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Effects of two weight-loss diets on health-related quality of life

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Abstract
Purpose To compare the effects of two diets on health-related quality of life (HRQOL).
Methods Overweight volunteers ($n = 119$) were randomized to follow a low-carbohydrate, ketogenic diet (LCKD) or a low-fat diet (LFD) for 24 weeks. HRQOL was measured every 4 weeks using the Short Form-36 and analyzed using linear mixed-effects models.
Results The mean age was 45 years and mean baseline body mass index was 34 kg/m^2; 76% were women. At 24 weeks, five subscales (Physical Functioning, Role-Physical, General Health, Vitality, Social Functioning) and the Physical Component Summary score improved similarly in both diet groups. Bodily Pain improved in the LFD group only, whereas the Role-Emotional and Mental Health subscales and the Mental Component Summary (MCS) score improved in the LCKD group only. In comparison with the LFD group, the LCKD group had a statistically significant greater improvement in MCS score (3.1; 95%CI 0.2–6.0; effect size = 0.44) and a borderline significant greater improvement in the Mental Health subscale (5.0; 95%CI −0.3–10.4; effect size = 0.37).
Conclusions Mental aspects of HRQOL improved more in participants following an LCKD than an LFD, possibly resulting from the LCKD's composition, lack of explicit energy restriction, higher levels of satiety or metabolic effects.

Keywords Diet therapy · Ketones · Mental health · Quality of life

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Introduction

Obesity is associated with multiple debilitating chronic illnesses and explains a large percentage of health care costs [1–4]. Not surprisingly, obesity has also been associated with reduced health-related quality of life (HRQOL), particularly the physical aspects of HRQOL, in multiple cross-sectional studies [5–8]. Perhaps surprisingly, however, few controlled weight-loss trials have demonstrated significant improvements in HRQOL [9].

Low-carbohydrate, ketogenic diets (LCKDs) have been successfully used for weight loss and, compared with control diets, typically result in greater short-term weight loss and improvements in certain serum lipid parameters [10–15]. In addition to their clinical benefits, these diets

may have favorable impacts on HRQOL because there is no limitation on the quantity of certain food groups, unlike energy-restricted diets that explicitly limit total daily calorie intake [10, 12, 14, 16]. Other potential indirect benefits of the greater initial weight loss from LCKDs are improved body image, physical function, and mood.

On the other hand, in one randomized, controlled trial, an LCKD induced a higher frequency of symptomatic side-effects (e.g., constipation, headache, halitosis, muscle cramps), which might adversely impact HRQOL [16]. An LCKD may also result in anxiety and difficulties in social role functioning if LCKD followers experience criticism of their diet from family, friends, and the media, or have limited food choices at social engagements.

The purpose of this study was to examine how two different diet strategies impacted change in HRQOL in individuals seen on an outpatient basis for 6 months during a randomized clinical trial for weight loss [16].

Methods

Study participants

Participants who were above recommended weight range and who had hyperlipidemia were recruited for a randomized trial comparing an LCKD with a low-fat, energy-restricted diet (LFD) [16]. Inclusion criteria were body mass index (BMI) 25–50 kg/m^2; age 18–65 years old; and total cholesterol >200 mg/dl, LDL-C >130 mg/dl, or triglycerides >200 mg/dl. Exclusion criteria were ongoing serious medical conditions, prescription medication in the past 2 months (except stable estrogen or thyroid hormone therapy), weight-loss diet or medication in past 6 months, baseline ketonuria, and pregnant or nursing mother. Participants were allocated to one of the two diets using a computer-generated simple randomization list. The randomization sequence was concealed from study personnel during the screening process. Prior to enrollment, volunteers provided written informed consent approved by the institutional review board.

Intervention

Low-carbohydrate, ketogenic diet group

Participants assigned to this diet were counseled by trained research personnel to reduce carbohydrate intake initially to less than 20 g per day using handouts and a popular lay press diet book [17]. As they approached their desired weight, they were taught how to systematically add carbohydrates back into their diet while continuing to lose weight or maintaining their weight once at goal weight. This group was also provided daily nutritional supplements (multivitamin, essential oils, diet formulation, and chromium picolinate).

Low-fat diet group

Participants assigned to this diet were counseled by a registered dietitian to follow a diet of <30% of daily energy intake from fat, <10% of daily energy intake from saturated fat, and <300 mg cholesterol daily using a booklet and additional handouts [18, 19]. Participants also were counseled to decrease energy intake by 500–1,000 kcal from their calculated weight-maintenance intake [20].

Additional interventions provided to both diet groups

Participants met in small groups every other week for 3 months, then monthly for 3 months. Group meetings were scheduled so that participants of different diet assignment could not mix. The hour-long sessions consisted of body measurements, self-administered questionnaires, educational and supportive counseling led by a research assistant or registered dietitian, and group interaction. In addition, participants from both diet groups were regularly advised to drink 6–8 glasses of fluids daily and encouraged to exercise aerobically for 30 min three or more times per week. No monetary incentives were provided.

Outcome measures

HRQOL was measured at baseline and weeks 4, 8, 12, 16, 20, and 24 using the Medical Outcomes Study Short Form-36 (SF-36) [21]. The SF-36 is a 36-item, self-administered instrument that contains subscales in eight domains: Physical Functioning, Role Limitations due to Physical Functioning (Role-Physical), Bodily Pain, General Health, Vitality, Social Functioning, Role Limitations due to Emotional Functioning (Role-Emotional) and Mental Health. Each of these subscales is scored on a range from 0 (lowest level of HRQOL) to 100 (highest level of HRQOL). The subscales can also be combined to create the Physical Component Score (PCS) and the Mental Component Score (MCS). The SF-36 has demonstrated good construct validity, internal consistency, and test–retest reliability [22–24].

The PCS and MCS are our primary outcome variables for this study. For both the PCS and MCS we formalized our primary outcome measure as the mean difference between groups of the mean changes from baseline to 24 weeks within groups. A change in score of 3–5 points on any one subscale is generally accepted as clinically significant [25, 26].

Statistical analysis

Health-related quality of life

As the primary analysis, linear mixed-effects models (LMMs) that included fixed and random effects were used to examine the change in HRQOL over time in the two treatment groups [27, 28]. The outcome variables used were the eight separate subscales, the PCS, and the MCS. The fixed effects included in the models were time and group assignment, with linear and quadratic time-by-group interaction terms. The random effects in the models were the intercept and linear slope terms. In all of the models, the random-effect terms were assumed to follow a normal distribution with an unstructured covariance matrix; and the residual error terms were assumed to follow a mean-zero normal distribution with an independent covariance structure. All observed data points from baseline to 24 weeks were used to fit the LMMs. The fitted models were used to calculate the following values for the eight separate subscales, and for the MCS and PCS: mean score at each time point for each group, within-group change in mean scores between baseline and 24 weeks for each group, mean difference between groups (LCKD versus LFD) in change scores from baseline to week 24 (i.e., the between-groups difference at week 24), and effect sizes for the between-groups difference. Effect sizes were calculated as the between-groups difference divided by the pooled (i.e., combined across the two groups) standard deviation of change scores from baseline to week 24. The 95% confidence intervals were computed for the within-group changes and the between-groups differences. The between-groups differences for the PCS and MCS were our primary contrasts of interest; for each contrast, a P-value of ≤ 0.05 was regarded as statistically significant.

As a secondary, observational data analysis, we included lagged measures (i.e., from the previous data time point) of time-varying body weight as covariates in the LMMs in order to explore the association between diet assignment (LCKD versus LFD) and HRQOL net of body weight. Therefore, in each longitudinal model (e.g., Physical Functioning), weight measured at baseline is a predictor at week 4, weight measured at week 4 is a predictor at week 8, and so on. The SF-36 administered at clinic visits assessed HRQOL in the 2 weeks preceding the visit. Therefore, lagged weight measures were used (as opposed to concurrent weight) in order to respect the temporal ordering of weight as a variable on the causal pathway between diet assignment and HRQOL. In order to minimize possible bias introduced by adjusting for a post-randomization factor (weight), we included the following baseline covariates commonly correlated with weight and HRQOL: age, race, gender, education, physical activity level, tobacco use, systolic and diastolic blood pressure, and ketonuria level [29].

Handling of missing data

The LMMs employed in our primary analyses provide unbiased estimates of within-group and between-groups change effects under the assumption that outcome missingness is ignorable conditional on treatment assignment and previous outcome values. Further, unlike analysis of covariance (ANCOVA) methods which employ a case-deletion strategy for subjects with incomplete longitudinal outcome measurements (i.e., "completers" analysis), which may lead to bias, LMMs use all available measurements; that is, all patients with at least one occasion of the longitudinal measurements are included in the data analysis. The ignorability assumption can be relaxed by including other non-missing covariates in the LMM that predict outcome missingness. This was done as a stability analysis by including baseline covariates in the LMMs that predicted outcome missingness. Covariates were included in the adjusted LMMs if they significantly predicted outcome missingness (P-value <0.10) in logistic generalized estimating equation (GEE) regressions for each baseline covariate, separately. The following baseline covariates were considered: age, race, gender, education, other SF-36 subscales, physical activity level, tobacco use, systolic and diastolic blood pressure, heart rate, body weight, body mass index, body composition (% body fat, fat mass, fat-free mass, total body water) by bioelectric impedance, and ketonuria level. Missing data were handled differently for the secondary (observational) analyses. Because these analyses adjust for weight, subjects with missing weight values were (necessarily) excluded.

Data were analyzed using PROC MIXED (for the LMM regressions) and PROC GENMOD (for the GEE regressions) in SAS Statistical Software, version 9.1 (SAS Institute, Cary, NC).

Results

Participants

From July 2000 to July 2001, 1,051 volunteers were screened for eligibility and 120 underwent randomization. Sixty volunteers were randomized to the LCKD and 60 were randomized to the LFD (more details on the patient sample and loss to follow-up have been published elsewhere) [16]. One participant randomized to the LCKD discontinued the study prior to receiving the intervention; therefore, the final sample size for these analyses is 119 volunteers. All available data were used for the

Table 1 Baseline characteristics by diet group

Variable	LCKD	LFD
Demographics	($n = 59$)	($n = 60$)
Age		
Years, mean (SD)	44.2 (10.1)	45.6 (9.0)
Gender		
Female	75%	78%
Race		
Caucasian	75%	78%
African–American	22%	18%
College degree	37%	45%
Weight (kg)		
Mean (SD)	97.8 (15.0)	96.8 (19.2)
BMI (kg/m^2)		
Mean (SD)	34.6 (4.9)	34.0 (5.1)
Baseline SF-36 variables	($n = 58$)	($n = 59$)
Physical Functioning		
Mean (SD)	85.3 (13.3)	81.9 (16.8)
Role-Physical		
Mean (SD)	80.1 (31.0)	81.8 (32.1)
Bodily Pain		
Mean (SD)	79.8 (17.5)	76.7 (20.1)
General Health		
Mean (SD)	73.6 (17.2)	75.8 (17.5)
Vitality		
Mean (SD)	57.5 (19.4)	62.2 (16.9)
Social Functioning		
Mean (SD)	89.7 (15.4)	88.9 (17.8)
Role-Emotional		
Mean (SD)	83.9 (28.8)	88.7 (26.7)
Mental Health		
Mean (SD)	79.9 (13.8)	81.7 (13.7)
PCS		
Mean (SD)	49.9 (6.7)	48.9 (8.2)
MCS		
Mean (SD)	51.8 (8.7)	53.8 (7.7)

LCKD low-carbohydrate, ketogenic diet; *LFD* low-fat diet; *SD* standard deviation; *PCS* Physical Component Summary score; *MCS* Mental Component Summary score

longitudinal analyses, including those from the 40 participants who discontinued the study before completing the 24 weeks of follow-up. Baseline characteristics are displayed in Table 1. The mean age was approximately 44 years; the majority of participants were women and of White race. The mean body mass index (BMI) was approximately 34 kg/m^2. There were no differences between the diet groups in the SF-36 subscale scores at baseline (all $P > 0.05$).

The between diet group effects on weight loss for this sample have been reported elsewhere [16]. Briefly, the model predicted mean change in body weight over the 24 weeks was greater in the LCKD group (−12.0 kg; 95%CI −13.8, −10.2) than in the LFD group (−6.5 kg; 95%CI −8.4, −4.6) with a difference between the groups of −5.5 kg (95%CI −8.1, −2.9) [16].

SF-36 data completeness

The SF-36 survey was completed at baseline by 58 of the 59 LCKD participants and by 59 of the 60 LFD participants (Table 2). The SF-36 survey was completed at 24 weeks by 45 (75% of original 60) of the LCKD participants and by 33 (55% of original 60) of the LFD participants. The primary reason for outcome missingness was patient discontinuation (Table 2). Thus, for any fixed patient in our study, nearly identical missing data patterns were observed across the ten different SF-36 measures. At any time point, one or more items on the SF-36 were missing for 2–8% of questionnaires completed by LCKD participants and for 0–10% of questionnaires completed by LFD participants.

Because missing data patterns were nearly identical for each of the outcome measures, the same set of covariates were found to be predictive of missingness for each of the outcome variables in the GEE analyses (each had similar strengths of association; results not shown). Tobacco use at baseline and higher body fat percentage at baseline were associated with a higher probability of missingness in the outcome. White race and higher levels at baseline of Social and Physical Functioning scores, diastolic blood pressure,

Table 2 Participant retention and SF-36 form completeness

Clinic visit	Participant retention			SF-36 Form completeness		
	Total sample ($n = 120$)	LCKD ($n = 60$)	LFD ($n = 60$)	Total sample ($n = 120$)	LCKD ($n = 60$)	LFD ($n = 60$)
Week 0	119 (99%)	59 (98%)	60 (100%)	117 (97%)	58 (97%)	59 (98%)
Week 4	107 (89%)	54 (90%)	53 (88%)	103 (86%)	54 (90%)	49 (82%)
Week 8	100 (83%)	51 (85%)	49 (82%)	97 (81%)	50 (83%)	47 (78%)
Week 12	94 (78%)	50 (83%)	44 (73%)	92 (77%)	49 (82%)	43 (72%)
Week 16	85 (71%)	47 (78%)	38 (63%)	82 (68%)	46 (77%)	36 (60%)
Week 20	80 (67%)	45 (75%)	35 (58%)	74 (62%)	42 (70%)	32 (53%)
Week 24	78 (65%)	45 (75%)	33 (55%)	78 (65%)	45 (75%)	33 (55%)

LCKD low-carbohydrate, ketogenic diet; *LFD* low-fat diet

and education were all associated with a lower probability of outcome missingness. Results based on the baseline covariate-adjusted LMMs were stable; effectively the same conclusions can be drawn from the stability analyses as compared to the primary analyses presented below.

Health-related quality of life

In LMM regression analyses of within-group changes over time, the following SF-36 subscales improved in both the LCKD and LFD groups from baseline to 24 weeks: Physical Functioning, Role-Physical, General Health, Vitality, and Social Functioning (Table 3). Bodily Pain improved a statistically significant amount in the LFD group whereas the improvement in the LCKD group was at the borderline of statistical significance. The Role-Emotional and Mental Health subscales improved over time in the LCKD group only.

In regard to the primary outcomes, the PCS improved over the 24 weeks in the LCKD group (2.9; 95%CI 1.3–4.4; percent change 5.8%) and in the LFD group (3.9; 95%CI 2.1–5.6; percent change 7.9%) (Table 3). The MCS improved over time in the LCKD group only. In comparisons between the two diet groups, the MCS improved more in the LCKD group (4.0; 95%CI 2.0–5.9; percent change 7.7%) than in the LFD group (0.9; 95%CI −1.3–3.1; percent change 1.5%) (between-groups difference = 3.1; 95%CI 0.2–6.0; $P = 0.04$) whereas changes in PCS were similar.

In terms of effect sizes, the LCKD group demonstrated mild to moderately better improvements over 24 weeks, compared with the LFD group, along the mental aspects of HRQOL (Table 3; the exception is Social Functioning). Regarding the physical aspects of HRQOL, the effect sizes were small negative (slightly better improvement in the LFD group), small positive, or close to zero. In particular, the effect size for the between-groups difference for the MCS was 0.44, whereas the effect size for the PCS was −0.16.

Compared with the LFD group, the LCKD group demonstrated better improvement in MCS from baseline at every clinic visit post-randomization (Fig. 1), the largest difference occurring at week 16 (difference = 4.2; 95%CI 1.8–6.6). For PCS, on the other hand, there was no evidence of a between-groups difference at any time point post randomization.

The association between diet and HRQOL outcomes (net of body weight) was investigated as a secondary analysis. The impact of lagged weight on subsequent MCS and PCS (averaged over all time points) was negligible ($P = 0.86$ for MCS; $P = 0.79$ for PCS, Fig. 2). The results are similar to the results of the primary analyses, though the magnitude of the effect at each time point is

Table 3 Within-group and between-groups changes in health-related quality of life domains from baseline to week 24

SF-36 scale	SF-36 subscale	Low-carbohydrate, ketogenic diet				Low-fat diet				Between-groups comparison[c]	
		Week 0[a]	Week 24[a]	Change (95%CI)	Percent change	Week 0[a]	Week 24[a]	Change (95%CI)	Percent change	Difference (95%CI)	Effect size
PCS[b]		50.4	53.3	2.9 (1.3, 4.4)	5.8	49.1	53.0	3.9 (2.1, 5.6)	7.9	−1.0 (−3.3, 1.3)	−0.16
	Physical Functioning	85.7	93.3	7.6 (4.4, 10.8)	8.9	82.4	90.8	8.4 (4.8, 11.9)	10.2	−0.73 (−5.4, 4.0)	−0.06
	Role-Physical	81.6	93.1	11.5 (3.3, 19.7)	14.1	82.0	93.6	11.6 (2.8, 20.4)	14.1	−0.04 (−12.0, 11.9)	−0.001
	Bodily Pain	80.5	84.9	4.4 (0.0, 8.8)	5.5	77.3	83.7	6.4 (1.4, 11.3)	8.3	−2.0 (−8.6, 4.6)	−0.10
	General Health	74.5	80.2	5.7 (2.0, 9.4)	7.7	75.9	80.2	4.3 (0.3, 8.4)	5.7	1.3 (−4.1, 6.8)	0.10
MCS[b]		51.8	55.8	4.0 (2.0, 5.9)	7.7	54.0	54.8	0.9 (−1.3, 3.1)	1.5	3.1 (0.2, 6.0)	0.44
	Vitality	58.1	73.9	15.8 (11.4, 20.1)	27.2	63.7	74.2	10.5 (5.6, 15.3)	16.5	5.2 (−1.2, 11.8)	0.31
	Social Functioning	90.0	95.0	5.0 (0.6, 9.3)	5.6	88.6	93.8	5.2 (0.4, 9.9)	5.9	−0.22 (−6.6, 6.2)	−0.02
	Role-Emotional	85.0	95.3	10.3 (3.4, 17.2)	12.1	88.7	94.2	5.5 (−2.0, 12.9)	6.2	4.8 (−5.2, 14.9)	0.18
	Mental Health	79.7	85.8	6.1 (2.5, 9.7)	7.7	82.2	83.2	1.0 (−2.9, 5.1)	1.2	5.0 (−0.3, 10.4)	0.37

[a] Values are expected means at week 0 and week 24 by linear mixed-effects model analyses using all data points from baseline to 24 weeks

[b] Primary outcomes: *PCS* Physical Component Summary score; *MCS* Mental Component Summary score

[c] Between-groups comparison of within-group mean changes by linear mixed-effects model analyses; *P*-values for primary outcomes: PCS, $P = 0.2$; MCS, $P = 0.04$

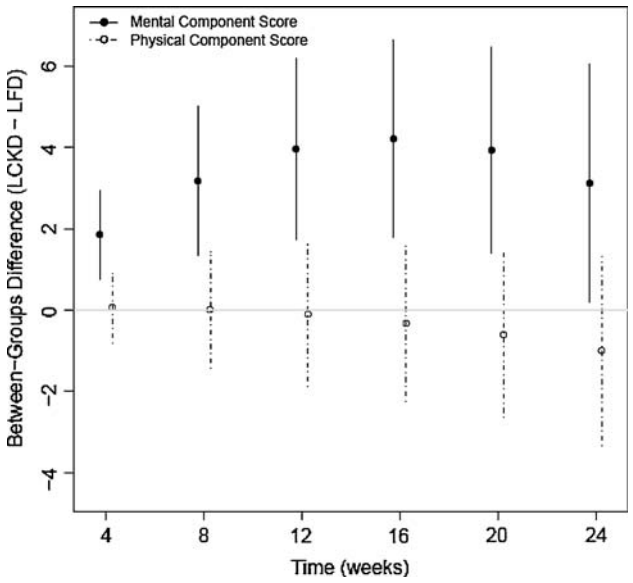

Fig. 1 Between-groups differences (with 95%CIs) in mean change scores on the PCS and MCS at each interval from baseline PCS = Physical Component Summary score; MCS = Mental Component Summary score. Each point represents the difference (with 95%CI) in mean changes from baseline at each time point (i.e., mean change score for LCKD minus mean change score for LFD). For example, for the MCS at 24 weeks, the point corresponds to 4.0−0.9 = 3.1

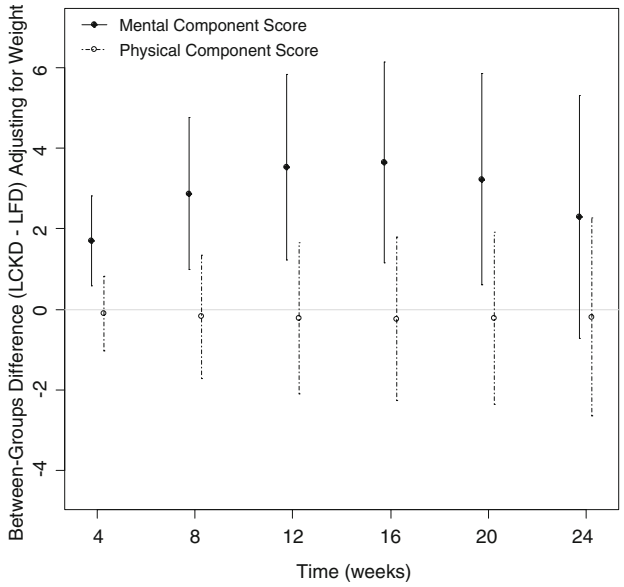

Fig. 2 Between-groups differences (with 95%CIs) in mean change scores on the PCS and MCS at each interval from baseline adjusting for weight; PCS = Physical Component Summary score; MCS = Mental Component Summary score. Each point represents the difference (with 95%CI) in mean changes from baseline at each time point (i.e., mean change score for LCKD minus mean change score for LFD) while adjusting for body weight

slightly diminished. Specifically, the results suggest that the association between diet assignment and change from baseline in MCS over the duration of the study persists after accounting for subsequent body weight (omnibus test for between-groups difference in mean change in MCS from baseline: $P = 0.03$), although diet assignment was not significantly predictive of the change from baseline in MCS at week 24 (difference = 2.29; 95%CI −0.72–5.30; $P = 0.16$). As with the primary analysis, there was no statistically (or clinically) significant between-groups difference in PCS over the duration of the trial ($P = 0.98$ for the omnibus test).

Discussion

In a randomized trial comparing two diets for weight loss over 24 weeks, the Mental Component Score improved more in the LCKD group than in the LFD group, and there were a greater number of HRQOL domains that improved over time in the LCKD group. Moreover, as seen in Fig. 1, the greater improvement in MCS for the LCKD group was seen at each time point during the study, with the separation between the groups peaking at 16 weeks. For the LFD group, improvements occurred predominantly in the physical aspects of HRQOL whereas in the LCKD group improvements occurred in both the physical and mental aspects of HRQOL.

In a systematic review of randomized trials of weight loss, six studies using the SF-36 (or a related instrument) to measure HRQOL showed variable effects of weight-loss interventions on HRQOL, and infrequent impact on the mental aspects of HRQOL [9]. For instance, a four-arm study randomized 316 subjects with knee osteoarthritis and mean BMI 35 kg/m^2 to a hypocaloric diet, an exercise program, diet/exercise combined, or a control situation over 18 months [30]. Compared with the control group, the combined treatment group had greater mean weight loss (−4.4% versus −1.3%), a 5–12 point improvement in Physical Functioning, Role-Physical, Bodily Pain, General Health, Social Functioning, and a three-point improvement in the Physical Component Score. In another study comparing sibutramine with placebo over 24 weeks in 175 subjects with mean BMI 34 kg/m^2, mean weight loss was greater in the sibutramine group (−4.3 kg versus −0.4 kg) but HRQOL improved more only in the General Health domain [31]. A trial of laparoscopic versus open gastric bypass surgery found that the mean subscale scores improved over 3 months by a range of 3.1–39.3 points in the two groups, but the mean Mental Health score changed the least (laparoscopic: +9.9; open: +3.1) [32].

In a randomized trial of a very-low-energy diet (VLED) versus no intervention over 8 months in 38 men with mean BMI 39 kg/m^2, mean weight loss was −17.3 kg versus +0.2 kg [33]. On the SF-36, Bodily Pain, General Health, and Vitality improved transiently in the VLED group whereas Physical Functioning and Social Functioning

remained significantly improved at the end of follow-up. In another study of 902 participants who received a diet and physical activity intervention, the domains of general health, energy or fatigue, general functioning, satisfaction with physical abilities, and social functioning improved in a graded fashion, but change in mental health score was not associated, with increasing quintile of weight loss [34]. The only study intervention that showed greater improvements in Mental Health compared with a control used a delayed intervention (i.e., no intervention) for the comparison group [35]. In this study of 80 premenopausal women with average BMI 30 kg/m^2 followed over 12 weeks, a hypocaloric diet (WeightWatchers^{TM}) plus physical activity counseling resulted in mean weight and Mental Health score changes of −6.1 kg and +10.4 points, respectively, versus +1.3 kg and +2.3 points in the control group.

More recently, in a randomized trial comparing laparoscopic adjustable gastric banding to an intensive medical weight-loss program (VLED, meal replacements, orlistat) in 80 subjects, HRQOL improved over 2 years in all eight subscales in the surgical group and in three subscales (Physical Functioning, Vitality, Mental Health) in the medical group [36]. The changes were greater in the surgical group than in the medical group in five subscales (Physical Functioning, Role-Physical, General Health, Vitality, Role-Emotional), and the scores in these same five subscales improved from baseline by approximately 25–30 points. The mean Mental Health score improved approximately 10 points in the surgical group and 5 points in the medical group (P = NS for comparison).

Results of the present study contrast with most of these studies in that seven of the SF-36 domains improved in the LCKD group and six improved in the LFD group. Such widespread improvement in HRQOL was seen only in the two studies of bariatric surgery where weight loss was substantially more than that seen in the studies with non-surgical interventions. Additionally, a differential effect between interventions on a mental health domain, as occurred in the current study, was observed in only one other study [35].

There are several competing hypotheses that might explain this result. First, the greater weight loss experienced by the LCKD group might have reinforced the impact of weight-loss treatment on the mental aspects of HRQOL, yet this effect was not seen in several other studies with differential weight loss. Moreover, an association between weight loss and HRQOL outcomes was lacking in our exploratory analyses.

Second, the ability of patients to lose weight on the LCKD without explicit limitations on the quantity of certain foods or total energy intake may garner the quality-of-life benefits of weight loss minus the drawbacks of hunger or craving of forbidden foods seen with calorie-restricted diets. This factor combined with the simpler dietary instructions and greater weight loss of the LCKD may lead an individual to have greater perceived control, which is related to lower levels of depression, better health-related quality of life, and greater success at lifestyle modification [37–39]. Third, it is also possible that the lower glycemic load of LCKDs results in smaller fluctuations in serum glucose and insulin, which might improve vitality and mood [40, 41].

There are several limitations to our study. The intervention was only 6 months in duration so it is unclear whether HRQOL improvements would be sustained beyond 6 months. Some studies have shown a steeper rate of weight regain after 6 months on the LCKD than on the LFD, but these studies have not reported HRQOL effects [12, 15]. Notably, the only randomized trial with follow-up beyond 1 year found that weight regain leveled off in the LCKD participants and remained greater than in the LFD participants throughout year 2 [42]. Additionally, the LCKD intervention in the present study included nutritional supplements in that group only, but the supplements did not contain ingredients known to enhance weight loss [16]. Some of the ingredients have been used for the treatment of depression but a recent systematic review found either unconvincing (e.g., methionine, inositol) or negative (e.g., omega-3 fatty acids, tyrosine) evidence for their efficacy, and none were mentioned in a clinical guideline for the treatment of depression [43–45]. Only healthy subjects were enrolled so that changes observed in HRQOL over time and differences in HRQOL between groups may not generalize to medical patients who follow these diets and lose weight. Also, we did not measure obesity-specific HRQOL, which might be more sensitive to the HRQOL improvements that occur during weight loss. Furthermore, even an obesity-specific HRQOL instrument may not capture adequately certain subtle or complex quality-of-life changes experienced by dieters. Finally, we have limited ability to disentangle the effects of weight loss versus diet type on HRQOL. The introduction of weight (a post-randomization measure) as a covariate in the LMMs may lead to bias in the comparison of HRQOL between diet groups [29]. To minimize this potential bias, we adjusted for the available baseline covariates that could possibly relate to both weight and HRQOL.

A particular strength of this study is that all observed data points from baseline to 24 weeks were used in the LMM analyses. This has advantages in terms of handling missing data because we were not required to remove cases with incomplete data (e.g., a participant who drops out at week 10). In addition, using the full data set allowed us to characterize the between-groups difference in change over the course of the full study (Fig. 1). Figure 1 demonstrates that, for the MCS, the LCKD group's greatest improvement

over the LFD occurred at week 16. For the PCS, on the other hand, there is no evidence of a between-groups difference at any time point post randomization. These aspects of the data would have remained hidden had we just considered our primary endpoints at week 24 (Table 2).

Being obese is typically associated with reductions in the physical, not the mental, aspects of HRQOL. Similarly, *weight loss* resulting from various interventions typically has a stronger impact on the physical aspects of HRQOL. It may be the case that certain weight-loss diets, such as the LCKD, provide mental health benefits not found in other diets. The relationship between carbohydrate intake and the mental aspects of HRQOL should be considered further in qualitative studies, observational studies over long time periods, randomized clinical trials, and mediational analyses to better understand the contributions of weight-loss treatment and weight loss on HRQOL.

Conclusion

Compared with a low-fat diet, a low-carbohydrate diet led to similar improvements in the physical aspects of HRQOL and greater improvements in mental aspects of HRQOL as measured by the SF-36. The greater improvement in the mental aspects of HRQOL appeared to be related more to some aspect of the low-carbohydrate diet than to the greater weight loss that occurred on this diet.

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