

# Pilot Study of “Classic” 3:1 Ketogenic Diet Complete Meal Replacement Treatment of Obesity-Related Type 2 Diabetes

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## Abstract

**Introduction:** Low carbohydrate (CH) diets have been used in the management of obesity-related T2DM, with modest results. “Classic” ketogenic diets (KD) used in epilepsy are very low CH (10-20 g/day), very high fat (87-90% of calories) diets. We report a pilot study of treatment of obesity-related T2DM with “classic” 3:1 [fat]:[carbohydrate + protein] weight ratio diet using the novel approach of a complete ready-made meal replacement program.

**Methods:** In an open label study, T2DM patients with BMI  $\geq 30$  kg/m<sup>2</sup> were treated for 9 months with 3:1 KD (20 g CH/day, 1600 kcal/day), delivered as complete meal replacement (CMR). Weight, BMI, fasting plasma glucose (FPG), HbA1c, serum fasting insulin, lipid and leptin levels were evaluated monthly. Diabetic medications were adjusted as clinically indicated.

**Results:** Eleven patients participated. Ten patients were treated for  $\geq 4$  days (modified intent to treat population, mITT); 5/10 stopped treatment early, 5/10 completed the study per protocol (PP subgroup, n = 5), and 6/10 (5/5 of PP subjects) achieved sustained T2DM remission. In the mITT population, mean BMI declined by 11.62% from baseline 39.84 kg/m<sup>2</sup> (p = 0.008), FPG by 21.56 mg/dL from 137.7 mg/dL (NS), HbA1c by 1.16% from 7.36% (p = 0.016) and insulin level by 14.22 from 23.18  $\mu$ IU (NS). In the PP subgroup, mean BMI declined by 17.08% (p = 0.063), FPG by 47 mg/dl (p = 0.12), HbA1c by 1.36% (p = 0.063) and insulin by 14.76  $\mu$ IU (NS). Triglyceride levels declined and HDL increased in the mITT population. KD was well tolerated. Adverse events, all transient and generally mild, caused no discontinuation, and included constipation (6/10), hunger (6) and diarrhea (2).

**Conclusion:** Classic KD, delivered as CMR, may be effective in inducing remission in obesity-related T2D. Controlled studies are warranted.

## Keywords

BMI, Ketogenic diet, Low carb diet, Type 2 diabetes, Weight loss

## Key Messages

- Current pharmacological and lifestyle treatments of type 2 diabetes rarely induce remission. Those targeting obesity generally produce modest results.
- The present pilot study evaluates “classic”, rigorous 3:1 ketogenic diet with the novel approach of a complete, ready-made meal program using 3:1 KD recipes.
- 60% of subjects achieved sustained T2D remission and mean BMI overall reduction of 11.6%, 17.1% in the “per protocol” patient group.

**Trial registration:** NCT02069197. Registered 24 February 2014, <https://www.clinicaltrials.gov/ct2/show/NCT02069197> Klein P. 2014. Ketogenic Diet Treatment of Obesity With Co-morbid Type 2 Diabetes Mellitus and/or Obstructive Sleep Apnea (KGDobesity).

## Introduction

Diabetes is the largest health-care problem of the developed world. In 2015, diabetes affected 30.2 million US adults (12.2% of the adult population) [1]. An additional 84.1 million adults (33.9% of U.S. adults) have prediabetes [1]. Approximately 90% of T2DM is due to obesity [2]. The risk of developing T2DM increases in a "dose-dependent" manner with increasing BMI [2-5]. Rates of T2DM have increased over the last several decades in parallel with obesity. In 2014, 37.7% of US population was obese, defined as body mass index (BMI) of  $\geq 30$  kg/m<sup>2</sup> [6].

Obesity leads to insulin resistance, the pathophysiological hallmark of T2D [7]. In obese animals, weight loss results in reduction in insulin and blood glucose levels [8]. In patients with T2D weight loss reduces insulin resistance, improves glycemic control, reduces T2D-related complications and allows reduction of diabetic medication load [9-11]. Improvement in fasting blood glucose is directly related to the relative

amount of weight lost [12]. Modest improvements in FBG are observed with 5% weight loss [13]. Marked weight loss (30% of body weight) after gastric bypass surgery normalizes glycemic control in 40-95% of extremely obese patients with T2D [14].

The T2D and obesity epidemics have correlated with societal dietary change since the 1960s-70s of reducing proportion of daily calories derived from fat in favor of carbohydrates [15]. Before the discovery of insulin in 1921, dietary carbohydrate (CH) restriction was the standard treatment for both T2 and T1 diabetes [16]. Insulin and oral hypoglycemic agents which improve metabolic disposition of glucose replaced CH restriction as the means of reducing blood glucose levels and as the mainstay of diabetes treatment. Hypoglycemic medications normalize blood glucose level and improve HbA1c level, but do not affect the cause of the disease; in fact, insulin exacerbates weight gain. Weight loss with carbohydrate restriction is the natural treatment of obesity related T2DM- both symptomatically and to reverse the disease.

There is at present no uniformly accepted effective method of weight loss. Pharmacological treatment of obesity-related T2D is often effective in stabilizing the disease, but has had negligible impact on reversing it [9]. Treatment with the 5 FDA-approved long-term weight loss agents, orlistat, qysimia, lorcaserin, contrave and liraglutide achieve both weight loss and improvement in glycemic control in overweight/obese T2D patients, but the results are modest [17-23] Virtually no T2DM remissions are reported.

Lifestyle modifications involving diet, physical activity

and  $\geq 7\%$  of weight loss, are recommended by the American Diabetic Association as a cornerstone of treatment for all overweight or obese individuals with T2DM [14]. Most lifestyle/dietary intervention studies achieve mild to moderate weight reduction and associated improvement in glycemic control in T2DM obese patients [9, 24]. In the largest lifestyle/dietary intervention study to-date, the Look AHEAD (Action for Health in Diabetes) study, intensive lifestyle intervention (decreased caloric intake and increased physical activity) in T2D patients with overweight or obesity resulted in weight loss of 8.6% body weight, HbA1c reduction of 0.6% and FPG level reduction of 21.5 mg/dl [24, 25]. Sixty five percent of patients lost  $\geq 5\%$  of body weight (BW), 36% lost  $\geq 10\%$  of BW and 16% lost  $\geq 15\%$  of BW [25]. The magnitude of weight loss was strongly associated with improvements in glycemia. Five to ten percent weight loss led to a 0.5% reduction in HbA1c, 10-15% weight loss to -0.7% reduction and  $> 15\%$  weight loss to -0.9% reduction. Approximately 11.5% of patients had partial or complete T2D remission at 1 year [26].

There has been a growing interest in low carbohydrate diet as a possible treatment of obesity-related T2D. Low carbohydrate diets have been classified into very-low carbohydrate ketogenic diet (VLCKD), with net carbohydrate intake of 20-50 g/day or 10% of a 2000 kcal/day diet, and low carbohydrate or 130 g net CH/day [15]. Meta-analyses of randomized studies of LC diet vs. other diets suggest that LC may affect weight and glycemic control in obese T2DM patients similarly to other diets [27-29]. In most of the randomized studies, however, CHs make up 20-40% of caloric intake- not very low.

A number of studies have shown that a proportion of obese T2D patients treated with very low CH diets can reduce diabetic medication load, including some that may achieve remission [30-35]. The proportion of patients reported to achieve remission in these studies has ranged from 0-25%.

"Classic" ketogenic diet (KD) is used for treatment of intractable epilepsy [36, 37]. It is a high fat, very low carbohydrate diet which is more restrictive than VLCKD or LC diets. "Classic" KD consists of long chain saturated triglycerides with a 3:1 or 4:1 [fat]: [protein + carbohydrate] ratio by weight. Approximately 87-90% of calories are derived from fat. Carbohydrates are restricted to  $\leq 20$  g/day [37] "Classic" KD differs from the commonly used LC/VLCKD diets in two aspects: (i) carbohydrate restriction is  $\leq 20$  g/day for the duration of the diet, whereas in other LC diets carbohydrate content is increased up to 40-130 g/day after the initial 2-4 weeks; and (ii) the fat content of KD is much higher: in 3:1 KD 87% of calories are derived from fat vs. 45-70% in "LC" diets which commonly have [fat]:[carbohydrate + protein] ratio of about 1:1 [37]

In a pilot study of adults with refractory epilepsy and co-morbid obesity treated adjunctively with 3:1 KD for  $> 6$  months we showed a marked weight loss with mean BMI reduction of 18.3%; 78% of overweight/obese patients had  $\geq 15\%$  BMI reduction [38]. Weight loss stabilized after 8-12 months [Klein P, unpublished observation]. One patient with co-morbid T2DM on 2 oral hypoglycemic agents achieved

complete T2DM remission within 1 month of KD initiation. She stopped the diet after 6 months but sustained T2DM remission for the 4 years of follow-up.

The goal of the present study was to evaluate the classic 3:1 KD treatment in patients with obesity and T2DM without epilepsy using complete meal replacement program.

## Subjects and Methods

This was a prospective, open label study of adjunctive KD treatment in adults with obesity-related T2DM. All procedures performed in studies were in accordance with the 1964 Helsinki declaration and its later amendments. The study was approved by the institutional review board of Holy Cross Hospital, Silver Spring, MD. All subjects signed IRB-approved consent form. The study was conducted at the Mid-Atlantic Epilepsy and Sleep Center, Bethesda, MD, and was registered as NCT02069197.

The initial study design was a randomized, open label three arm study comparing treatment of adults with obesity and T2DM for 9 months with (1) 3:1 [fat]:[protein+carbohydrate] ratio, 1600 kcal/day diet, (2) orlistat 360 mg/day and dietary/lifestyle counseling following the LEARN (Lifestyle, Exercise, Attitudes, Relationships, and Nutrition) program and (3) dietary/lifestyle counseling only, with 50 subjects per arm. The study was "front-loaded" so that the first 5 enrolled patients were in the KD group, after which randomization began. The study was self-funded and ran out of funds after recruitment of 19 subjects, 11 in the KD arm and 5 and 3 each in the orlistat/counseling and counseling-only arms. The small number of subjects in arms 2 and 3 made meaningful comparisons between the arms difficult. Because of this, we report only the results of the KD-treated subjects.

**Subjects:** Subjects were men and women aged 18-70 years with BMI  $\geq 30$  mg/kg<sup>2</sup> and T2DM. Hypoglycemic medications remained unchanged for  $\geq 2$  months prior to the study. Subjects were excluded if they had BMI change of  $\geq -3.0$  kg/m<sup>2</sup> of baseline BMI within past 12 months, history of bariatric surgery  $\leq 3$  years prior to enrollment, history of uncontrolled hyperlipidemia, change in the dose or type of hypoglycemic treatment  $\leq 2$  months prior to enrollment, history of uncontrolled hyperthyroidism, of cerebrovascular disease or unstable heart disease  $\leq 6$  months of enrollment or of any systemic illness or unstable medical condition that might pose additional risk, including unstable cardiac, metabolic, endocrine, renal or liver disease, past history of renal calculi, hyperuricemia, hypercalcemia, mitochondrial disease, known disorder of fatty acid metabolism, porphyria, and active cancer.

**Evaluations:** Subjects were evaluated in face-to-face visit at baseline (1-2 weeks before diet initiation), on days 7, 14 and 28 of treatment, then every four weeks. Baseline evaluations included T2DM and obesity history, weight, BMI, a.m. serum fasting lipids (cholesterol, TG, HDL, LDL and VLDL), fasting plasma glucose (FPG), insulin, HbA1c, basic metabolic profile, uric acid, and serum leptin levels. Patients were instructed to check urine ketone levels with Ketostix

(Bayer AG, IN, USA) twice daily, once in the morning fasted state and once two hours post-prandially in the evening. Subjects on oral hypoglycemic medications were instructed to check blood glucose levels at the same times as urine ketones (morning fasted and evening 2 hours post-prandial), and subjects on insulin were instructed to check blood glucose at least three times a day. Ketostix measures levels of acetoacetate using semi quantitative color scale with brackets of 5, 15, 40, 80 and 160 mg/ml. Patients recorded the values in a standardized ketone/glucose level diary which was reviewed at each visit. Subsequent evaluations also included weight, BMI, BP, waist circumference, adverse events (AEs) and treatment compliance. Laboratory evaluations were obtained at baseline, at 1 and 4 weeks after treatment initiation, and then every 4 weeks; evaluations included 8 a.m. FPG and fasting insulin levels, HbA1c, serum fasting lipid levels, serum beta-hydroxybutyrate (BOH), leptin levels, complete blood count (CBC), serum electrolytes (including calcium, phosphate and magnesium), renal and liver functions tests (LFTs), and uric acid. Hunger was evaluated with a 7-point Likert scale (range: extremely hungry to extremely full) at each visit.

Compliance with the diet was evaluated at each visit by review of patient's consumption of food supplied by the study, of extraneous food consumed in place of or in addition to the study food, and by urine ketone diaries. It was scored as a subjective composite of these factors on a 0-3 scale as 3 = complete compliance, 2 = partial, substantial compliance, 1 = partial, slight compliance, and 0 = complete non-compliance.

**Diet:** KD consisted of 3:1 [fat]: [protein + carbohydrate] ratio by weight, with daily 20 g CH, and approximately 1600 kcal/day. The diet was supplemented with vitamins, calcium and phosphorus supplements to meet the requirements of US Dietary Reference Intakes (DRI) standard. It was administered as complete meal replacement program which consisted of five ready-made meals, including breakfast, morning snack, lunch, afternoon snack and dinner. Meals were made according to designed recipes (Anemone LLC, Bethesda, MD) and both monounsaturated and saturated fat was used. Meal examples are shown in Supplementary table 1. Meals were prepared uniformly by one catering facility (Avalon Caterers, Alexandria, VA, USA), and were delivered frozen once a week. All participants received the same meal plan. Participants were counseled not to eat any other food or consume any calorie-containing beverages. One patient administered the diet on her own, using the same KD and caloric parameters as those employed in the complete meal replacement plan, but her own recipes.

**Diabetic medication adjustment:** For subjects on oral hypoglycemic medications, the medication dose was reduced by 25-50% on treatment day 1, and was then adjusted at each visit based on blood glucose diaries. For subjects on both oral hypoglycemic medications and insulin, oral hypoglycemics were tapered off first, commonly in 25-50% decrements every 1-2 weeks. Insulin taper was initiated once all oral hypoglycemic medications had been discontinued and occurred in 25% step/week reduction unless blood glucose levels suggested a different rate. Patients were given detailed

instructions for dealing with hypoglycemia in case their blood glucose level dropped to  $\leq 60$  and  $\leq 50$  mg/dl levels; they were asked to call the study staff immediately should this occur.

**Outcomes:** Primary outcome measures included weight, BMI and AEs. Secondary outcome measures included FPG, HbA1c, fasting serum insulin levels, diabetic medication change, waist circumference, BP, treatment compliance, and fasting serum lipid levels.

**Statistical analysis:** Continuous outcomes were compared using a Wilcoxon rank-sum test to evaluate the change from baseline at 9 months of treatment. The analysis was done on "intent to treat" basis for all subjects, and secondarily "per protocol" for all subjects who completed the study per protocol. For all outcome variables, a completer's analysis and last observation carried forward (LOCF) were performed. Analyses were performed using IBM SPSS version 23, with statistical significance at  $\leq 0.5$ .

**Table 1:** Demographics, disease characteristics and baseline treatment.

	ITT <sup>1</sup> (n = 10)
Gender	F = 6
Age <sup>2</sup> (mean, range)	55.1 (41-66)
Disease age onset <sup>2</sup> (mean, range)	47.4 (19-62)
Disease duration (years, range)	5.9 (1-21)
History of acute diabetic complications	1
History of chronic diabetic complications	7 (retinal 3, neuropathy 5, nephropathy 1, coronary artery disease 1) <sup>3</sup>
Family History of T2DM	7

<sup>1</sup> ITT = Intention to treat

<sup>2</sup> Years

<sup>3</sup> 3 patients had more than one complication

to inability to pick up food weekly from study site because of a long drive or work-related travel), and personal (n = 1: the subject thought he achieved his goal of T2D remission in the 4th month and stopped). No subject discontinued because of adverse events. All but one of the subjects who stopped treatment early were followed for 9 months.

**Table 2:** Diabetic medications at baseline, at the end of the study, time during the study when they were stopped and for patients who stopped and later re-started diabetic medications, time when the medications were re-started.

Subject #	Baseline	Study end	Study week/ mo when stopped	Early treatment stop (mo)	Study month when restarted
1	Metformin 2 g/d	0	2 wk	no	never
2	Metformin 1.5g/d, Glipizide 20 mg/d	Metformin 1.5 g/d	5 mo	yes (8)	9 mo
3	Metformin 1 g/d	same	1 wk	yes (2)	5 mo
4	NovoLog Mix 100 IU/d Humulin prn	same	2 mo	yes (3)	3 mo
5	0	0	n/a	no	n/a
6	Metformin 1 g/d	0	1 wk	no	never
7	Ins Lantus 80 IU/d, Novolog prn	same	1 mo	yes (2)	3 mo
8	Metformin 1g/d, Actos 15 mg/d	0	2 wk	no	never
9	Metformin 2.25 g/d	0	2 wk	no	never
10	Glipizide 8 mg/d	0	1 mo	yes (4)	never

## Results

**Subject disposition:** Eleven subjects were enrolled, (6 women; 5 African Americans, 4 Caucasians, 1 Indian; mean age 51.1 years [range 41-66], mean diabetes duration 5.9 years [range 1-21 years]). Subject demographics and disease characteristics are shown in table 1. All 11 subjects received at least one treatment ("intent to treat"). However, 1 subject discontinued the diet on day 4, for psychosocial reasons. She had bipolar affective disorder and anxiety, lived 40 miles from the study site, became anxious about dietary restriction and the drive to the study site and stopped. Because she received only 3 days of treatment, we excluded her from the analysis. We modified the "intent to treat" (mITT) criteria to include all subjects who received  $\geq 4$  days of treatment. Ten subjects were included in the mITT group; 5/10 subjects discontinued the study early (Table 2) and 5/10 completed 9 months of treatment per protocol (PP). Reasons for discontinuation were loss of motivation (n = 1), socioeconomic (n = 3, due

**Efficacy:** Weight, BMI, FPG, HbA1c and fasting insulin results are shown in table 3. In the modified intent to treat group, mean body weight (BW) declined by 28.8 lbs from baseline 244.8 lbs to 216 lbs (p = 0.008), mean BMI by 11.62% from 39.84 kg/m<sup>2</sup> to 35.21 kg/m<sup>2</sup> (p = 0.008), mean FPG by 21.56 mg/dL from 137.7 mg/dL to 116.14 mg/dl (NS), mean HbA1c by 1.16% from 7.36% to 6.2% (p = 0.016), and fasting insulin level by 14.23  $\mu$ IU from 23.18  $\mu$ IU to 8.95  $\mu$ IU (SD 5.68) (NS). Four of the mITT patients achieved  $\geq 15\%$  BMI reduction, of which 3 were PP patients and 1 a non-completer.

In the 5 per protocol subjects, mean weight declined by 35.6 lbs from 227.2 lbs to 191.6 lbs (p = 0.063), mean BMI by 17.08% from 37.46 kg/m<sup>2</sup> to 31.06 kg/m<sup>2</sup> (p = 0.063), FPG by 47 mg/dl from 135.8 mg/dl to 88.8 mg/dl (p = 0.12), HbA1c by 1.36% from 7.0% to 5.64% (p = 0.063), and fasting insulin level by 14.76  $\mu$ IU from 20.56  $\mu$ IU to 5.8  $\mu$ IU (NS).

Of the 10 mITT subjects, 9 were on hypoglycemic medications at study onset, including 2 on insulin (Table 2),

**Table 3:** Weight, body mass index (BMI), fasting plasma glucose (FPG, in mg/dL), HbA1c and fasting insulin levels (mIU/dL) in the modified intent to treat (mITT) patient population and per protocol (PP) subgroup.

	mITT (n = 10)					PP (n = 5)				
	Baseline Mean (SD) <sup>1</sup>	Study end Mean (SD)	Difference	Difference %	p	Baseline Mean (SD)	Study end Mean (SD)	Difference	Difference %	p
<b>Weight (lb)</b>	244.8 (59.25)	216 (70.22)	-28.8	-11.7	0.008	227.2 (62.3)	191.6 (65.59)	-35.6	-15.6	0.063
<b>BMI</b>	39.84 (9.74)	35.21 (11.16)	-4.63	-11.62	0.008	37.46 (4.59)	31.06 (5.07)	-6.4	-17.08	0.063
<b>FPG (mg/dl)</b>	137.7 (52.82)	116.14 (73.18)	-21.56	-15.66	0.37	135.8 (51.27)	88.8 (17.25)	-47	-34.61	0.12
<b>HbA1c (%)</b>	7.36 (1.42)	6.2 (1.29)	-1.16	-15.76	0.016	7 (1.33)	5.64 (0.4)	-1.36	-19.43	0.063
<b>Fasting Insulin (μIU/L)</b>	23.18 (16.27)	8.95 (5.68)	-14.23	-61.35	0.18	20.56 (10)	5.8 (3.54)	-14.76	-71.79	0.25

mITT = modified intent to treat. PP = per protocol; SD = standard deviation.

BMI = body mass index, kg/m<sup>2</sup>; FPG = fasting plasma glucose, HbA1c= glycosylated hemoglobin

**Table 4:** Fasting plasma lipid levels (mg/dl) and serum leptin levels (ng/ml) (rounded to the nearest two decimal points).

	mITT (n = 10)					PP (n = 5)				
	Baseline Mean (SD) <sup>1</sup>	Study end Mean (SD)/ SEM	Difference	Difference %	p	Baseline Mean (SD)	Study end Mean (SD)	Difference	Difference %	p
<b>Chol (mg/dL)</b>	175 (57.31)	200.28 (32.01)	+25.28	+14.45	0.46	163.8 (35.4)	184.6 (13.59)	+20.8	+12.7	0.12
<b>TG (mg/dL)</b>	150.4 (91.76)	103.42 (76.05)	-47	-31.3	0.031	155.4 (115.82)	71.2 (22.79)	-84.2	-54.18	0.063
<b>HDL (mg/dL)</b>	43.7 (9.53)	53.82 (12.77)	+9.58	+21.92	0.031	43.6 (9.73)	53.4 (12.66)	+9.8	+22.48	0.12
<b>LDL (mg/dL)</b>	102.51 (46.33)	125.89 (26.14)	+23.63	+23.05	0.4	91.62 (23.51)	116.8 (20.82)	+25.18	+27.48	0.06
<b>Leptin (ng/ml)</b>	22.91 (16.88)	17.48 (19.3)	-5.43	-23.7	0.31	16.05 (13.31)	8.76 (5.99)	-7.29	-45.42	0.25

<sup>1</sup> SD = standard deviation

and one had diet-treated diabetes (with a non-LC diet). At study end, 6/10 modified intent to treat subjects (60%) achieved T2D remission, including 4 complete remission (defined as FPG mgdl and HbA1c 6.0%, off all hypoglycemic medications) and 2 partial remission (defined as FPG 126 mg/ml and HbA1c 6.4%, off all hypoglycemic medications) [39]. Subjects who achieved sustained T2D remission included 5/5 PP subjects and 1 non-completer; 5/9 (56%) of the patients on hypoglycemic medications at baseline achieved sustained remission. All subjects on diabetic medications at baseline had all medication discontinued while on the diet. All medications were eliminated within 1-2 months of treatment for all but one subject. This included 2 subjects on insulin, one on 100 units/day and one on 80 units/day, who stopped insulin 1 and 2 months after KD initiation. Both subjects on insulin

stopped the diet after 2 months because of logistic difficulties in picking up the food. Four of the 5 subjects who stopped the diet early ended up resuming diabetic medication by month 9 of the study, 3 on the same medications/doses and one, insulin-treated, with 25% reduction of insulin dose.

The speed by which glycemic normalization occurred was fast. Pre-treatment FPG was elevated in 5 patients; it normalized in 3 patients after 1 week of treatment, in 1 patient by 4 weeks treatment, and in 1 (insulin-treated) by 6 weeks treatment. The other patients had normal FPG before study but were able to discontinue medications by 1 week - 2 months after KD initiation, except for one poorly-compliant patient.

Eight patients had co-existing hypertension. Three were able to stop anti-hypertensives after 2-3 months with

normalization of blood pressure (all PP patients).

**Long term remission:** The study lasted 9 months. However, the patients were followed clinically afterwards for 2.3–4.7 years from enrollment. Four of the six patients who were in remission at the end of the study (4/10 [40%] of all mITT subjects) remained in remission for 2.3–4.7 years (2.3, 3.5, 4.1 and 4.7 years). Two patients relapsed, 1.5 and 1.7 years after achieving remission.

**Safety and tolerability:** KD was well tolerated. No patient discontinued the diet because of AEs. Six patients had transient hunger that was mild in all but 1 patient. Six patients had transient constipation, 2 had transient diarrhea, and 2 had transient fatigue on diet initiation (without hypoglycemia).

Serum lipid levels are shown in table 4. There was statistically significant reduction in triglyceride levels and increase in high density cholesterol levels (HDL) in the mITT group, and a trend to increase cholesterol, HDL and low density lipid cholesterol level in the PP group; all other changes were statistically non-significant. Seven mITT patients were on lipid-lowering medications at study onset; one had the dose of simvastatin increased from 40 mg qd to 80 mg qd, with no other changes. There were no significant changes in CBC, CMP, serum calcium or uric acid (results not shown).

**Compliance:** Three patients were fully compliant for the entire study duration (all PP patients). Three patients were fully compliant during the first three months of the study, one of them then stopped because he felt that he had achieved his goal (T2D remission); the other 2 completed the study but became partially compliant after 3 months (compliance grade 2/3 during study months 4–7), and 1/3 during months 8–9. Three patients were fully compliant during the first 2 months but then became non-compliant and stopped treatment after 2–4 months. One patient was partially compliant (1/3) throughout the study; she stopped the study at 8 months. Compliance was impaired by dislike of the food in 1 subject, and issues with long term food restriction of any kind in 5 subjects.

## Discussion

This pilot study suggests that classic 3:1 [fat]:[carbohydrate + protein] weight ratio ketogenic diet may be effective in inducing T2DM remission in obese individuals with T2DM. Sixty percent of subjects treated for  $\geq 1$  week achieved T2D remission, and 100% of subjects who completed the full protocol achieved T2D remission. BMI loss, 11.6% for all subjects and 17.1% for per protocol patients, was amongst the highest of any reported in previous dietary or pharmacological intervention studies [30, 31, 33–35, 40], and was similar to the 18.3% BMI reduction seen in our 3:1 KD study in patients with refractory epilepsy and obesity [38]. Four of the 10 mITT patients achieved BMI reduction of 15%. The diet was well tolerated with no serious or severe adverse events and no discontinuations because of AEs.

The study has significant limitations. It is an open

label, uncontrolled study with a small sample. There was a high rate (54.5%) of early treatment discontinuation. This discontinuation rate is higher than that in many controlled LC studies. The main reasons for early discontinuations were psychosocial, chiefly inability of patients to pick up the food once a week from a central site because of lifestyle (out of town work, inability to drive long distance). Delivery of meals to the patients' home may improve retention. One patient with history of anxiety and bipolar affective disorder became very anxious about the change in diet. It is possible that the complete meal replacement ketogenic diet treatment may not be suitable for patients with unstable psychiatric disease. The caloric restriction of approximately 1600 kcal was the same for all individuals, regardless of gender, baseline caloric intake or energy expenditure, which were not estimated.

To our knowledge this is the first study of "classic" 3:1 KD in T2DM and obesity. 3:1 KD is used in refractory epilepsy, where weight loss is a recognized side effect. 3:1 KD differs from the commonly used low CH or very low CH ketogenic diets in that the CH content is limited to 20 g/day for the duration of the diet (not just during the initiation phase) and fat content is much higher, 87% caloric content vs. approximately 50% in the usual low or very low CH diet [37]. These differences may explain the rapid remission of T2DM (very low dietary CH resulting in normalization of FPG and of hyperinsulinemia) and the sustained nature of T2D remission (large weight loss reversing obesity-induced insulin resistance and hyperinsulinemia). In this small study, the 60% T2D remission in the intent to treat group was higher than rates seen in low and very low CH diet studies published to-date (0–25%) as was the weight loss [27–35, 40] EMBASE (2010–May 2015. HbA1c reduction of 1.16% and FPG reduction of 21.56 mg/dL in the intent to treat group were comparable to other low/very low carbohydrate studies.

The caloric restriction of our diet was not large - approximately 1600 kcal/day. It was associated with hunger in 6 subjects; in 5/6 this was mild and short-lasting. The relative lack of hunger may be due to very low carbohydrate and high fat content of the diet [41]. Lack of hunger in LC diets has been noted before [42]. Spontaneous reduction in caloric intake is observed when carbohydrates are restricted to 5–10% of caloric intake [43, 44]. In one study, hunger was reduced by 50% after 1 week of LCD [42]. Hunger suppression may be mediated by reduced serum leptin and insulin levels [45].

The mechanism of the diabetic remission is not clear - the study was not designed to elucidate this. However, the fast rate of glycemic normalization, before substantial weight loss occurred, suggests that the initial glycemic normalization is due to carbohydrate intake restriction. The finding is similar to a previous in-patient study of LC diet with 20 g CH/day in which glucose levels normalized and insulin sensitivity improved by 75% after 2 weeks [43]. The fact that all patients who discontinued study in < 3 months resumed hypoglycemic medication suggests that weight loss is required for long term reversal of insulin resistance.

The study is the first study that we are aware of that has applied complete meal replacement using cooked meals (rather

than off the shelf snacks) to obesity-related T2D. Weight loss and glycemic control utilizing meal replacements may be more effective for management of T2D with overweight/obesity than diets without meal replacement [46-48]. In the Look Ahead study partial meal replacement (PMR) of 2 meals with liquid shakes or bars for 4 months, followed by 1 MR for 6 months, was associated with greater weight loss than standard diet [49]. The greater the degree of PMR the greater the benefit [47]. Previously published and commercially available meal replacement programs (such as Medifast, Jenny Craig and others) are *partial* meal replacement programs. A major difficulty with any diet in adults is the self discipline it requires. Diet adherence may be easier if there is no choice - or if non-adherence is obvious to the dieting individual. This is the case with the complete meal replacement program we used where 100% of calories were derived from completely prepared meals. However, compliance in the present study was mixed - only 3/10 subjects treated for  $\geq 1$  week were fully compliant for the whole study, with the remaining subjects partially compliant.

Another advantage of a complete meal replacement program is its potential for scalability. Most currently applied dietary intervention approaches rely on dietary counseling. Recently, a low CH study combining continuous care intervention with intense monitoring of T2D biomarkers and individualized counseling achieved substantial T2D medication reduction with HbA1c, FPG and insulin level improvements [50]. However, the large time commitment required of both the healthcare provider and the patient, and the limited number of health care providers trained to deliver dietary counseling limits the counseling dietary approach to counter the T2D/obesity epidemic. The complete meal replacement is less labor- time- and resource-intensive than lifestyle/dietary counseling programs, and has therefore the potential to be applied on a large scale.

In summary, this pilot study suggests that "classic" 3:1 KD using the novel approach of a complete ready-made meal replacement program may be safe, well tolerated and effective in treatment of obesity-related T2DM. The efficacy, simplicity and scalability of the program suggest a potential for wider use of this approach in the treatment of obesity related T2DM. A larger, controlled study is warranted.

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## Authorship

All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their

approval for this version to be published.

## Disclosures

Pavel Klein is a founder and majority owner of Anemone LLC, Bethesda, MD, which developed recipes used in the study.

Pavel Klein has acted as a consultant to a number of neuropharma companies, namely UCB Pharma, Sunovion, Lundbeck and Engage Pharmaceuticals, has been on advisory boards of Lundbeck, Sunovion, UCB Pharma, is on speaker's bureau of Eisai Inc., Sunovion, and UCB Pharma, and has received research funding for projects on epilepsy from Eisai Inc. and Lundbeck.

Ivana Tyrlikova, Nicholas Pirolli, Arkady Barber, Lenka Goldman and Mojmir Tyrlik, declare that they have no conflict of interest.

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