

# A 12-Week Low-Calorie Diet plus Behavioral Modification Acutely Improves Glycemic Parameters in Type 2 Diabetes Mellitus

Bobbie G Paull Forney<sup>1</sup>, Justin B Moore<sup>1,2</sup>, Frank Dong<sup>2\*</sup>, Elizabeth Ablah<sup>2</sup> and James L Early<sup>2,3</sup>

<sup>1</sup>Via Christi Weight Management, Via Christi Hospitals Wichita, Inc, USA

<sup>2</sup>University of Kansas School of Medicine-Wichita, Wichita, USA

<sup>3</sup>Health Management Resources, Boston, Massachusetts, USA

## Abstract

**Background:** This study sought to determine the effect of a 12-week low-calorie diet (LCD) and behavioral modification program on fasting plasma glucose (FPG) levels, glycated hemoglobin (GHb) levels, use of hypoglycemic agents, and change in glycemic parameters in an overweight or obese population with type 2 diabetes mellitus.

**Methods:** This was a retrospective review of 129 participants with type 2 diabetes. Logistic regression analysis was conducted to explore predictors associated with improvement in glycemic parameters.

**Results:** FPG decreased from  $7.77 \pm 2.62$  mmol/l at baseline to  $6.66 \pm 1.93$  mmol/l after 12 weeks ( $p=0.0013$ ). GHb decreased from  $7.34 \pm 1.38\%$  at baseline to  $6.55 \pm 0.95\%$  after 12 weeks ( $p<0.001$ ). Use of hypoglycemic agents decreased from  $1.69 \pm 1.09$  hypoglycemic agents per patient at baseline to  $1.01 \pm 0.93$  hypoglycemic agents per patient after 12 weeks ( $p<0.005$ ). The prevalence of optimal glycemic parameters, defined as a GHb under 6.5% and an FPG under 7.0 mmol/l while off medications, increased from 1.4% ( $n=1$  of 71) at baseline to 23.9% ( $n=17$  of 71) after 12 weeks. Males were more likely to achieve optimal glycemic parameters at 12 weeks than were females (OR 3.7, 95% CI [1.2, 11.8]). Participants with a baseline GHb  $\leq 7.0\%$  were more likely than those with a GHb  $>7.0\%$  to achieve optimal glycemic parameters after 12 weeks (OR 4.6, 95% CI [1.4, 15.7]).

**Conclusions:** A 12-week low-calorie diet combined with a behavioral modification program is effective in reducing FPG, GHb, and use of hypoglycemic agents and it is associated with acute improvement in glycemic parameters in obese subjects with type 2 diabetes mellitus. Mechanisms controlling skeletal muscle mass to that of the lean, while reducing body mass.

**Keywords:** Type 2 diabetes; Glycated hemoglobin; Low-energy diet; Weight loss

## Introduction

The coexistence of diabetes and obesity among individuals is well established [1-3]. In 2009-2010, 35.7% of adult Americans were obese, and 33.1% were overweight [4]. In 2010, 25.8 million Americans, or 8.3% of the US population, had type 2 diabetes and an estimated 79 million Americans ages 20 years and older had either impaired fasting glucose or impaired glucose tolerance [3]. Obesity and type 2 diabetes are associated with increasing healthcare costs, with the total estimated cost of diabetes exceeding \$174 billion annually in the United States [5,6].

Dietary modification and physical activity are considered first-line treatments for type 2 diabetes [7]. Multiple recent randomized controlled trials have examined the effect of weight loss surgery (WLS) on remission of type 2 diabetes, with results less favorable for dietary modification [8,9]. Caloric restriction as a treatment for diabetes mellitus was perhaps first described by Frederick Madison Allen in 1920. Though multiple studies have confirmed the effectiveness of low-calorie diets (LCDs) and behavioral interventions on preventing diabetes in persons with obesity, impaired fasting glucose, or impaired glucose tolerance, the effectiveness of low-calorie diets, combined with intensive lifestyle interventions on decreasing glycosylated hemoglobin (GHb), fasting plasma glucose (FPG), and hypoglycemic agent use in type 2 diabetes is not well established [1,2]. Study of aggressive dietary and behavioral interventions for diabetes is especially important given the recent publication of randomized clinical trials comparing bariatric surgery to "medical management." If the conventional medical therapy in such studies is not sufficiently aggressive, the superiority of surgery may be overstated.

The purpose of this study was to assess changes in weight, body mass index (BMI), FPG, GHb, use of hypoglycemic agents, and glycemic control status from baseline to week 12 in overweight or obese patients with type 2 diabetes who participated in a medically supervised weight loss intervention consisting of a low-calorie diet and multi-component lifestyle intervention. Additionally, this study examined which variables, if any, predict reduction in hypoglycemic medications or acute achievement of optimal glycemic control parameters, defined as a GHb under 6.5% and an FPG under 7.0 mmol/l while off all hypoglycemic agents.

## Research Design and Methods

This was a retrospective analysis of a maintained, de-identified clinical dataset of adult patients (18 years of age and older) who voluntarily enrolled and attended the first class in the Via Christi Weight Management (VCWM) program from January 1, 2009 to December 31, 2010. The study was approved by the Institutional Review Board of Via Christi Hospitals, Incorporated, and by the Human Subjects Committee at the University of Kansas School of Medicine-Wichita.

\*Corresponding author: Frank Dong, University of Kansas School of Medicine-Wichita, 1010 N Kansas St, Wichita, KS, 67228, USA, Tel: (316) 293-2627; Fax: (316) 293-2695; E-mail: fdong@kumc.edu

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## Weight loss program

Patients in an urban weight management clinic (Via Christi Weight Management [VCWM], Wichita, Kansas) voluntarily enrolled in a medically supervised LCD (minimum 800 kilocalories per day; Health Management Resources® [HMR], Boston, MA) coupled with a behavioral modification program for a minimum of 12 weeks. Health Management Resources is a comprehensive, high intensity lifestyle intervention that includes the use of meal replacements, increased physical activity, and weekly coaching. The medical supervision protocol and the methodology of the multi-component lifestyle intervention have been described previously [10]. Briefly, the LCD limits food choices to meal replacements (shakes, soup, cereal, and entrees) during the weight loss phase. Participants must consume a minimum of five meal replacements (shakes, soup, or cereal) and two vitamin-mineral tablets per day, and may consume meal replacement entrees as needed. The LCD provides more than 100% of most of the vitamins and minerals from the United States Recommended Dietary Allowance (RDA) guidelines [11]. Low calorie diet participants are required to consume a minimum of 800 kilocalories per day and are encouraged to expend at least 2000 kilocalories per week in physical activity. Participants are taught to monitor and convert minutes of physical activity to calories expended based on intensity level, and values are self-reported to behavioral staff during weekly visits. During the weight loss phase, attendance at weight management classes and medical visits are mandatory for continued participation in the program.

## Participant data

Detailed patient questionnaires were used to obtain participant demographics, diabetes history, and current medications. Height and weight were collected and verified by the medical staff during a required baseline medical evaluation. Fasting venous samples were collected for measurement of serum glucose and GHb at baseline and +/- 2 weeks of the 12 week end date. Verified weights and behavioral data were recorded and entered into a clinical data set every four weeks. Hypoglycemic agents and dosages were recorded at the week 12 visit.

## Patient selection

All patients met the requirements of HMR's medical guidelines for participation, which specifically exclude individuals who are pregnant, engaged in active substance abuse, engaged in active eating disorders or behaviors, who have been diagnosed with severe liver disease or renal failure, who have been diagnosed with an active malignancy, or who have been diagnosed with a wasting disease (i.e., Cushing syndrome, bacterial endocarditis, osteomyelitis, or tuberculosis), and who have undergone mal absorptive bariatric surgical procedures. Participants were excluded from this analysis if they had a BMI less than 25.0 kg/m<sup>2</sup>, were diagnosed with type 1 diabetes, were less than 18 years of age, or failed to complete 12 weeks of the intervention.

## Variables

Outcomes of interest included the change in FPG, GHb, and use of hypoglycemic agents from baseline to 12 weeks. Variables collected for analysis included: participant age, gender, race, ethnicity, years with a diagnosis of type 2 diabetes at baseline, and self-reported use of hypoglycemic agents. Biometric variables collected at baseline and week 12 included height, weight, BMI, FPG, and GHb.

Body mass index (BMI) was calculated using the formula: current mass in kilograms/ (current height in meters)<sup>2</sup>. Percent of Initial Body Weight lost (%IBWL) was calculated using the formula: ((baseline weight - week 12 weight)/baseline weight)×100. Participants with a

GHb level ≤ 7.0% were considered to have their diabetes controlled. Hypoglycemic agents were totaled per patient at baseline and at 12 weeks. For the purpose of this analysis, long-acting insulin, short-acting insulin, and mixed insulin were considered separate hypoglycemic agents. Hypoglycemic agent categories were classified by number of agents: 0, 1, 2 and ≥ 3.

Participants were considered to have achieved acute optimization of glycemic parameters if all the following criteria were met: 1) FPG <7 mmol/dl, 2) GHb less than 6.5%, and 3) discontinuation of all hypoglycemic agents. The term "optimization" was used as this study did not include the one-year laboratory data to meet the definition of "partial diabetes remission" proposed by Buse et al. [12].

## Statistical Analysis

All analyses were using the SAS Software for Windows (Version 9.3, Cary, NC). All data were analyzed on an aggregate level. Descriptive statistics were used to summarize the data. Continuous variables were presented as means (M) and standard deviations (SD), and categorical variables were presented as frequencies and percentages.

Within-group comparisons between baseline and 12 weeks were compared using a paired t test. Repeated measurement analysis was conducted to explore the effect of gender and age at program-start on subject weight at baseline and weeks 4, 8 and 12. Intention-to-treat analysis was not performed; only data from participants who completed the intervention were included in the 12-week analysis. Logistic regression analysis was conducted to explore the relationship between the response and the predictors, with the response being the optimization of glycemic parameters (achieved or not achieved), and the predictors being gender, ethnicity, baseline BMI category (overweight, class 1, class 2, or class 3), and baseline GHb category (controlled [≤ 7.0%] or uncontrolled [>7.0%]). All statistical tests were two-sided. A p-value of 0.05 or less was considered statistically significant.

## Results

Among the 440 patients included in the database, 131 were previously diagnosed or newly diagnosed with type 2 diabetes at the baseline medical evaluation. Further screening of the database identified two patients with type 1 diabetes. As a result, 129 participants with type 2 diabetes were included in the final analysis. More than half (56.6%, n=73) were female, and the majority (89.1%, n=115) were Caucasian (Table 1). The average age was 53.2 ± 11 years

The average weight at baseline was 132.5 ± 31.0 kg and the average weight at week 12 was 116.0 ± 27.0 kg (p<0.001, Table 2). Repeated analysis on weight at baseline and weeks 4, 8, and 12 suggested that

	Frequency	Percentage
Gender		
Female	73	56.6
Male	56	43.4
Total	129	100
Ethnicity		
Caucasian	115	89.1
African American	7	5.4
Hispanic	5	3.9
Asian	2	1.6
Total	129	100
Age, Mean ± SD	53.2 ± 11.0	

**Table 1:** Demographic Characteristics of Included Patients with Type 2 Diabetes (N=129).

Outcome Measure	Baseline	Week 12	P-value
Weight (kg)	132.5 ± 31.0	116.0 ± 27.0	<0.001
FPG (mmol/l)	7.77 ± 2.62	6.66 ± 1.93	0.0013
GHb (%)	7.34 ± 1.38	6.55 ± 0.95	<0.001
Hypoglycemic Agent Use (#)	1.69 ± 1.09	1.01 ± 0.93	<0.005

**Table 2:** Summary of Weight, FPG, GHb, Hypoglycemic Agent Use between Baseline and Week 12.

	Baseline		Week 12	
	Meeting acute optimization criterion [N (%)]	Not meeting acute optimization criterion [N (%)]	Meeting acute optimization criterion [N (%)]	Not meeting acute optimization criterion [N (%)]
FPG	50 (51.6)	47 (48.4)	67 (69.1)	30 (30.9)
GHb	17 (23.3)	56 (76.7)	40 (54.8)	33 (45.2)
Hypoglycemic agent use	13 (13.0)	87 (87.0)	35 (35)	65 (65)
All three criteria combined	1 (1.4)	70 (98.6)	17 (23.9)	54 (76.1)

\*The FPG optimization criterion was defined as FPG ≤ 6.94 mmol/l. The GHb optimization criterion was defined as GHb ≤ 6.4%. Hypoglycemic agent optimization was defined as hypoglycemic agent use=0.

**Table 3:** Pre-LCD and Week 12 Summary based on FPG, GHb, and Hypoglycemic Agent Use.

there was a steady decrease in weight for both men and women. Women were expected to lose a mean of 13.56 kg, whereas men were expected to lose a mean of 18.23 kg (p=0.03). The average baseline FPG was 7.77 ± 2.62 mmol/l, and the average week 12 FPG was 6.66 ± 1.93 mmol/l (p=0.0013 by paired t-test). The average baseline GHb was 7.34 ± 1.38% and the average post-LCD GHb was 6.55 ± 0.95% (p<0.001 by paired t-test).

Use of hypoglycemic agents decreased from 1.69 ± 1.09 agents per participant at baseline to 1.01 ± 0.93 agents per participant after 12 weeks (p<0.005). Chi-square analysis suggested a significant difference between pre-LCD hypoglycemic agent category and post LCD hypoglycemic agent category (p<0.001 by Fisher's exact test).

A summary of glycemic parameter status based on the predictive variables FPG, GHb, and hypoglycemic agent use is presented in Table 3. One patient who had been diagnosed with type 2 diabetes prior to entering the program were found to have optimal glycemic parameters at baseline. The rate of optimal glycemic parameters increased from 1.4% (n=1 of 71) at baseline to 23.9% (n=17 of 71) at week 12. Logistic regression analysis suggested a significant difference between the baseline and week 12 glycemic status (p<0.001). Participants were 21.8 times (95% CI [4.6, 103.0]) more likely to have achieved optimal glycemic parameters after the LCD than at baseline. Males were 3.7 times (95% CI [1.2, 11.8]) more likely than females to achieve optimal glycemic parameters. Participants with a baseline GHb ≤ 7.0% were 4.6 times more likely (95% CI [1.4, 15.7]) to have achieved optimal glycemic parameters after the LCD than were participants with a baseline GHb>7.0%. The concordance statistic was 0.820, which demonstrate excellent discrimination of the proposed model. Effects of ethnicity and baseline BMI category were not evaluated due to the unbalanced data distribution.

## Discussion

In an overweight and obese population with type 2 diabetes, an intervention consisting of a 12-week LCD and intensive behavioral modification program is effective at reducing weight, BMI, FPG, GHb, and use of hypoglycemic agents. Optimization of glycemic parameters occurred in 23.9% of participants. Use of hypoglycemic agents decreased by 0.68 agents per participant from baseline to 12 weeks, and was not predicted by %IBWL, age, or gender.

Results of this study build on previous work, suggesting strength in focused interventions for obesity, overweight, and metabolic syndrome [10,13-18]. Studies reporting weight loss interventions' effectiveness in

treating, rather than preventing, type 2 diabetes are limited, however, and comparison of the presented results with prior work is difficult due to varying methodologies, varying reporting methods, inconsistent time frames, and inconsistent definitions of remission or optimization of control of type 2 diabetes. Malandrucio et al. suggested that a one week very low calorie diet (400 kcals/day) reduced blood glucose levels, weight, and body fat, but did not comment on medication use nor type 2 diabetes status [19]. Jazet et al. demonstrated that a very low calorie diet (450 kcals/day consisting of 50 g protein, 60 g carbohydrate, and 9 g fat) resulted in the loss of 50% of excess body weight (-20.3+/-2.2 kg) in 10 obese subjects with type 2 diabetes. The weight loss was associated with a reduction in FPG and a reduction in serum fructosamine levels while off hypoglycemic agents [20].

In a trial of drug-naive overweight subjects with type 2 diabetes, Esposito et al. compared a Mediterranean- style diet (restricted caloric intake with<50% of kcals from carbohydrates, ≥ 30% from fat) to a low-fat diet designed using guidelines from the American Heart Association. Both groups were encouraged to participate weekly in a minimum of 175 minutes of physical activity. At follow-up years one through four, participants of both interventions achieved decreases in FPG and GHb levels, with decreases significantly greater in the Mediterranean-style group than the American Heart Association group [17]. After four years, approximately 44% of participants in the Mediterranean diet group and 70% in the low-fat diet group required hypoglycemic agents to treat type 2 diabetes [17]. Findings from their study suggest that conventional therapies, such as the Mediterranean diet, may be effective interventions for improving glycemic control measures as well as delaying the need for hypoglycemic agents.

In randomized trials, laparoscopic gastric banding, Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy, and biliopancreatic diversion (BPD) have had positive results in diabetes remission versus "conventional therapy," with approximately 75-95% of individuals with type 2 diabetes achieving remission [8,9,21,22]. The definition of conventional therapy in these trials, though, typically includes a dietary and behavioral intervention that is less robust than the intervention described in this study. In a RCT of laparoscopic banding versus conventional therapy, Dixon and O'Brien reported a 13% remission rate of diabetes in an obese population (BMI 30 to 40) at two years follow-up [8]. Participants in that trial were instructed to reduce fat intake to <30% of caloric intake, consume a low glycemic load diet, and high-fiber foods [8]. In a RCT comparing RYGB or gastric sleeve to conventional therapy, Schauer et al. defined "conventional therapy" as pharmacologic

treatment and lifestyle counseling for weight management according to ADA guidelines, with counseling by a diabetes educator [22]. Similarly, in an RCT comparing RYGB or BPD to conventional therapy, participants were instructed to reduce total daily energy and fat intake (<30% total fat, <10% saturated fat, and consume high fiber foods) and increase physical activity ( $\geq 30$  minutes of daily brisk walking), with a goal of moderate-intensity aerobic exercise at least twice a week [9]. In contrast to the current study, the conventional therapy groups in all three trials failed to experience a reduction in use of hypoglycemic agents.

The superiority of WLS to conventional treatment for diabetes in randomized trials may be overstated when the behavioral and dietary therapy in the “conventional” arm of trials is not optimized. The current study suggests that among patients with a GHb level near normal, acute optimization of glycemic parameters in type 2 diabetes, including discontinuation of hypoglycemic agents, may occur at a high rate with use of an intense LCD and behavioral intervention. This further suggests that subsequent trials on the effect of surgical interventions on remission rates of diabetes or use of hypoglycemic agents require a more intense “control” intervention, possibly similar to that described here.

Strengths of the study include its rigorous behavioral methodology and its setting; participants were seen in a community-based clinic, and no payments or incentives were provided for subject participation. Additionally, this study’s definition of “optimal glycemic parameters” was identified based on the spirit of recommendations of a panel of experts convened by the American Diabetes Association (ADA) [12]. Hypoglycemic agent discontinuation was not by protocol, however, and many participants chose to remain on metformin, even after normalization of plasma glucose levels, possibly reducing the observed power of the LCD to optimize glycemic parameters.

The study is limited by its retrospective design and by its predominantly Caucasian population, as obesity and type 2 diabetes are over-represented in minority groups [3]. It is further limited by the inability to adjust outcomes for education level, economic status, smoking status, physical activity levels, alcohol intake, or fat intake. Participants in the program were asked to abstain from alcohol, however, and the fat content of the diet is less than 10 percent total kilocalories. Participants were encouraged to expend at least 2,000 kilocalories per week in physical activity, but all physical activity data are self-reported. The study period for the intervention ended at 12 weeks, so the durability of changes; particularly type 2 diabetes statuses are unknown.

## Conclusions

A low calorie diet, coupled with an intensive behavioral intervention for weight management, is effective at producing clinically significant weight loss along with reductions in FPG, GHb, and hypoglycemic agent use in overweight or obese subjects with type 2 diabetes. Most notably, the LCD and behavioral intervention were associated with a high rate of optimization of glycemic parameters. Male participants and participants with a GHb  $\leq 7.0\%$  at baseline were more likely than their counterparts to achieve optimal glycemic parameters.

## Authors Contribution

B.P.F wrote the manuscript and researched data. J.B.M reviewed/edited the manuscript and performed the literature review. F.D. performed all statistical analyses and reviewed/edited the manuscript. E.A. contributed to the discussion and reviewed/edited the manuscript.

J.L.E researched data and contributed to the discussion. B.P.F. is responsible for the contents of this article.

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