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Two Diets with Different Hemoglobin A_{1c} and Antiglycemic Medication Effects Despite Similar Weight Loss in Type 2 Diabetes.

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Abstract

We analyzed participants with type 2 diabetes (n=46) within a larger weight loss trial (n=146) who were randomized to 48 weeks of a low-carbohydrate diet (LCD; n=22) or a low-fat diet + orlistat (LFD+O; n=24).

At baseline, mean BMI was 39.5 kg/m² (SD 6.5) and HbA_{1c} 7.6% (SD 1.3). Although the interventions reduced BMI similarly (LCD -2.4 kg/m²; LFD+O -2.7 kg/m², p= 0.7), LCD led to a relative improvement in hemoglobin A_{1c}: -0.7% in LCD vs. +0.2% in LFD+O (difference -0.8%, 95% CI= -1.6, -0.02; p=0.045). LCD also led to a greater reduction in antiglycemic medications using a novel medication effect score (MES) based on medication potency and total daily dose; 70.6% of LCD vs. 30.4% LFD+O decreased their MES by 50% (p=0.01).

Lowering dietary carbohydrate intake demonstrated benefits on glycemic control beyond its weight loss effects, while at the same time lowering antiglycemic medication requirements.

Keywords

Glycemic control; Medication therapy management; Low carbohydrate diet; Low fat diet; Orlistat

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Introduction

Weight loss is the cornerstone of type 2 diabetes treatment. Specifically which dietary recommendations to give patients with diabetes, however, remains elusive (1). Another quandary is that many antiglycemic agents may hinder weight loss, (2) yet changes to antiglycemic medications during weight loss can obscure the glycemic improvements achieved. A method for summarizing the antiglycemic medication regimen could aid comparative effectiveness research of weight loss interventions.

The purpose of this study is to determine the glycemic, weight, and pertinent adverse effects of two weight-loss diet plans in patients with type 2 diabetes, and to compare the intensity of antiglycemic agent use.

Methods

This study analyzes 46 patients with type 2 diabetes from a weight loss study (n=146) performed at the Veterans Affairs clinics in Durham, NC (3). Each participant provided informed consent. Adults, 70 years with BMI of 27-30 kg/m² plus an obesity-related disease, or BMI 30 kg/m² were included. Excluded were patients with type 1 diabetes, unstable chronic disease, or disease that would interfere with participation; specifically, serum creatinine >1.5 mg/dL in men or >1.3 mg/dL in women, and hemoglobin A_{1c} (HbA_{1c}) >11% were exclusions (3). Eligible participants were stratified by gender and presence of type 2 diabetes, and randomized to group counseling sessions teaching LCD or LFD+O.

LCD instructions were to initially limit daily carbohydrate intake to 20g but calories were not restricted. Carbohydrate intake was slowly liberalized if participants approached their goal weight or cravings threatened adherence. LFD+O instructions were to restrict daily intake of total fat (<30% energy), saturated fat (<10% energy), cholesterol (<300mg), and calories (500-1000 kcal deficit), and take orlistat 120mg three times per day. In both arms, antiglycemic medications were individually adjusted following an algorithm to prevent hypoglycemia and minimize medications that hinder weight loss.

At each visit, trained personnel weighed participants using a calibrated digital scale, measured resting blood pressure twice in the non-dominant arm, and recorded medication changes. Four-day food records, urine and serum labwork were obtained at pre-specified time points.

A medication effect score (MES) assessed overall utilization of antiglycemic agents. First, the percentage of each medication's maximum daily dose was determined. Maximum daily dose of insulin was defined as 1 unit per kilogram of baseline weight, delineating insulin resistance (4). All daily insulin was summed. Next, the percentage of maximum daily dose for each medication was multiplied by an adjustment factor, and these products were summed for the final MES. Adjustment factors were the reported median absolute decrease in HbA_{1c} for each medication (2), e.g., for metformin and the sulfonylureas, the adjustment factor is 1.5; for insulin: 2.5.

Primary outcomes were HbA_{1c}, and MES. The Pearson chi-square test was used to compare MES change categories between groups. Linear mixed models were used to test differences over time for continuous outcomes, adjusting for age, sex, race, education, employment, and baseline weight in kg (the model with weight as an outcome did not include baseline weight as a covariate). All available data, including data from patients who discontinued the study, were used in the models. A random-coefficient approach was used for the body and vital measurements, with fixed effects of linear time (for blood pressure), cubic time (all other

measurements), treatment group, and treatment-by-time interaction; random effects included intercept and linear slope. A repeated-measures approach with categorical time, treatment group, and treatment-by-time interaction was used for the blood test outcomes. An unstructured covariance structure was used for lab outcomes measured at 3 or 5 time points (HbA_{1c}, microalbuminuria, and lipid profile) while a compound symmetry structure was used for those measured at 6 time points (glucose and creatinine).

Results

Baseline characteristics were similar for LCD and LFD+O participants (Table 1). For the primary outcome, estimated mean HbA_{1c} in LCD was 7.6% (95% CI=7.0, 8.1) at baseline and 6.9% (95% CI=6.4, 7.5) at week 48; in LFD+O, HbA_{1c} was 7.6% (95% CI=7.0, 8.1) at baseline and 7.7% (95% CI=7.2, 8.2) at week 48 (Table 2). The estimated difference of change in HbA_{1c} between the groups was -0.8% (95% CI= -1.6, -0.02; p=0.045). The estimated MES decreased by -1.24 (95% CI: -1.80, -0.69) in LCD vs. -0.82 (95% CI: -1.33, -0.31) in LFD+O (p= 0.27 for comparison). Of the participants with complete medication data (LCD n=17; LFD+O n=23), 70.6% of LCD vs. 30.4% LFD+O had decreases in MES by ≥ 50% (p=0.01).

There were 22 patients (n=11 LCD; n=11 LFD+O) with complete food records. In LCD, mean daily carbohydrate intake was 75.9 g (SD = 76.9), total fat 103.2 g (SD = 58.1), and energy 1707.9 kcal/day (SD = 741.1). In LFD+O, mean daily carbohydrate intake was 155.8 g (SD = 78.5), total fat 55.5 g (SD = 41.7), and energy 1419.6 kcal/day (SD = 634.1). In LFD+O, 79.2% of participants who returned pill bottles took ≥ 80% of their pills.

BMI, weight and % change in weight were significantly and similarly improved in both arms. Systolic and diastolic blood pressure changes favored the LCD group, as seen in the overall sample (3). No statistically significant differences between groups occurred in glomerular filtration rate, microalbuminuria, or serum lipids.

Conclusions

In this group of overweight/obese patients with type 2 diabetes, both LCD and LFD+O led to weight loss and reduction in antidiabetic medications. We found HbA_{1c} improved for LCD compared with LFD+O despite similar weight loss. The lack of improved HbA_{1c} for LFD+O may be due to our strategy of reducing antidiabetic medications in an effort to enhance weight loss (7), yet there were greater antidiabetic medication reductions in LCD.

Other studies have found glycemic improvement with low-carbohydrate diets in type 2 diabetes. In one systematic review, glycemic improvement was noted but attributed to weight loss (5). In another review, five trials showed relative glycemic improvement with a low carbohydrate diet but 4 others found no difference between the two diets (1). Subsequent to these reviews, a 12 month RCT found improved HbA_{1c} with a low versus a high carbohydrate diet despite comparable weight loss (6).

The greater improvement in glycemia in LCD might be explained by a greater reduction in glycemic index and carbohydrate amount and/or greater improvement in insulin sensitivity. Use of insulin or secretagogues, however, precluded insulin resistance calculations. Two small feeding studies (8; 9) found that after a low carbohydrate diet, insulin sensitivity improved, as measured by mean rate of glucose infusion required to maintain euglycemia, either by increasing mean peripheral glucose uptake (9), or by reducing glycogenolysis (8).

Our study presents a novel method of antglycemic medication consolidation for comparison of diverse regimens among participants. Our approach allows greater sensitivity to regimen and dosage changes compared to simpler medication scores (12).

This study has the inherent limitations associated with subgroup analyses such as loss of power and multiplicity of testing. The characteristics of our sample (87% men and 54% black) may limit generalizability but may also contribute to the literature which has previously focused on white women.

We found that LCD led to greater improvement in HbA_{1c} compared with LFD+O, which occurred despite similar weight loss and despite greater antglycemic medication reduction in the LCD as summarized using a unique method of medication consolidation.

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S.B.M. conceived the study and wrote the manuscript. W.S.Y. conceived the study and reviewed and edited the manuscript. A.S.J. performed the analyses and reviewed and edited the manuscript. M.K.O. conceived, oversaw and performed the analyses and reviewed and edited the manuscript. J.R.M. conceived the study and reviewed and edited the manuscript. M.N.F. reviewed and edited the manuscript.

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Table 1

Baseline Characteristics for Participants with Diabetes

Characteristics ^I	Low Carbohydrate Diet (n=22)	Low Fat Diet + Orlistat (n=24)	P value
Age, y, mean (SD)	56.6 (7.3)	54.7 (8.4)	0.43
Weight, kg, mean (SD)	118.6 (19.2)	124.2 (25.0)	0.40
BMI	38.3 (6.5)	40.6 (6.4)	0.22
Sex, male	19 (86.4%)	21 (87.5%)	1.00
Race			0.66
Black	11 (50.0%)	14 (58.3%)	
White	10 (45.5%)	10 (41.7%)	
Other	1 (4.5 %)	0 (0 %)	
Education			
College degree	12 (54.5%)	12 (50.0%)	0.78
Employed	7 (31.8%)	14 (58.3%)	0.09
Current smoking status	1 (4.5%)	3 (12.5%)	0.61
Hypertension	16 (72.7%)	22 (91.7%)	0.13
Hyperlipidemia	14 (63.6%)	18 (75.0%)	0.53
Duration of diabetes years, mean (SD)	5.9 (4.4)	7.3 (8.9)	0.80
Antiglycemic medication regimen			0.92
Insulin +/- oral agents	7 (31.8%)	8 (33.3%)	
Oral agents only	12 (54.6%)	14 (58.3%)	
No agents	3 (13.6%)	2 (8.3%)	

^I Baseline characteristics reported as N (%), unless otherwise specified. For categorical variables, exact chi-square tests were used to assess differences in study arms. For continuous variables, t-tests were used with one exception. The duration of diabetes variable has a skewed distribution so we used the Wilcoxon Rank Sum Test.

Table 2

Estimated Clinical and Laboratory Measurements for Participants with Diabetes

Measurement	Low Carbohydrate Diet		Low Fat Diet + Orlistat		LCD – LFD+O Difference of Change at 48 weeks (95% CI) ^{1,2}	P value
	Wk 0	Wk 48 ³	Wk 0	Wk 48 ³		
Clinic measures						
BMI (kg/m ²)	38.7	36.3	40.0	37.3	0.3 (–1.5, 2.2)	0.7
Body weight (kg)	116.9	109.4	125.1	117.0	0.6 (–5.4, 6.7)	0.8
% change Body weight	0	–6.7	0	–7.3	0.7 (–5.1, 6.4)	0.8
Systolic BP, mmHg	134.2	128.3	124.6	129.7	–11.0 (–18.6, –3.3)	0.006
Diastolic BP, mmHg	85.2	80.2	79.0	80.1	–6.0 (–10.8, –1.3)	0.013
Laboratory tests						
Hemoglobin A1C %	7.6	6.9	7.6	7.7	–0.8 (–1.6, –0.02)	0.045
Fasting glucose, mg/dL	152.6	133.7	149.0	146.8	–16.6 (–44.6, 11.3)	0.2
Total cholesterol, mg/dl	172.5	170.5	163.8	152.8	9.0 (–10.3, 28.4)	0.4
Triglycerides, mg/dL	157.8	122.2	148.2	137.6	–25.0 (–74.4, 24.5)	0.3
LDL-C, mg/dL	105.1	104.3	100.5	90.0	9.7 (–7.1, 26.4)	0.3
HDL-C, mg/dL	34.9	37.5	34.6	35.8	1.3 (–2.6, 5.3)	0.5
Creatinine,mg/dL	1.0	1.0	1.1	1.1	0.003 (–0.11, 0.12)	1.0
⁴ GFR, ml/min/1.73sq.m	89.4	88.6	86.3	85.8	–0.4 (–7.8, 7.1)	0.9
⁵ Microalbumin/Cr, mg/g ³	45.1	48.6	32.3	30.4	5.5 (–34.2, 45.1)	0.8
Antiglycemic medication analysis						
Estimated MES	1.78 (1.07, 2.47)	0.53 (0.06, 1.00)	2.13 (1.46, 2.80)	1.31 (0.89, 1.74)	–0.42 (–1.18, 0.33)	0.27
% Achieving 20% decrease in MES		76.5%		56.5%		0.19 ⁶
% Achieving 50% decrease in MES		70.6%		30.4%		0.01 ⁶

Abbreviations: LCD, low carbohydrate diet , LFD+O, low fat diet + orlistat; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density

SI conversion factors: To convert cholesterol and triglycerides to millimoles per liter, multiply by 0.0259 and 0.0113 respectively; and hemoglobin A1c to a proportion of total hemoglobin, multiply by 0.01

¹ Model estimates, 95% CI and p values derived from linear mixed models adjusted for age, sex, race (white vs. non-white), education (college degree vs. no college degree), employment (employed full or part-time vs. not employed), and baseline weight in kg. (Excluding the model with weight as an outcome, which did not include baseline weight as a covariate.)

² Negative values indicate a greater decrease in the outcome measure occurred in the Low Carbohydrate Diet group compared with the Low Fat Diet +Orlistat group.

³ 37 patients (N=16 LCD; N=21LFD+O) had complete data at 48 weeks.

⁴ GFR calculated by CKD-EPI equation: $GFR = 141 \times \min(Scr/\kappa, 1)^\alpha \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] $\times 1.159$ [if black]; Where Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is –0.329 for females and –0.411 for males, min indicates the minimum of Scr/ κ or 1, and max indicates the maximum of Scr/ κ or 1

⁵ There was one patient in the LCD group with substantially increased microalbuminuria at the midpoint assessment in the study (microalbuminuria at baseline=147mg/g Week 24 = 600; Week 48 = 123). The results of the model excluding this patient's readings show a difference of change at 48 weeks of 22.9 (95% CI: -32.7, 78.4) with a p-value of 0.4

⁶ P-values were calculated from a Chi-square test.