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Effect of a low-carbohydrate diet on pain and quality of life in female patients with lipedema: a randomized controlled trial

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Abstract

Objective: The primary objective of this study was to evaluate the effect of a low-carbohydrate diet (LCD) compared with a control diet on pain in female patients with lipedema. The secondary objectives were to compare the impact of the two diets on quality of life (QoL) and investigate potential associations of changes in pain with changes in body weight, body composition, and ketosis.

Methods: Adult female patients with lipedema and obesity were randomized to either the LCD or control diet (energy prescription: 1200 kcal/day) for 8 weeks. Body weight and body composition, pain (Brief Pain Inventory measured pain), and QoL (RAND 36-Item Health Survey [RAND-36], Impact of Weight on Quality of Life [IWQOL]-Lite, and Lymphoedema Quality of Life [LYMQOL]) were measured at baseline and at postintervention.

Results: A total of 70 female patients (age, mean [SD], 47 [11] years; BMI 37 [5] kg/m^2) were included. The LCD group had greater weight loss (−2.8 kg; 95% CI: −4.1 to −1.0; $p < 0.001$) and larger reduction in pain now (−1.1; 95% CI: −1.9 to −0.3; $p = 0.009$) compared with the control group. No association was found between changes in pain now and weight loss. Both groups experienced improvements in several QoL dimensions.

Conclusions: Diet-induced weight loss in women with lipedema can improve QoL. An energy-restricted LCD seems to be superior to a standard control diet in reducing pain.

INTRODUCTION

Lipedema is an obesity-related, mis- and underdiagnosed chronic disease. It is characterized by a symmetrical increase of subcutaneous adipose tissue in the lower extremities, sparing the waist area [1]. Lipedema primarily affects female individuals and typically appears during puberty, pregnancy, or menopause [2]. Female patients with lipedema report daily pain, tenderness, and reduced quality of life (QoL) [3, 4]. Lipedema is insufficiently documented in medical literature and is rarely recognized by general practitioners [1]. The lack of epidemiological studies and a diagnostic code makes the prevalence of lipedema uncertain [5].

The etiology and pathogenesis of lipedema are not fully understood, but genetics; the endocrine, lymphatic, and vascular systems; and inflammation are likely to be involved [5, 6]. There is no cure for lipedema, and current treatments aim primarily at relieving symptoms and preventing progression and complications of the condition [7]. Complications of the condition include the development to lipo-lymphedema due to disruption of the lymphatic system [8]. Conservative treatment of lipedema includes manual lymphatic drainage, compression garments, exercise and physical therapy, weight management, psychosocial therapy, and education on self-management [7].

The pain in lipedema is described as dull, heavy, and pressing [9]. Chronic pain, decreased limb mobility, and weight stigma are proposed as factors that cause poor QoL in female patients with lipedema [10, 11]. Mental stress seems to lower the pain threshold and lead to reinforcement of pain perception [12]. Depression and anxiety increase inflammatory markers unrelated to underlying somatic disease [13]. Consequently, a vicious cycle may occur, with psychological symptoms intensifying the pain through inflammatory mediators, which, in turn, increases mental stress [10].

The majority of women with lipedema have obesity (>78%) [14, 15], making weight management critical because weight gain seems to aggravate the condition [16, 17]. Additionally, a higher symptom burden is associated with lower QoL [10]. Lipedema-affected subcutaneous adipose tissue is thought to be resistant to conventional weight loss diets and exercise, resulting in weight loss only in nonaffected adipose tissue [1, 14]. However, intervention studies on lifestyle-induced weight loss are scarce in this patient group [2, 17]. Recent studies have shown that a low-carbohydrate (CHO) diet (LCD) [15, 18–20] and Mediterranean diets [21] may improve body composition [15, 18, 20, 21], pain, and lipedema-related symptoms [18, 19]. Pain reduction has been suggested to result from reduced inflammation, prevention of fibrosis, reduction of edema or tissue water content, and/or alterations in metabolism and hormonal function following these diets [22].

Even though preliminary evidence has seemed to suggest that an LCD may relieve lipedema-related pain [19, 22] and thereby improve QoL, there is a lack of randomized controlled trials (RCTs) investigating the effect of LCD on pain and QoL in female patients with lipedema. Therefore, the primary objective of this study was to evaluate the effect of an 8-week LCD compared with an isoenergetic standard diet (control diet) on pain intensity in female patients with lipedema. The secondary objectives were to compare the impact of the two diets on QoL and investigate potential associations of changes in pain with changes in body weight, body composition, and ketosis.

Study Importance

What is already known?

- A ketogenic diet has been proposed to relieve pain in female patients with lipedema; however, randomized controlled trials are nonexistent.
- Female patients with lipedema have a lower quality of life (QoL) compared with the general population.

What does this study add?

- A low-carbohydrate diet (LCD) can relieve pain in female patients with lipedema, independently of weight loss.
- Weight loss seems to improve QoL in female patients with lipedema, independently of the diet used.

How might these results change the direction of research or the focus of clinical practice?

- Our results suggest that an LCD might be a good dietary treatment option for female patients with lipedema.
- Weight loss using standard low-energy diets might be suggested as a treatment option for female patients with lipedema if contraindications for implementing an LCD exist.

METHODS

Study design

This study is an RCT comparing a low-energy LCD with a low-energy diet (control) in female patients with lipedema. The study was approved by the Regional Ethics Committee for Medical and Health Research Ethics (REK; 93888) and registered in ClinicalTrials.gov (NCT04632810). All participants provided written informed consent

in line with the Helsinki Declaration before entering the study. Participants were randomized (1:1) by block randomization with stratification by body mass index (BMI) categories (30.0–34.9, 35.0–39.9, and 40.0–44.9 kg/m^2). Randomization was performed by a web-based randomization system developed and administered by the Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology (NTNU; Trondheim, Norway). The data collection was done by using eFORSK, a web-based system developed and administered by Helse Midt-Norge information technology (IT; Central Norway Regional Health Authority's IT department).

Study population

Female patients diagnosed with lipedema, aged 18 to 75 years old and with BMI between 30 and 45 kg/m^2, were invited to participate in the study. Participants were diagnosed with lipedema by physical therapists before inclusion, and type and stage of lipedema were assessed at baseline (BL) [6, 16]. Inclusion criteria included weight stability for the last 3 months (±3 kg). Exclusion criteria included acute and chronic kidney disease/failure, previous bariatric surgery, malignant disease, infectious disease, diabetes, psychosocial disorders, breastfeeding, pregnancy, current medication known to affect body weight, no mastery of a Scandinavian language, and enrollment in another obesity/lipedema treatment program (except for regular physical therapy). Those participants using pain medication and/or compression garments or pulsators continued using them throughout the study.

Dietary interventions

Diets were matched for energy (1200 kcal/day) and protein (60 g; energy percentage [E%], 20 E%) but differed in CHO and fat content. The LCD consisted of 75 g of CHO (25 E%) and 73 g of fat (55 E%), whereas the control diet consisted of 180 g of CHO (60 E%) and 27 g of fat (20 E%). The LCD consisted mainly of meat/poultry/fish, eggs, nuts, small amounts of low-CHO fruits and vegetables, and dairy. Butter and whole-fat dairy were replaced with healthy fats such as olive oil and food rich in polyunsaturated fatty acids (PUFAs). The control diet consisted mainly of whole grains, including bread, pasta, and rice; legumes, fruits, and vegetables; and moderate amounts of eggs, meat/poultry/fish, and low-fat dairy.

The dietary plans were adjusted with respect to food preferences, intolerances, and allergies. Participants were advised to take a multivitamin/mineral supplement and to drink a minimum of 2 L of calorie-free drinks daily. The participants were asked not to change their physical activity levels throughout the study period.

Compliance

Participants had weekly follow-ups, either by phone or face-to-face, depending on convenience. Body weight was measured, ketosis was assessed (see "Ketosis" section), and potential side effects of the diets discussed, aiming at enhancing compliance and preventing dropouts. Necessary changes and adjustments in the diets were made within the limitations of energy and macronutrient distribution.

Participants were asked to fill out daily food records throughout the intervention period. These were then analyzed for intake of energy (kilocalories per day) and macronutrients (grams per day, E%) using a web-based analysis program [23] based on the Norwegian Food Composition Table [24] and were discussed at the weekly follow-ups.

Ketosis

Ketostix reagent test strips (Ascensia Diabetes Care Holdings AG, Basel, Switzerland) were used in the weekly follow-ups to measure urinary acetoacetate (AcAc) concentration. A cutoff level <0.5 mmol/L was used for negative AcAc. ß-hydroxybutyrate (HB) concentration was also measured in whole blood (FreeStyle Precision Neo, Abbott Laboratories, Green Oaks, Illinois) using finger pricks at BL, week (W) 5, and W9. Participants with a ß-HB concentration ≥ 0.3 mmol/L were categorized as being in nutritional-induced ketosis [25]. If a participant in the ketosis group presented with negative AcAc during the weekly follow-ups, the CHO level was reduced, whereas the opposite was done in the control group if a participant presented with positive AcAc. If the participants in the LCD group were out of ketosis or if participants in the control group were in ketosis more than twice throughout the study period, they were excluded from the per-protocol (PP) analysis.

Outcome variables

The following variables were assessed in the obesity outpatient clinic at St. Olav's University Hospital (Trondheim, Norway) at BL and W9.

Anthropometrics and body composition

Weight (kilograms) was measured with Seca 876 (SECA, Hamburg, Germany) to the nearest 0.1 kg. Body composition was assessed in a fasting state with bioelectrical impedance analysis (BIA; InBody720, Seoul, South Korea). Fat mass (FM), fat-free mass (FFM), total body water (TBW), intracellular body water (ICW), and extracellular body water (ECW) were included in the analysis.

Pain

Pain was assessed with the validated Brief Pain Inventory (BPI) [26] on a numerical rating scale (where 0 = no pain and 10 = worst imaginable pain). The BPI assesses whole-body pain intensity: strongest pain; weakest pain; average pain; pain now; and pain interference with daily activities, mood, walking, regular work, relationships, sleep, and life joy. A pain severity score was calculated as an average of pain intensity items, whereas a pain interference score was computed as

the average of all pain interference items. Participants filled out the questionnaire (paper-based) in a non-fasting state at around 10 a.m., after body composition assessment. Each participant filled out the questionnaire alone in a room inside our laboratory.

QoL

Three different questionnaires were used to assess QoL. A generic questionnaire, RAND 36-Item Health Survey (RAND-36) [27, 28], assessed health-related QoL, where a higher score represents better health [29]. The Impact of Weight on Quality of Life (IWQOL)-Lite questionnaire [30] was used to assess obesity-specific QoL, where a higher score represents better health. The Lymphoedema Quality of Life (LYMQOL) questionnaire [31] was used to measure disease-specific QoL, where a lower score represents better health for all domains, except for the total QoL score. LYMQOL is a validated questionnaire originally developed for assessing QoL among women with limb lymphedema [31].

Statistical analysis

Statistical analysis was performed using Stata (StataCorp LLC version 18, College Station, Texas), and data were presented as means ± SD or estimated marginal means with a corresponding 95% confidence interval (CI). Residuals were checked for normality with a Shapiro–Wilk test and visual inspection of histograms. Statistical significance was assumed at $p < 0.05$ unless otherwise stated. Group differences in the changes from BL were estimated by linear mixed-effect models. The fixed part was specified in terms of two dummy variables: one for time and one for group differences (LCD vs. control diet) post intervention (W9) because the BL means can be assumed to be the same given the randomized design [32, 33]. The mean difference in changes from BL is equivalent to the estimated mean group difference post intervention. A random intercept for patient was included to account for within-patient correlations. Differences between groups in mean daily energy and macronutrient intake were assessed with an independent-sample *t* test. Linear regression was used to investigate the associations of changes in pain with changes in body weight, body composition, and ketosis after adjusting for diet group. Associations between changes in pain and changes in QoL were analyzed using Pearson or Spearman correlation coefficients, depending on the normality of the data. Figures were generated using GraphPad Prism (version 10.0.2 for Windows, GraphPad Software, Boston, Massachusetts).

Intention-to-treat analysis was performed with all included participants, whereas PP analysis included only participants who were compliant with the interventions (as previously described).

Power calculation

A difference in mean pain intensity score of two units on a numeric rating scale ranging from zero to ten was considered clinically relevant. To find a difference of at least two units in pain between groups, with an SD of 2.1 [19], a statistical power of 80%, and a significance level of 0.05, 19 participants per group would be needed (38 in total). To account for a potential 20% dropout rate and risk of nonnormally distributed data (a 15% increase in sample size was deemed necessary), 28 participants per group (56 in total) would be needed.

RESULTS

Participants

A total of 70 female patients with lipedema and obesity were included in this study (Figure 1), with 35 in each group, an average age of 47.3 ± 10.9 years, and an average BMI of 36.9 ± 4.9 kg/m^2. Participants' characteristics at BL are presented in Table 1.

Anthropometrics and body composition

Changes in body weight and body composition are presented in Table 2. Both groups experienced a significant loss of weight, FM, and FFM, as well as a significant reduction in ICW, ECW, and TBW. However, the LCD group had a significantly larger reduction in body weight (−2.8 kg; 95% CI: −4.1 to −1.5; $p < 0.001$) and FM (both kilograms and percentage) compared with the control group (−2.5 kg; 95% CI: −4.4 to −0.7; $p = 0.006$ and −4.3%; 95% CI: −6.7% to −1.9%; $p < 0.001$, respectively).

Compliance

Participants' daily energy and macronutrient intake; ß-HB concentrations at BL; and W5, W9, and weekly AcAc urine concentrations are presented in Table 3. Average energy intake for the LCD and control groups was 1176.4 ± 29.6 and 1194.8 ± 109.0 kcal/day, respectively ($p = 0.369$). CHO intake was 66.6 ± 5.2 g/day (23 E%) and 204 ± 18.3 g/day (69 E%; $p < 0.001$), fat intake was 75.5 ± 2.8 g/day (58 E%) and 24.5 ± 3.1 g/day (18 E%; $p < 0.001$), and protein intake was 69.2 ± 6.6 g/day (23 E%) and 56.1 ± 6.9 g/day (19 E% $p < 0.001$) in the LCD and control groups, respectively.

Pain

Reported pain scores in both groups over time are presented in Table 4. The LCD group reported a significant reduction in strongest pain; weakest pain; average pain; pain now; pain severity score; and pain interference with daily activities, walking, regular work, relationships, and sleep. There was no change in the control group for any of the variables, and the reductions in strongest pain, weakest pain, pain now, and pain severity score were significantly larger in the LCD group compared with the control group. Both groups had a significant

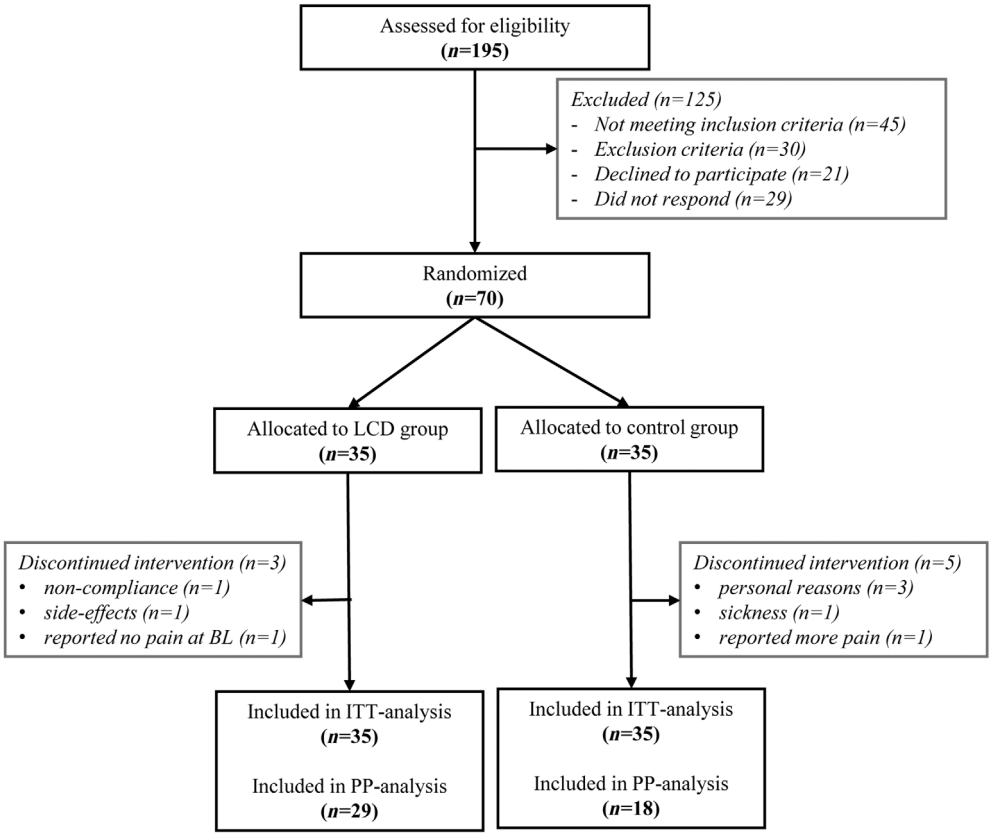

FIGURE 1 Flowchart of the study. ITT, intention-to-treat; PP, per-protocol; LCD, low-carbohydrate diet.

TABLE 1 Baseline characteristics of the participants.

	All participants ($n = 70$)	LCD ($n = 35$)	Control diet ($n = 35$)
Age (y)	47.3 ± 10.9	48.4 ± 8.9	46.2 ± 12.6
Height (cm)	167.2 ± 6.1	167.0 ± 6.6	167.4 ± 5.8
BMI (kg/m^2)	36.9 ± 4.9	36.7 ± 4.6	37.1 ± 5.3
Weight (kg)	103.2 ± 14.6	101.2 ± 13.7	104.2 ± 15.6
Lipedema type			
1	4 (6)	2 (6)	2 (6)
1 + 4	1 (1)	1 (3)	0 (0)
2	11 (16)	6 (18)	5 (14)
2 + 4	4 (6)	2 (6)	2 (6)
3	14 (20)	3 (9)	11 (31)
3 + 4	27 (40)	17 (50)	10 (30)
5	8 (12)	3 (9)	5 (14)
Lipedema stage			
1	13 (19)	6 (18)	7 (20)
2	46 (67)	22 (64)	24 (69)
3	10 (14)	6 (18)	4 (11)

Note: Data presented as means ± SD and numbers (percentage). Type 1: pelvis, buttocks, and hips; type 2: buttocks to knees; type 3: buttocks to ankles; type 4: arms; and type 5: lower legs. Stage 1: normal and smooth skin surface; stage 2: uneven skin where indentions of fat are visible; and Stage 3: expansions of tissue causing deformations, most common on the thighs and around knees [6, 16].
Abbreviation: LCD, low-carbohydrate diet.

reduction in pain interference with mood and life joy and pain interference score.

No associations were found between changes in pain now and weight or FM loss; changes in ICW, ECW, or TBW; or AcAc urine concentrations and ß-HB blood concentrations at W9 (data not shown).

QoL

Results on QoL from RAND-36 are presented in Figure 2 and Table S1. The LCD group reported a significant improvement in role limitations due to physical health and emotional problems, as well as in emotional well-being, social functioning, and pain. Both groups reported significant improvements in physical functioning, energy, and general health. However, the LCD group reported a significantly larger increase in energy, emotional well-being, social functioning, and change compared with the control group.

Results on QoL from IWQOL-Lite are presented in Figure 2 and Table S1. Both groups had an improvement in physical function, self-esteem, work, and total QoL, whereas only the LCD group had an improvement in sexual life. However, no significant differences between the groups were found.

Results from LYMQOL are presented in Figure 2 and Table S1. Both groups reported a significant improvement in function and

TABLE 2 Body weight and body composition at BL and end of the intervention and changes within and between groups.

	BL	W9	Change from BL to W9			Difference in change between groups		
LCD vs. control diet	Means ± SD	Means ± SD	EMM	95% CI	*p* value	EMM	95% CI	*p* value
Body weight (kg)								
LCD	101.2 ± 13.7	92.1 ± 13.4	−10.2	−11.1 to −9.3	**<0.001**	−2.8	−4.1 to 1.5	**<0.001**
Control diet	104.2 ± 15.6	94.9 ± 15.8	−7.4	−8.2 to −6.4	**<0.001**			
FM (%)								
LCD	48.4 ± 3.7	44.5 ± 4.6	−3.9	−5.2 to −2.5	**<0.001**	−2.5	−4.4 to −0.7	**0.006**
Control diet	48.3 ± 5.4	47.0 ± 4.6	−1.3	−2.7 to 0.0	0.059			
FM (kg)								
LCD	50.8 ± 9.4	42.3 ± 9.7	−8.6	−10.3 to −6.9	**<0.001**	−4.3	−6.7 to −1.9	**<0.001**
Control diet	50.8 ± 11.8	45.7 ± 11.5	−4.3	−6.1 to −2.6	**<0.001**			
FFM (kg)								
LCD	53.4 ± 6.2	50.8 ± 5.5	−2.8	−4.0 to −1.6	**<0.001**	−0.5	−2.2 to 1.2	0.544
Control diet	53.6 ± 6.0	50.7 ± 5.7	−2.3	−3.5 to −1.0	**<0.001**			
ICW (L)								
LCD	24.1 ± 2.8	22.9 ± 2.4	−1.1	−1.3 to −0.8	**<0.001**	−0.2	−0.6 to 0.2	0.360
Control diet	24.7 ± 4.3	22.8 ± 2.6	−0.9	−1.2 to −0.6	**<0.001**			
ECW (L)								
LCD	15.2 ± 1.9	14.3 ± 1.7	−0.7	−0.8 to −0.5	**<0.001**	0.0	−0.2 to 0.3	0.874
Control diet	15.3 ± 1.9	14.2 ± 1.8	−0.7	−0.9 to −0.5	**<0.001**			
TBW (L)								
LCD	39.0 ± 5.1	37.4 ± 3.5	−1.4	−2.0 to −0.7	**<0.001**	0.3	−0.7 to 1.3	0.532
Control diet	40.1 ± 5.8	37.0 ± 4.3	−1.7	−2.4 to −1.0	**<0.001**			

Note: Results from linear mixed model are presented as estimated marginal means (EMM) with corresponding 95% CI and value. Significant *p* values are bolded. LCD: $n = 35$ at BL, $n = 29$ at W9; control diet: $n = 35$ at BL, $n = 31$ at W9.
Abbreviations: BL, baseline; ECW, extracellular water; FFM, fat-free mass; FM, fat mass; ICW, intracellular water; LCD, low-carbohydrate diet; TBW, total body water; W, week.

appearance. Only the LCD group reported a significant improvement in symptoms, feelings, and total QoL; however, no significant differences between groups were found.

Changes in pain now were associated with changes in several indexes of QoL (Table S2).

PP analysis

Results of the PP analysis for body weight and body composition, pain, and QoL are presented in Tables S3, S4, and S5, respectively. Outcomes were similar to the intention-to-treat analysis.

DISCUSSION

The primary objective of this study was to evaluate the effect of an 8-week low-energy LCD compared with an isoenergetic low-fat control diet on pain intensity in female patients with lipedema. The secondary objectives were to compare the impact of the two diets on QoL and investigate potential associations of changes in pain with changes in body weight, body composition, and ketosis. The LCD group had a reduction in strongest, weakest, and average pain; pain now; and pain interference with daily activities and a larger reduction compared with the control group in strongest pain, weakest pain, and pain now. Both groups reported improvement in several QoL variables, namely physical functioning, energy, general health, self-esteem, work, total QoL, and appearance.

Although not reaching an absolute reduction in pain of two units, participants randomized to the LCD group experienced a 33% reduction in pain (pain now), a relative reduction that is considered to be clinically relevant [34]. This finding is in line with previous research [18–20]. Indeed, our pilot study reported similar results after 6 weeks of a eucaloric LCD [19], and a case study reported pain reduction after 2 years on an energy-restricted ketogenic diet [18]. Also, a recently published pilot study found a reduction in pain after a combination of a ketogenic diet and carboxytherapy, despite no effect of the ketogenic diet alone. However, pain was measured by Fibromyalgia Assessment Status, which investigates asthenia, pain, and sleep disturbance [20], not pain as a single domain, which might help explain the discrepancies in the results.

A mean pain reduction of 1.3 units was observed in the LCD group in the present study. This is smaller than what was found in the

TABLE 3 Daily energy and macronutrient intake and ketosis in both diet groups over time.

	Energy (kcal/d)	CHO (g/d)	Fiber (g/d)	Protein (g/d)	Fat (g/d)	AcAc (mmol/L)	ß-HB (mmol/L)
BL							
LCD						0.0 ± 0.1	0.1 ± 0.1
Control diet						0.0 ± 0.0	0.1 ± 0.1
W2							
LCD	1189.0 ± 63.3	70.1 ± 8.8	25.7 ± 5.0	71.8 ± 9.8	75.2 ± 5.3	2.3 ± 2.3	
Control diet	1212.3 ± 98.7	208.3 ± 14.4	30.6 ± 4.7	56.9 ± 8.0	26.8 ± 6.0	0.5 ± 1.0	
W3							
LCD	1181.6 ± 37.0	68.0 ± 7.6	24.7 ± 4.4	69.7 ± 11.3	75.8 ± 7.2	2.8 ± 2.2	
Control diet	1209.1 ± 122.1	206.6 ± 20.6	29.6 ± 5.5	55.8 ± 7.2	24.4 ± 3.9	0.1 ± 0.3	
W4							
LCD	1190.4 ± 39.6	68.7 ± 6.9	24.6 ± 3.3	69.3 ± 11.5	76.7 ± 5.0	2.6 ± 2.3	
Control diet	1178.6 ± 139.8	201.6 ± 27.6	28.8 ± 6.7	56.5 ± 9.1	24.1 ± 4.6	0.4 ± 0.8	
W5							
LCD	1165.1 ± 66.3	68.0 ± 7.8	24.7 ± 3.9	67.4 ± 10.7	75.7 ± 5.6	2.1 ± 2.4	0.6 ± 0.4
Control diet	1186.1 ± 180.6	205.0 ± 32.4	29.7 ± 7.0	55.3 ± 10.0	24.0 ± 4.6	0.1 ± 0.3	0.2 ± 0.1
W6							
LCD	1170.7 ± 59.4	66.9 ± 8.2	23.8 ± 3.9	68.9 ± 7.7	77.0 ± 5.0	2.3 ± 2.3	
Control diet	1168.0 ± 176.6	203.5 ± 32.5	29.1 ± 6.9	55.4 ± 8.8	22.6 ± 4.8	0.1 ± 0.2	
W7							
LCD	1160.9 ± 64.7	64.1 ± 6.8	23.3 ± 3.2	67.8 ± 7.1	76.9 ± 5.2	1.8 ± 1.8	
Control diet	1189.1 ± 143.7	203.8 ± 24.8	29.5 ± 5.4	54.4 ± 8.3	24.2 ± 5.0	0.1 ± 0.2	
W8							
LCD	1184.7 ± 47.8	64.8 ± 6.6	23.1 ± 2.7	68.0 ± 7.3	78.4 ± 4.9	2.0 ± 2.1	
Control diet	1213.8 ± 112.9	208.7 ± 20.3	30.5 ± 5.7	56.7 ± 8.4	24.6 ± 4.4	0.2 ± 0.4	
W9							
LCD	1173.0 ± 61.7	63.8 ± 9.2	23.5 ± 4.2	69.5 ± 7.8	77.2 ± 4.4	1.7 ± 2.4	0.7 ± 0.5
Control diet	1194.5 ± 99.5	205.9 ± 21.1	29.9 ± 6.1	56.6 ± 9.2	24.0 ± 4.7	0.2 ± 0.7	0.2 ± 0.1

Note: Data presented as weekly means ± SD. Data assessed by participant 24-h dietary records, urinary AcAc (mmol/L), and whole-blood β-HB (mmol/L).
Abbreviations: AcAc, acetoacetate; BL, baseline; CHO, carbohydrate; ß-HB, beta-hydroxybutyrate; LCD, low-carbohydrate diet; W, week.

pilot study (2.3) [19]. This might be due to lower baseline pain scores (3.9 in the LCD group) in this present study compared with 4.6 in Sørlie et al., as well as the fact that a broader pain assessment was performed in the present study.

The LCD group had a larger weight loss compared with the control group, but the magnitude of weight loss was not associated with changes in pain, which is similar to Sørlie et al. [19]. This suggests that the pain relief found in the LCD group is independent of weight loss. However, the effect of weight loss alone needs to be further investigated with a study including a control group with no weight loss intervention.

The pain associated with lipedema has been suggested to be caused by pressure on the nerves, fluid accumulation in the affected tissue, and/or inflammation [8, 22]. It has been suggested that an LCD may relieve pain by reducing tissue water or edema, inflammation, and fibrosis and/or by altering metabolic and hormonal function [22]. Increased concentrations of β-HB have previously been shown to reduce the level of inflammation by decreasing the secretion of proinflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor α (TNF-α) [35, 36]. However, no association was seen between changes in pain and β-HB whole-blood concentrations at W9 in the present analysis, suggesting that other mechanisms might be involved. In addition to limiting CHO intake, an LCD also allows for a higher intake of PUFAs. The ratio between omega-3 and omega-6, the two main groups of PUFAs, seems to be particularly important concerning inflammation [37], which might also explain why a Mediterranean diet could be appropriate for patients with lipedema [21].

Despite an isocaloric prescription, the LCD group lost more weight. Different mechanisms can be proposed to explain this difference. First, there might have been differences in dietary adherence that were not detected by the food records. LCDs have been shown to increase satiety likely through increased protein intake [38]. Indeed, protein intake was higher in the LCD group, despite the prescription of the same amount of protein in both groups.

TABLE 4 Pain at BL and W9 in both groups and changes within and between groups.

	BL	W9	Change from BL to W9			Difference in change between groups		
LCD vs. control diet	Means ± SD	Means ± SD	EMM	95% CI	*p* value	EMM	95% CI	*p* value
Pain now								
LCD	3.9 ± 2.3	2.6 ± 2.1	−1.3	−1.9 to −0.7	**<0.001**	−1.1	−1.9 to −0.3	**0.009**
Control diet	3.7 ± 2.2	3.4 ± 2.5	−0.2	−0.8 to 0.5	0.590			
Strongest pain								
LCD	5.3 ± 2.3	3.9 ± 2.9	−1.4	−2.1 to −0.7	**<0.001**	−1.0	−1.9 to −0.1	**0.031**
Control diet	5.1 ± 2.2	4.7 ± 2.4	−0.4	−1.1 to 0.3	0.250			
Weakest pain								
LCD	2.3 ± 1.7	1.7 ± 1.7	−0.7	−1.2 to −0.2	**0.009**	−0.8	−1.5 to −0.1	**0.025**
Control diet	2.5 ± 2.1	2.6 ± 2.0	0.1	−0.4 to 0.6	0.642			
Average pain								
LCD	4.7 ± 1.5	3.7 ± 2.3	−1.1	−1.7 to −0.5	**<0.001**	−0.6	−1.4 to 0.2	0.143
Control diet	4.9 ± 2.0	4.3 ± 2.5	−0.5	−1.2 to 0.1	0.091			
Pain severity score								
LCD	4.1 ± 1.7	3.0 ± 2.1	−1.1	−1.6 to −0.7	**<0.001**	−0.9	−1.6 to −0.2	**0.009**
Control diet	4.0 ± 1.9	3.7 ± 2.2	−0.2	−0.7 to 0.3	0.343			
PI: daily activities								
LCD	4.4 ± 3.1	3.0 ± 3.1	−1.4	−2.4 to −0.4	**0.006**	−0.7	−2.1 to 0.6	0.292
Control diet	4.5 ± 2.6	3.8 ± 3.3	−0.7	−1.7 to 0.4	0.196			
PI: mood								
LCD	4.1 ± 2.9	2.3 ± 2.3	−1.8	−2.7 to −1.0	**<0.001**	−0.8	−1.9 to 0.4	0.184
Control diet	4.2 ± 2.7	3.0 ± 3.0	−1.1	−1.9 to −0.2	**0.019**			
PI: walking								
LCD	3.2 ± 2.7	2.0 ± 2.3	−1.5	−2.4 to −0.6	**0.001**	−1.0	−2.2 to 0.3	0.125
Control diet	4.3 ± 3.1	3.5 ± 3.5	−0.5	−1.5 to 0.4	0.265			
PI: regular work								
LCD	3.5 ± 2.9	2.6 ± 2.8	−1.3	−2.2 to −0.4	**0.007**	−0.4	−1.6 to 0.8	0.533
Control diet	4.6 ± 2.5	3.3 ± 3.5	−0.9	−1.8 to 0.1	0.070			
PI: relationships								
LCD	2.6 ± 2.5	1.6 ± 2.0	−1.2	−2.1 to −0.2	**0.016**	−0.6	−1.8 to 0.7	0.396
Control diet	3.3 ± 2.9	2.5 ± 3.8	−0.6	−1.6 to 0.4	0.212			
PI: sleep								
LCD	3.7 ± 3.2	2.9 ± 3.1	−1.0	−1.9 to −0.1	**0.028**	−0.2	−1.5 to 1.0	0.716
Control diet	5.0 ± 3.4	4.0 ± 3.9	−0.8	−1.7 to 0.1	0.099			
PI: life joy								
LCD	3.6 ± 2.8	2.1 ± 2.4	−1.8	−2.7 to −0.9	**<0.001**	−0.5	−1.7 to 0.7	0.382
Control diet	4.5 ± 2.7	3.1 ± 3.5	−1.3	−2.2 to −0.3	**0.008**			
PI score								
LCD	3.6 ± 2.3	2.4 ± 2.3	−1.4	−2.2 to −0.7	**<0.001**	−0.6	−1.6 to 0.4	0.263
Control diet	4.3 ± 2.2	3.3 ± 3.2	−0.8	−1.6 to −0.1	**0.029**			

Note: Results from linear mixed model are presented as estimated marginal means (EMM) with corresponding 95% CI and *p* value. Significant *p* values are bolded. LCD group: $n = 35$ at BL, $n = 32$ at W9. Control group: $n = 35$ at BL, $n = 30$ at W9.
Abbreviations: BL, baseline; LCD, low-carbohydrate diet; PI, pain interference; W, week.

Additionally, ketosis has been shown to prevent the increase in appetite otherwise seen with weight loss [25], which, again, could explain increased adherence to the hypocaloric prescription in the LCD group. Another possibility is that an LCD increases energy expenditure [39]; however, this mechanism remains controversial. Regardless of the mechanisms involved, the greater weight loss observed

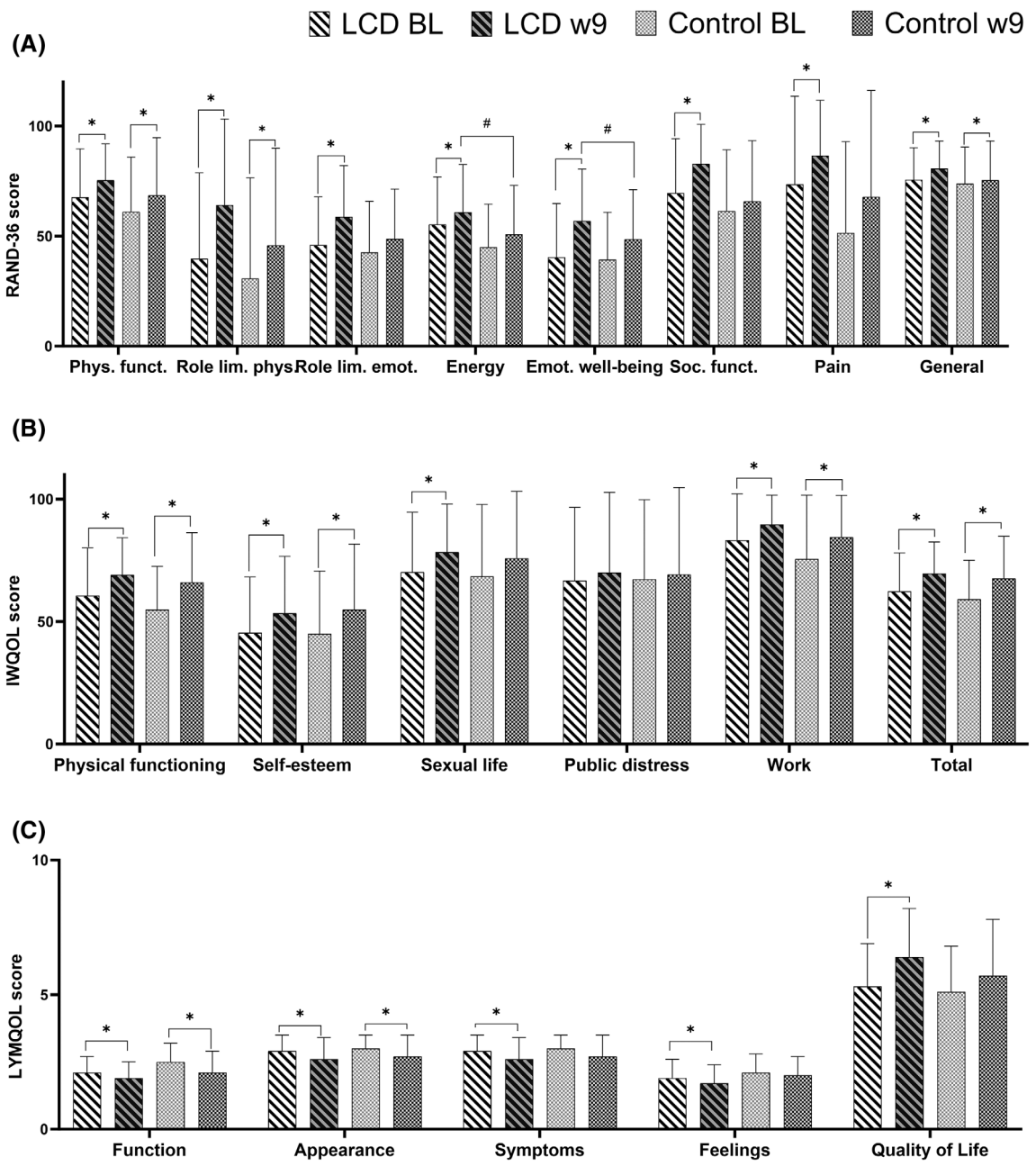

FIGURE 2 Quality of life (QoL) scores assessed by (A) RAND 36-Item Health Survey (RAND-36; physical functioning, role limitations due to physical health, role limitations due to emotional health, energy/fatigue, emotional well-being, social functioning, pain, and general health), (B) Impact of Weight on Quality of Life (IWQOL)-Lite (physical function, self-esteem, sexual life, public distress, work and total), and (C) Lymphoedema Quality of Life (LYMQOL; function, appearance, symptoms, feelings, and QoL) in both groups at baseline (BL) and week (W) 9 (intention-to-treat analysis). Data presented as means ± SD. Changes within and between groups were analyzed using linear mixed-effect models. $^{*}p < 0.05$, significant change within group from BL to W9. $^{\#}p < 0.05$, significant difference in change between groups. BL, baseline; LCD, low-carbohydrate diet.

in the LCD group, despite the isocaloric prescription, is of relevance in the clinical practice.

The LCD group also experienced a larger FM loss. However, no association was found between changes in pain and FM loss. Keith et al. suggested that a ketogenic diet may result in loss of lipedema-affected adipose tissue [22], which has previously been described to be unaffected by energy restriction [1, 14]. However, it remains unknown whether the loss of FM is a result of better compliance with the diet in the LCD group or a shift in energy metabolism from CHO to fat oxidation [22]. Additionally, the effect on subcutaneous adipose tissue also needs to be investigated in the extremities affected by lipedema, not only in the whole body.

Both groups had a reduction in TBW, including both ICW and ECW, with no difference between groups. Moreover, no associations were found between changes in pain and changes in ICW, ECW, or TBW. Although ketogenic diets result in water loss due to glycogen depletion [40], it is unlikely that water depletion was a cause of the pain reduction seen in the LCD group because there was no difference between groups in the change in water compartments. The exact mechanisms underlying the possible pain-relieving effect of an LCD need to be further investigated.

Lipedema is associated with reduced QoL [3, 4], which might be explained by the severity of the symptoms, appearance-related distress, and depression [41]. The results from the three QoL questionnaires employed in this study were mostly overlapping. However, the results from the disease-specific questionnaire, i.e., LYMQOL, revealed an improvement in symptoms and QoL only in the LCD group. These specific measures may detect small changes, which are especially important for this patient group [42]. In the obesity-related questionnaire, i.e., IWQOL-Lite, and the generic questionnaire, i.e., RAND-36, both groups reported an improvement in QoL. This may suggest that overall QoL improves with weight loss, induced by either an LCD or a control diet. However, disease-specific QoL only improved in the LCD group, potentially through pain reduction. Dudek et al. found that appearance-related distress and symptom severity was an important aspect of psychological functioning in women with lipedema [41]. The results of the present study are in line with previous research showing a reduction in pain from RAND-36 in one case study after 2 years on a ketogenic diet [18], as well as an improvement in symptoms from the LYMQOL after a 6-week eucaloric LCD [19]. These results emphasize the importance of using a disease-specific QoL questionnaire in this patient group and suggest which domains should be prioritized when treating these patients.

The generic measures of QoL are important for comparisons with other populations [42]. Several studies have found significantly lower (i.e., worse) QoL in domains from RAND-36 in female patients with lipedema compared with the average of the female populations in their country [4, 43]. The LCD group in the present study presented with a higher (i.e., better) RAND-36 pain score at BL (73.5 ± 40.0) compared with the study by Romeijn et al. (57.2 ± 21.1) in a Dutch lipedema population [43] and Falck et al. (43.9 ± 24.0) in a Swedish lipedema population [4]. The pain score after the intervention in the present study (86.5 ± 25.2) was similar to the Dutch female average (80.0 ± 25.4) [43] and the Swedish female population (77.1 ± 20.7 in the same age group) [4], suggesting a normalization toward the average values seen in the general population after the LCD. Moreover, the RAND-36 general health score after the intervention in both groups (80.6 ± 12.6 and 75.3 ± 17.9) was similar to the average values seen in Norwegian female individuals in the same age group (75.1 ± 22.9) [27].

The present study suggests that an LCD might be a good treatment option for this patient group because it had a positive effect on both pain and QoL. Even though weight loss itself did not affect pain, it had a positive effect on QoL, and a low-energy, low-fat diet may be recommended if contraindications exist for implementing an LCD. Even though LCD and ketogenic diets have been shown to increase low-density lipoprotein cholesterol in the general population [44] and female patients with lipedema [45], beneficial effects of these diets have been reported on glucose, liver function, triglycerides, and high-density lipoprotein cholesterol in female patients with lipedema adopting an LCD for 7 months [45].

This study has both strengths and limitations. The first strength is its design, constituting the first RCT, to our knowledge, evaluating the effect of a dietary intervention on pain and QoL in female patients with lipedema. Second, both generic and disease-specific tools were used to measure QoL, allowing comparisons with both the general population, patients with obesity, and patients with lipedema. Finally, the study had a low dropout rate (11%) and strong dietary compliance, possibly attributed to close follow-ups and a wide variety of food choices. However, this study also has limitations. Due to COVID-19, many participants were not able to meet for face-to-face follow-ups as often as planned, which resulted in fewer measurements of ß-HB in blood. Additionally, given the nature of the study, the participants were not blinded to the intervention; therefore, the results may be affected by participants being biased toward the effect of the allocated intervention. Even though the participants were diagnosed with lipedema before entering the study, given the lack of standardized diagnostic criteria for lipedema, the specific criteria used might have differed among practitioners. This study might also be underpowered to look at differences in QoL between groups given that it was powered to look at differences in our main outcome variable, i.e., pain. Finally, this is a short-term study, and larger and longer studies are needed to fully understand the effects of a ketogenic diet on pain and QoL in this patient group.

CONCLUSION

A low-energy LCD seems to be superior to a standard low-fat control diet in reducing pain in female patients with lipedema. However, improvements in QoL can be achieved regardless of the dietary approach. Further studies with a larger sample size are needed to confirm these findings and to explore the underlying mechanisms.

AUTHOR CONTRIBUTIONS

Siren Nymo, Catia Martins, and Julianne Lundanes formulated the research question and designed the study. Frida Sandnes, Sissel Salater, and Julianne Lundanes carried out the study. Kari Hanne Gjeilo was involved in assessing pain and quality of life. Julianne Lundanes, Siren Nymo, Catia Martins, Kari Hanne Gjeilo, Frida Sandnes, and Patrik Hansson were involved in interpretations of the results. Julianne Lundandes analyzed the data and wrote the first draft of the manuscript, and all authors were involved in writing the manuscript and approved the final version.

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CONFLICT OF INTEREST STATEMENT

The authors declared no conflict of interest.

CLINICAL TRIAL REGISTRATION

ClinicalTrials.gov identifier: NCT04632810.

DATA AVAILABILITY STATEMENT

Data described in the manuscript will be available upon request pending approval.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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