicosapentaenoic acid	5	0	0	4	0	0
Angiotensin converting enzyme inhibitor	11	0	0	4	0	0
Angiotensin II receptor blockers	12	0	3	20	0	4
Calcium channel blockers	21	0	2	21	0	4

* $p < 0.05$.
** $p < 0.02$.

For example, FD might improve metabolic parameters by itself. To confirm this hypothesis, we calculated the improvement rates (%) of parameters per 1% body weight reduction among high risk subjects.

As shown in Table 4, visceral fat area, systolic and diastolic blood pressures, HbA_{1c}, non-HDL-cholesterol, triglyceride and HDL-cholesterol showed greater improvement rates in FD than in CD, with significant improvements in most parameters (HbA_{1c} at weeks 16 and 24, triglyceride at week 8, and HDL-cholesterol at week 24). Considering that insulin, sulfonylurea and thiazolidinedione dose reductions were clearly more prominent in FD than in CD during intervention, these data might suggest that FD per se has some ameliorating effect on metabolic parameters. One possible explanation might be due to the compositional differences in protein, fat and carbohydrate between FD and CD. FD is rich in protein and poor in carbohydrate. The effect of FD might be consistent with the findings for high-protein and low-carbohydrate diets [22,30,31].

In addition, as for improvement of blood pressure, sodium salt restriction might be involved, because formula diet contained only 320 mg sodium salt/pack. When one pack of formula diet was taken in place of conventional diet, 2—3 g of sodium salt might be restricted.

It is reported that diet-induced weight loss results in a decrease in a plasma leptin concentration [32]. In our study, leptin level decreased in FD, but not in CD (Table 3.2). The reason why leptin increased in CD, especially at 24 weeks is unclear, but a little body weight gain compared to 12 weeks might be involved. Adiponectin [25,26] and lipoprotein lipase mass [27,28] are considered to be markers of insulin sensitivity. Both markers were increased by both diet therapies (Table 3.2). But, the improving degrees of both marker were not different each other significantly, although those of FD looks better. HOMA-IR also looked better in FD than in CD (Table 3.1), but the difference was not significant. The effect of FD on the expression of those markers seemed not so greater than that of CD. The effect of FD on the improvement rates of cardiovascular risk markers as shown in Table 4 might be mainly due to energy restriction, itself.

Further studies are required to elucidate the precise mechanism by which FD ameliorates coronary risk factors.

Limitations: There were some limitations in this study.

1. The achievement of dose reduction or discontinuation of sulfonylurea and thiazolidinedione was greater in FD than CD (Table 6). Therefore, the real metabolic parameter changes in FD would be much better than the changes obtained in the present studies. However, further studies are required to substantiate this conjecture.
2. Analysis of dietary composition during the period of intervention was done using the food records at one point in one institute.
3. We found no serious adverse effect of the formula diet during the study period, but our data do not provide information on long-term effects or occasional dangerous adverse effects.
4. The term of this study is 24 weeks. The real effect of this method should have to be evaluated after a few years with following clinical events. Based on this study, such long term study might be worthwhile.

Table 7 Clinical laboratory findings of conventional group and formula diet group.

Clinical Backgrounds	Conventional diet group (CD)		$n = 110$		Formula diet group (FD)		$n = 119$	
	Before	8 W	16 W	24 W	Before	8 W	16 W	24 W
Total protein (g/dl)	7.8 ± 6.7	7.5 ± 0.4	7.5 ± 0.5	7.6 ± 0.5	7.6 ± 0.5	7.6 ± 0.6	7.6 ± 0.6	7.7 ± 0.5
AST (IU/l)	25.5 ± 12.6	24.0 ± 11.2	27.0 ± 21.0	24.5 ± 10.5	25.0 ± 11.0	22.2 ± 7.6	22.3 ± 8.8	24.0 ± 11.3
ALT (IU/l)	33.4 ± 22.9	31.0 ± 21.7	33.8 ± 27.9	29.8 ± 17.5	31.1 ± 19.2	26.0 ± 14.	26.2 ± 17.0	28.2 ± 20.5
γ-GTP (IU/l)	46.6 ± 58.3	41.4 ± 42.5	52.7 ± 74.2	43.1 ± 47.6	43.1 ± 36.9	42.8 ± 49.	40.5 ± 42.0	42.4 ± 44.0
Uric acid (mg/dl)	5.5 ± 1.6	5.5 ± 1.4	5.5 ± 1.5	5.5 ± 1.4	5.3 ± 1.3	5.2 ± 1.1	5.3 ± 1.2	5.3 ± 1.2
BUN (mg/dl)	15.0 ± 5.2	15.3 ± 5.8	14.6 ± 4.3	14.9 ± 5.6	14.5 ± 4.3	15.2 ± 4.8	15.8 ± 5.1	15.5 ± 4.8
Creatinin (mg/dl)	0.7 ± 0.3	0.7 ± 0.3	0.7 ± 0.2	0.7 ± 0.3	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2
Clinical Backgrounds	Conventional diet (CD)		$n = 110$ group		Formula diet group (FD)		$n = 119$	
	Before	12 W		24 W	Before	12 W		24 W
RBC ($\times 10^6$ ml^{-1})	4.67 ± 0.45	4.60 ± 0.46		4.63 ± 0.47	4.73 ± 0.41	4.65 ± 0.42		4.66 ± 0.45
WBC (ml)	6899 ± 2050	6779 ± 1756		6541 ± 1780	6743 ± 1900	6523 ± 1753		6603 ± 1977
Hb (g/dl)	14.1 ± 1.5	13.9 ± 1.6		14.1 ± 1.7	14.2 ± 1.4	14.0 ± 1.5		13.9 ± 1.6
Ht (%)	42.1 ± 3.8	41.6 ± 4.3		42.3 ± 4.9	42.3 ± 3.7	41.6 ± 4.2		41.6 ± 4.5

RBC, red blood cell; WBC, white blood cell; Hb, hemoglobin; Ht, hematocrit. Values are expressed as mean ± S.D.

Conclusion

Weight reduction was greater using the formula diet MicroDiet® once a day in combination with low-caloric diet than conventional low-caloric diet alone. Furthermore, improvement rates of metabolic parameters per weight reduction appeared to be superior to conventional Japanese low-caloric diet, in addition to the reduction or discontinuation of sulfonylureas and thiazolizine. These results suggest that subcaloric diet therapy using formula diet once a day may be useful tool for weight control and improvements of metabolic parameters in obese diabetic patients.

Acknowledgments

This study was supported by the non-profitable organization Weight Control Association in Japan. The funding source had no role in the design, conduction of reporting of the study or in the decision to submit the manuscript for publication. MicroDiet® was kindly provided by Sunny Health Co. Ltd (Tokyo, Japan).

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