research letter

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Two diets with different haemoglobin A1c and antiglycaemic medication effects despite similar weight loss in type 2 diabetes

RESEARCH LETTER

We analysed 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 body mass index (BMI) was 39.5 kg/m^2 (s.d. 6.5) and haemoglobin A1c (HbA1c) 7.6% (s.d. 1.3). Although the interventions reduced BMI similarly (LCD −2.4 kg/m^2; LFD + O −2.7 kg/m^2, p = 0.7), LCD led to a relative improvement in HbA1c: −0.7% in LCD versus +0.2% in LFD + O [difference −0.8%, 95% confidence interval (CI) = −1.6, −0.02; p = 0.045]. LCD also led to a greater reduction in antiglycaemic medications using a novel medication effect score (MES) based on medication potency and total daily dose; 70.6% of LCD versus 30.4% LFD + O decreased their MES by ≥50% (p = 0.01). Lowering dietary carbohydrate intake demonstrated benefits on glycaemic control beyond its weight loss effects, while at the same time lowering antiglycaemic medication requirements.

Keywords: glycaemic control, low-carbohydrate diet, low-fat diet, medication therapy management, 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 antiglycaemic agents may hinder weight loss, [2] yet changes to antiglycaemic medications during weight loss can obscure the glycaemic improvements achieved. A method for summarizing the antiglycaemic medication regimen could aid comparative effectiveness research of weight loss interventions.

The purpose of this study is to determine the glycaemic, weight and pertinent adverse effects of two weight-loss diet plans in patients with type 2 diabetes, and to compare the intensity of antiglycaemic 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 body mass index (BMI) of 27–30 kg/m^2 plus an obesity-related disease, or BMI ≥30 kg/m^2 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 haemoglobin A1c (HbA1c) >11% were exclusions [3]. Eligible participants were stratified by gender and presence of type 2 diabetes, and randomized to group counselling sessions teaching low-carbohydrate diet (LCD) or low-fat diet + orlistat (LFD + O).

LCD instructions were to initially limit daily carbohydrate intake to ≤20 g 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 (<300 mg) and calories (500–1000 kcal deficit), and take orlistat 120 mg three times per day. In both arms, antiglycaemic medications were individually adjusted following an algorithm to prevent hypoglycaemia 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 prespecified time points.

A medication effect score (MES) assessed overall utilization of antiglycaemic agents. First, the percentage of each medication's maximum daily dose was determined. Maximum daily dose of insulin was defined as 1 unit/kg 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 HbA1c for each medication [2], for example, for metformin and the sulfonylureas, the adjustment factor is 1.5; for insulin: 2.5.

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Primary outcomes were HbA1c and MES. The Pearson chi-squared 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 three or five time points (HbA1c, microalbuminuria and lipid profile) while a compound symmetry structure was used for those measured at six time points (glucose and creatinine).

Results

Baseline characteristics were similar for LCD and LFD + O participants (Table 1). For the primary outcome, estimated mean HbA1c in LCD was 7.6% [95% confidence interval (CI) = 7.0, 8.1] at baseline and 6.9% (95% CI = 6.4, 7.5) at week 48; in LFD + O, HbA1c 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 HbA1c 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 versus −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 versus 30.4% LFD + O had decreases in MES by ≥50% (p = 0.01).

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

BMI, weight and percentage change in weight were significantly and similarly improved in both arms. Systolic and diastolic blood pressure changes favoured 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 antiglycaemic medications. We found HbA1c improved for LCD compared with LFD + O despite similar weight loss. The lack of improved HbA1c for LFD + O may be due to our strategy of reducing antiglycaemic medications in effort to enhance weight loss [5], yet there were greater antiglycaemic medication reductions in LCD.

Other studies have found glycaemic improvement with LCDs in type 2 diabetes. In one systematic review, glycaemic improvement was noted but attributed to weight loss [6]. In another review, five trials showed relative glycaemic improvement with a LCD but four others found no difference between the two diets [1]. Subsequent to these reviews, a 12-month randomized controlled trial (RCT) found improved HbA1c with a low versus a high-carbohydrate diet despite comparable weight loss [7].

The greater improvement in glycaemia in LCD might be explained by a greater reduction in glycaemic index and carbohydrate amount and/or a 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 LCD, insulin sensitivity improved, as measured by mean rate of glucose infusion required to maintain euglycaemia, either by increasing mean peripheral glucose uptake [9], or by reducing glycogenolysis [8].

Our study presents a novel method of antiglycaemic medication consolidation for comparison of diverse regimens among participants. Our approach allows greater sensitivity

Table 1. Baseline characteristics for participants with diabetes.*

Characteristics*	Low-carbohydrate diet (n = 22)	Low-fat diet + orlistat (n = 24)	p Value
Age, years, mean (s.d.)	56.6 (7.3)	54.7 (8.4)	0.43
Weight, kg, mean (s.d.)	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
Hyperlipidaemia	14 (63.6%)	18 (75.0%)	0.53
Duration of diabetes years, mean (s.d.)	5.9 (4.4)	7.3 (8.9)	0.80
Antiglycaemic 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%)	

BMI, body mass index.
*Baseline characteristics reported as N (%), unless otherwise specified. For categorical variables, exact chi-squared 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	LCD		LFD + O		LCD − LFD + O Difference of change at 48 weeks (95% CI)†‡	p Value
	Week 0	Week 48§	Week 0	Week 48§		
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
Percentage 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						
Haemoglobin 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
GFR‖ ml/min/1.73 m^2	89.4	88.6	86.3	85.8	−0.4 (−7.8, 7.1)	0.9
Microalbumin ¶, mg/g Cr	45.1	48.6	32.3	30.4	5.5 (−34.2, 45.1)	0.8
Antiglycaemic 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
Percentage achieving 20% decrease in MES		76.5%		56.5%		0.19**
Percentage achieving 50% decrease in MES		70.6%		30.4%		0.01**

BP, blood pressure; BMI, body mass index; CI, confidence interval; GFR, glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LCD, low-carbohydrate diet; LDL-C, low-density lipoprotein cholesterol; LFD + O, low-fat diet + orlistat; MES, medication effect score.

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

†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.)

‡Negative values indicate a greater decrease in the outcome measure occurred in LCD compared with LFD+O.

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

‖GFR calculated by Chronic Kidney Disease Epidemiology Collaboration (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) × 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 [11].

¶There was one patient in the LCD group with substantially increased microalbuminuria at the midpoint assessment in the study (microalbuminuria at baseline = 147 mg/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

**p Values were calculated from a chi-squared test.

to regimen and dosage changes compared with simpler medication scores [10].

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 not only 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 HbA1c compared with LFD + O, which occurred despite similar weight loss and despite greater antiglycaemic medication reduction in the LCD as summarized using a unique method of medication consolidation.

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are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or Duke University. S. B. M. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of Interest

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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