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Title: **Effect of a ketogenic diet on pain and quality of life in patients with lipedema: The LIPODIET pilot study**

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Abstract

Background: Lipedema is an underdiagnosed condition in women, characterized by a symmetrical increase in subcutaneous adipose tissue (SAT) in the lower extremities, sparing the trunk. The lipedema SAT has been found to be resistant to diet, exercise and bariatric surgery, in regard to both weight loss (WL) and symptom relief. Current experience indicates that a low carbohydrate and high fat (LCHF-diet) might have a beneficial effect on weight and symptom management in lipedema.

Objective: To assess the impact of an eucaloric low carbohydrate, high fat (LCHF)-diet on pain and quality of life (QoL) in patients with lipedema.

Methods: Women diagnosed with lipedema, including all types and stages affecting the legs, (age 18-75 years, BMI 30-45 kg/m^2) underwent 7 weeks (wk) of LCHF-diet and, thereafter 6 wk of a diet following the Nordic nutrition recommendations. Pain (visual analog scale) and QoL (questionnaire for lymphedema of the limbs), weight and body composition were measured at baseline, wk 7 and 13.

Results: Nine women (BMI: 36.7±4.5kg/m^2 and age: 46.9±7 years) were recruited. The LCHF diet induced a significant WL -4.6±0.7 kg (-4.5±2.4%), P<0.001 for both, and reduction in pain (-2.3±0.4 cm, P=0.020). No correlation was found between WL and changes in pain at wk 7 (r = 0.283, P = 0.460). WL was maintained between wk 7 and 13 (0.3±0.7 kg, P=0.430), but pain returned to baseline levels at wk 13 (4.2±0.7 cm ,P=0.690). A significant increase in general QoL was found between baseline and wk 7 (1.0 (95% CI (2.0, 0.001), P=0.050) and 13 (1.0 95% CI (2.0, 0.001) P=0.050), respectively.

Conclusion: A LCHF-diet is associated with reduction in perceived pain and improvement in QoL, in patients with lipedema. Larger randomized clinical trials are needed to confirm these findings.

Keywords: Ketogenic Diet, Obesity, Obesity Phenotype, Quality of life, Bodyfat distribution.

Introduction

Lipedema is an obesity related, underdiagnosed health condition affecting women exclusively, and is characterized by a symmetrical increase of subcutaneous adipose tissue (SAT) in the lower extremities, sparing the trunk (1). As many as 50% of patients with lipedema may present with excess body weight, hence lipedema is often misdiagnosed as overweight or obesity (2). Disease onset of lipedema is usually at puberty, during pregnancy or at menopause (2, 3). Lipedema affects women almost exclusively, but it has also been observed in men with hormonal imbalances or liver disease (4, 5). The diagnosis of lipedema is made clinically by family- and medical history, visual inspection and physical examination, as there are no blood or urine biomarkers for lipedema (3). Based on what body parts are involved, lipedema is differentiated into five types and it may progress through four stages (3). The main criteria to diagnose lipedema is bilateral and symmetrical fat deposits downward from the hips, while the feet are spared. Moreover, non-pitting edema, easy bruising, tenderness and pain in the affected regions are common in this patient group, even though they cannot be used as diagnostic criteria (4). However, clinical practice has shown that lipedema fat tissue can also be found in other areas of the body that not legs and arms, namely the abdomen (6). Most importantly, these patients have no or little response on loss of lipedema fat from traditional obesity treatments, such as lifestyle modification or bariatric surgery (2, 3, 7, 8). Little is known about the etiology of lipedema, but the vascular and lymphatic systems seem to be implicated (9).

Even though the etiology of pain in this patient group remains unknown, it might reflect an active state of inflammation within the SAT (9, 10). The Lipedema UK and The British Lymphology Society (2012) (11) reported that 87% of the 250 females interviewed agreed that

lipedema had a negative effect on quality of life (QoL). Since it is unknown what is causing the pain, an optimal and effective treatment is unclear (12, 13). Today's treatment options consist of conservative physical therapy, surgical liposuction and lifestyle modifications, including altering dietary intake and increasing physical activity (7).

Patients´ experiences seems to indicate that a low-carbohydrate and high-fat diet (LCHF-diet), also called a ketogenic diet (KD), may have an effect on weight and symptom management in lipedema (14-16). KD are characterized by a reduction in carbohydrates, usually to less than 50 g/day (17), and a relative increase in the proportions of fat (70-75 E%), and protein (20 E%), inducing a ketogenic metabolic state (18). "The lipedema project", by Seo and Keith, promote a Ketogenic Way of Eating (WOE) for patients with lipedema, and has reported successful outcomes (19, 20). Women on the ketogenic WOE report reduction or elimination of swelling and pain, and weight loss (WL) (14, 20). However, these reports came from patients' experiences, not clinical trials, therefore more research is needed to confirm these findings and to investigate if KD is a possible treatment option for lipedema. Recently, Renzo et al (2021) reported a reduction in fat mass (FM) and an improvement in QoL with a Mediterranean diet in patients with lipedema (21).

The main objective of this study was to assess if an eucaloric LCHF-diet lead to change in pain and QoL in patients with lipedema. The second aim was to assess if a LCHF diet led to change in body composition in patients with lipedema. The hypothese of the study were that a LCHF-diet would lead to a reduction in pain and increase in QoL, independently of WL, in lipedema patients.

Methods

Selection and descriptions of participants

Participants

Women (18-75 years old) with obesity (BMI: 30-45 kg/m^2) and diagnosed with lipedema, including all types and stages affecting the legs, were included in the study. The participants had to be weight stable (< 2 kg variation within the last 3 months) and not currently dieting to lose weight or on a KD. Exclusion criteria was pregnancy or breast feeding, history of infectious diseases, medication known to affect body weight and enrolment in any other obesity treatment. Moreover, those with a history of psychological disorders, not mastering a Scandinavian language, having a malign disease or any disease that leads to dietary advice that is not consistent with the intervention, or difficulties following the instructions, were not accepted into the study. Participants were recruited via announcement at obesity treatment facilities and internet, (Lipedema-groups on Facebook and the intranet at the University Hospital in Trondheim), posters in the region, and through the Norwegian lymphedema- and lipedema association. All participants provided a written informed consent before commencement.

Technical information

Study design

This was a repeated measures study, where females with lipedema underwent 7 weeks of an eucaloric LCHF-diet, followed by 6 weeks of an isocaloric diet in line with the Nordic Nutrition Recommendations. The LIPODIET is a controlled, prospective clinical trial approved by the

Regional Committee for Medical Research Ethics in Norway (2018/307) and registered in ClinicalTrials.gov (NCT03710798) (https://www.clinicaltrials.gov/ct2/show/NCT03710798). The study design is illustrated in Figure 1.

LCHF-phase

All participants followed a seven-week eucaloric LCHF-diet (fat: 70-75 E%, carbohydrate: 5-10 E%, protein: 20 E%). They received individual dietary plans at baseline, together with a recipe booklet. Dietary plans were based on individual calculated energy needs (resting energy expenditure (REE) x physical activity levels (PAL)) aiming at maintaining baseline weight. REE was measured in the fasting state by indirect calorimetry (Vmax Encore 29N; CareFusion), at baseline, using a canopy system and following standard procedures (22). PAL was measured with armbands (SenseWear, Body Media, Pittsburg, USA).

Nordic nutrition recommendations-phase

During week 8, the participants were gradually introduced to a 6-week eucaloric diet (dietary plans and a recipe booklet as for the LCHF-phase) based on the Nordic nutrition recommendations (NNR). The control diet used in this study was based on the NNR that constitutes the scientific basis for national nutrient recommendations and dietary guidelines in Norway. The purpose is to help prevent chronic diet-related diseases in the population (23).

Compliance:

The participants had 30-minutes weekly follow-ups with the dietitian aiming to ensure compliance with the diets. Moreover, patients were asked to fill out daily food records throughout the study period. Food records from baseline, weeks 6 and 11 were then analyzed for macro- and micronutrient composition using Kostholdsplanleggeren (Norwegian Food Safety Authority and Norwegian Directorate of Health, Oslo, Norway, 2016) (24). Acetoacetate (AcAc) was measured in the first urine of the day at the weekly follow-ups, using ketostix

(Bayer Corp, Elkhart, IN, USA), as a measure of compliance during the LCHF diet. Participants were asked not to change their activity throughout the study and armbands (SenseWear, Body Media, Pittsburg, USA) were used for 7 days, at pre-baseline, week 6 and week 12, to check for compliance. For data to be considered valid, participants had to wear the armbands for < 7 days, including at least 1 weekend day, and more than 95% of data needed to be available over a 24-hour period. PAL-value and number of steps/day were analyzed (25).

Data collection

The following variables were measured at baseline, week 7 and week 13.

Pain

To measure the perceived pain, a visual analogue scale (VAS) was used (26, 27). Participants were asked to place a perpendicular line on the VAS-scale to represent their current pain-intensity at baseline, W7 and W13. The question used was: "In how much pain are you right now?" (0 = No pain at all 10 = As much pain you can possibly imagine)

Quality of life

The Norwegian version of the QoL questionnaire for lymphedema of the legs, a validated health-related QoL questionnaire (28) was used. The questions cover four domains: symptoms, body image/appearance, function, and mood. Each item in each domain was scored after the Likert's scale, 1-4: not at all = 1, a little = 2, quite a bit = 3, a lot = 4.

Weight and body composition

Height was measured following standard procedures (29), using a measuring tape installed on the wall**.** Bioelectrical impedance analysis (BIA) was used (InBody 720 (BIA), Seoul, South Korea) at baseline, week 7 and week 13 to measure body weight (BW) and to analyze body

composition (30-32). Waist, hip, thigh, and calf circumference were measured at baseline, week 7 and week 13 using a measuring tape. The waist was defined as the midway between the lower rib and the iliac crest (33). The participants were asked to breathe normally, and the measurement was taken as they exhaled. Hip circumference was measured over the largest part of the buttocks (33-35). The thigh and calf circumferences were measured as the participants were lying on a bench and measured where the circumference of the thigh/calf apparently was largest. To ensure that the thigh and calf circumference was measured at approximately the same place each time, the length (cm) from the foot to the point, was measured and recorded for the next measurement. These circumference measures were taken only wearing underwear.

Blood samples

Blood samples were collected in fasting at baseline, week 7 and week 13, at the laboratory of the University Hospital in Trondheim, to ensure that the participants tolerated the diet and that the diet did not lead to elevated blood lipids and/or deteriorated kidney function (18, 36). The parameters measured in the blood were C-reactive protein (CRP), high-density lipoprotein (HDL) cholesterol, low-density protein (LDL) cholesterol, triglycerides, glucose, glycated hemoglobin (HbA1c), alanine transaminase (ALAT), gamma-glutamyl transferase (GT), alkaline phosphatase (ALP), natrium and potassium.

Statistical Analyses

Statistical analysis was carried out using IBM SPSS Statistics 26 (SPSS Inc., Chicago, IL) and statistical significance assumed at 5%, unless otherwise stated, and data presented as mean ± SEM, except for baseline anthropometric data, where mean ± SD was used. Data was analyzed using linear mixed models (LLM) and Bonferroni adjustment were used for comparison between timepoints (baseline, week 7 and week 13). Correlation analysis between

WL at week 7 and week 13 and change in perceived pain was performed using Spearman r correlation.

Results

Nine participants met study entry criteria and were included in the study with an average age of 46.9±9.0 years and with a BMI of 36.7±4.5 kg/m^2. One participant did not show up for testing at week 13, due to illness, but was included in the analysis. Mean attendance of weekly follow-up meetings throughout the study period was 85.7 % (range: 71.4-100.0%).

Body weight and composition

Changes in body weight and composition overtime can be seen in Table 1. The LCHF induced a significant WL (-4.6±0.7 kg (-4.5±2.4%), P<0.001), which was maintained at week 13 (-4.1±0.7 kg (-4.0± 2.4%), P<0.001). No significant change in BW was seen from week 7 to week 13 (P=0.430).

There was a significant decrease in waist (98.3±2.7 vs. 94.0±2.7 cm, P<0.001) and hip-circumference (125.2±1.6 vs. 123.0±1.6 cm, P=0.010) from baseline to week 7, and this was maintained at week 13. There was a significant decrease in calf-circumference (48.0±3.8 vs. 47.0±3.8 cm, P=0.030) from baseline to week 7, but no significant change in thigh-circumference (67.0±3.0 vs. 65.0±3.0 cm, P=0.200) during the same period.

Compliance

Diet

All participants achieved ketosis, as positive AcAc (> 0.5 mmol/L) was detected in urine during the LCHF-diet, according to objective observations of color change on the ketostix. AcAc increased from baseline to week 7 (>0.05-8 mmol/L) and returned to baseline levels at week 13 (< 0.03).

Changes in energy, macro- and micronutrients intake over time are shown in Table 2. There was no significant change in median total energy intake between any of the three time points. The total fat intake increased significantly from baseline to week 6 (88.0±8.6 vs. 146.0±8.6 g/day, P<0.001), and decreased significantly from week 6 to week 11 (146.0±8.6 vs. 73.0±8.6 g/day, P<0.001). Simultaneously the total intake of carbohydrates decreased significantly from baseline to week 6 (182.0±21.6 vs. 28.0±21.6 g/day, P<0.001) and increased from week 6 to week 11 (28.0±21.6 vs. 197±21.6 g/day, P<0.001). There were no significant differences between baseline and week 11 in any of the nutrients.

The daily intake of saturated fat, unsaturated fat, cholesterol, sugar, fiber, omega-3 and omega-6 are shown in Table 3. Between baseline and week 6 there was a significant increase in the total intake of saturated fat (32.0±3.6 g/day vs. 58.8±3.6 g/day, P<0.001), unsaturated fat (46.5±4.6 g/days. 67.7±4.6 g/day, P=0.03) cholesterol (325.4±53.0 g/day vs. 594.8±53.0 g/day, P=0.002), omega-3 (2.4±0.58 g/day vs. 6.5±0.58 g/day, P<0.001) and omega-6 fatty acids (10.2±1.6 g/day vs. 16±1.6 g/day, P=0.025). There was also a significant decrease from week 6 to 11 in total intake of saturated fat (58.8±3.6 g/day vs. 27.5±3.6 g/day, P<0.001), unsaturated fat (67.7±4.6 g/day vs. 37.5±4.6 g/day, P<0.001), cholesterol (594.8±53.0 g/day vs. 271.6±53.0 g/day, P<0.001), omega-3 (6.5±0.58 g/day vs. 2.7±0.58 g/day, P<0.001) and omega-6 fatty acids (15.6±1.6 g/day vs. 9.7±1.6 g/day, P=0.015). There was a significant decrease in intake of sugar (33.0±5.7 g/day vs. 3.1±5.7 g/day, P=0.01) from pre-baseline to week 6, followed by a significant increase in intake of sugar (3.1±5.7 g/day vs. 24.0±5.7 g/day, P<0.05) from week 6 to week 11.

There was a significant increase in the intake of main carbohydrate sources and a decreased intake of meat and eggs between weeks 6 and 11, when changing from the ketogenic to the NNR diet.

Physical activity

There were no significant differences in PAL or number of steps per day over time. These data are presented in Table 4.

Main outcome variables

Pain

Changes in pain overtime can be seen in Table 5. The LCHF-diet induced a significant reduction in pain from baseline to week 7 (4.6±0.69 vs. 2.3 ±0.69 cm, P=0.018). Perceived pain returned to baseline levels at week 13 (4.2±0.69 cm, P=0.69).

Quality of life

Changes in QoL can be seen in Table 6. There was a significant increase in *general life quality* from baseline to week 7 (5.1± 0.61 vs. 6.1± 0.61, P=0.05) and week 13 (5.1± 0.61 vs. 6.1± 0.61, P=0.05). There was a significant decrease in median score in the QoL subcategory; *body image/appearance* from baseline to week 7 (3.1±0.18 vs. 2.7±0.18, P=0.03). In the subcategory *symptoms*, there was a decrease in score from baseline to week 6 (2.8±0.23 vs. 2.3±0.23, P=0.02). There were no significant changes in any of the other subcategories of QoL (*function, body image, symptoms, feelings, total score*) between any of the time points.

Markers of glucose, lipid and electrolyte metabolism in the blood

Changes in glucose, lipid and electrolyte markers in the blood can be seen in Table 7. The LCHF-diet induced a significant reduction in triglyceride levels (1.12±0.12 vs 0.73±0.12, P=0.003), HbA1c (34.6±1.1 vs. 31.8±1.1, p=0.01) and ALP (73.4±5.3 vs. 66.7±5.36, p=0.01) measured in blood. Triglyceride levels then increase from week7 to week13 (0.73±0.12 vs. 1.1±0.12, p= 0.01), with no significant differences between week13 and baseline. No significant

changes were found in CRP, total cholesterol, HDL- and LDL-cholesterol, glucose, ALAT, GT, natrium or potassium at any timepoint.

Correlations

No significant correlation was found between WL at week 7 and change in perceived pain during the same time period (r=0.283, P=0.46), but there was a strong positive association between WL at week 13 and change in perceived pain (r=0.695, P=0.04).

Discussion

The aim of this pilot study was to investigate if an eucaloric LCHF-diet improved pain and QoL in females with lipedema, and if the diet caused any changes in weight and body composition. The main findings of this study were that a 7-week LCHF-diet induced a significant reduction in pain and WL. No correlation between WL and pain reduction was found, however during the NNR-phase the perceived pain increased, although WL was maintained. There was also an improvement in QoL for body image/appearance and symptoms in the LCHF-period.

The relief of pain with the 7-weeks LCHF-diet and maintenance of WL during the NNR-phase, with recurrence of pain supports our hypothesis that the pain reduction could be induced by the LCHF-diet itself, and not by the WL.

The mechanisms leading to pain reduction following KDs remain unknown. Whether a KD impacts on pain directly, through an increase in ketone bodies (KB), or indirectly, through changes in macronutrient and micronutrient intake remain to be established and further studies are needed to elucidate this (20) . The pain reduction may also be explained by the anti-inflammatory effects of an LCHF-diet, given the inflammation present in the lipedema fat (9, 10). Nutrients affects our immune system, and various macronutrients can be either pro- or anti-inflammatory (37). Omega-6, refined carbohydrates (white bread, pasta, and ultra-processed food) and saturated fats are nutrients with pro-inflammatory effects, while omega-3,

polyphenols (fruits and vegetables) and whole- grain products have anti-inflammatory properties (38). The intake of omega-3 fatty acids increased during the LCHF-period and decreased in the NNR-phase. Simultaneously the intake of sugar decreased in the LCHF-period. These findings may indicate that a decreased intake of refined carbohydrates, and increased intake of omega-3 fatty acids may be part of the explanation of the reduction in pain in these patients, due to their anti-inflammatory effects. Therefore, the Mediterranean diet could be more appropriate for lipedema patients, also allowing the consumption of more whole-grain products and some fruits (39). This is in line with a recent study by Renzo et al, showing improvements in antioxidant capacity with a Mediterranean diet in patients with lipedema (21). This is one of the few studies investigating the effect of diet on pain in patients with lipedema, which is the dominating symptom in lipedema and the one with the strongest negative impact on QoL. Liposuction has been shown to induce a reduction in pain (assessed with VAS), with a concomitant improvement in psychological stress (40). In an experimental study by Rapprich et al., 25 patients diagnosed with lipedema were examined before and after liposuction. These patients reported a significant reduction in pain from 7.2 to 2.1 cm on VAS-score, six months after liposuction (40). Liposuction is a highly invasive treatment, not suitable to or affordable by all patients. The participants in our study reported a lower VAS-score initially, and therefore the reduced pain reported after 6 weeks on a LCHF-diet illustrates a great significant and clinical effect on pain.

The KD did induce a small, but significant reduction in BW (-4.6 kg CI (3.2,6.2 kg)). Loss of total body water (TBW), due to depletion of glycogen in the muscles and liver, is likely to account to some of the weight reduction seen (approximately 1.5 to 2 kg) (41, 42). Similarly, the small, although not significant, weight gain during the NNR-phase, is likely due to hydration of the lean tissue, which accompanies glycogen storage. Crescenzi R. et al. found that tissue sodium content is elevated in the skin and SAT in women with lipedema, and that the relative

fat-to-water volume in the calf was elevated in lipedema, and skin sodium content was directly correlated with fat-to-water volume (7). This indicates that the water volume in the legs of women with lipedema may be elevated.

The reduction in waist- and hip-circumference being the most significantly compared to thigh- or calf-circumference during LCHF indicate that these was the areas mostly affected by the WL. This is in line with a review article by Herbst et al. (2012) that lipedema fat in the lower extremities of the body in lipedema patients is resistant to WL (3).

Child et al. presented the hypothesis that adipocyte proliferation induce hypoxia due to a pressure on the capillaries, resulting in adipocyte necrosis followed by macrophage infiltration and inflammatory responses (2). A LCHF-diet may reduce pain by reducing the amount of non-lipidemic fat in the legs, which then relieves the pressure on the blood vessels (43). The lack of change in tight circumference in the present study is in contrast to the findings of another KD intervention study conducted in a mixed sample of patients with either lip- and/or lymphedema, which found a reduction in volume of the lower limbs (16). The diversity in findings could be due to differences in methods of assessment, participant characteristics (sex, age, disease type and stage), and sample size.

The early diagnosis of Lipedema followed by WL and dietary changes may reduce non-lipidemic fat and inflammation. This may also potentially slow down the progression of the condition. However, even with strict diet and exercise regimens, the disease may progress, and further treatment may be necessary (12). People with obesity only need a modest WL of 5% to 10% of initial weight to have a significant impact on health (10). Therefore, regardless of whether the WL impacts the lipedema symptoms or alter the body composition of the affected limbs, it will have a positive impact on health in general.

The presented findings are in line with the recently published review by Keith et al. The authors summarize that KDs can improve the clinical features of lipedema in three areas: reduction of weight and excessive adipose tissue deposition, pain reduction, and QoL improvement. These improvements are likely to be the result of changes in metabolism and hormonal function, reduction in edema or tissue water content, reduction in inflammation, and fibrosis prevention and/or reduction (20).

This study has several strengths. First, compliance with the diet was excellent. Second, the measurements were performed at the same day and time each week in every participant. Third, the participants were relatively healthy with ongoing treatment, strengthening our findings of pain-reduction. Unfortunately, this study also has some limitations. Most importantly, the small sample size and lack of a control group. Without a control group, one cannot conclude on causality since is possible that participation in the study by itself had a positive effect. The results should therefore be interpreted with caution. The awareness around lipedema is limited, and so is the number of women diagnosed with this disease. Therefore, the recruitment of participants was challenging, hence the small sample size. No power calculation was performed, and this should be seen as a pilot study. The measurement of circumference should have been performed several times and at several points on both left and right leg, as the affected areas vary. The body composition should preferably be measured with dual-energy x-ray absorptiometry (DEXA). Measurement of pain using the VAS could also have been done weekly, to better capture changes overtime. Finally, KB should have been measured in blood and plasma, in addition to urine, as that is a more accurate measurement.

There might be an increase in number of women diagnosed with lipedema in the future, as the awareness among health care providers is increasing, and lipedema is underdiagnosed. To identify these patients, a physical examination is important. Therefore, the physical

examination of all patients with overweight and obesity should be performed as a regular part of the clinical practice in obesity.

In summary, this study showed that there was a reduction in pain in patients with lipedema after 7-weeks on a KD. Even though the exact mechanisms mediating this effect remain unknown, several hypotheses have been proposed, namely ketosis per se (37), the anti-inflammatory effects of a LCHF-diet or a potential effect of a reduction in TBW or WL.

Conclusion

A LCHF-diet leads to a reduction in perceived pain and improvement in general QoL, independently of WL. Randomized clinical trials are needed to confirm these findings and explore the potential mechanisms involved.

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Table 2. Total energy and macronutrients intake and changes over time

	Baseline (n = 9)	**W6** (n = 9)	**W11** (n = 8)	**Baseline to W6** Δ 95% CI p-value	**Baseline to W11** Δ 95% CI p-value	**W6 to W11** Δ 95% CI p-value
Energy, kcal/day	1927.0±137.0	1863.0±137.0	1878.0±137.0	Δ-63.0 (-336.6, 463.4) 0.75	Δ-48.0 (-351.8, 448.2) 0.81	Δ15.0 (-415.3, 384.8) 0.94
Fat, g/day *(E%)*	88.0±8.6 *(41)*	146.0±8.6 *(71)*	73.0±8.6 *(35)*	Δ57.0 (-80.7, -33.7) **<0.001**	Δ-15.0 (-8.2, 38.8) 0.19	Δ-72.0 (49.0, 96.0) **<0.001**
CHO, g/day *(E%)*	182.0±21.6 *(38)*	28.0±21.6 *(6)*	197.0±21.6 *(42)*	Δ-154.0 (91.1, 217.1) **<0.001**	Δ15.0 (-78.4, 47.6) 0.6	Δ170.0 (232.5, 106.6) **<0.001**
Protein, g/day *(E%)*	85.0±5.8 *(18)*	99.0±5.8 *(21)*	91.0±5.8 *(19)*	Δ14.0 (-31.3, 2.6) 0.09	Δ7.0 (-23.4, 10.5) 0.44	Δ-8.0 (-9.0, 25.0) 0.34

Data presented as estimated marginal means ± SEM. (W; week, E%; energy percent, CHO; carbohydrates, CI; confidence interval, Δ; Mean difference between the timepoints)

Table 3. Total daily intake and change of saturated fat, unsaturated fat, cholesterol, sugar, fiber, omega-3 and omega-6 over time.

	Baseline (n = 9)	**W6** (n = 9)	**W11** (n = 8)	**Baseline to W6** Δ 95% CI p-value	**Baseline to W11** Δ 95% CI p-value	**W6 to W11** Δ 95% CI p-value
Saturated fat, g *(E%)*	32.0±3.6 *(14.5)*	58.8±3.6 *(28.5)*	27.5±3.6 *(13.4)*	Δ26.8 (37.2, 16.4) **<0.001**	Δ-4.5 (-5.8, 15.0) 0.370	Δ-31.3 (20.9, 41.7) **<0.001**
Unsaturated fat, g *(E%)*	46.5±4.6 *(22.0)*	67.7±4.6 *(32.9)*	37.5±4.6 *(18.2)*	Δ21.2 (34.8, 7.8) **0.030**	Δ-9.0 (-4.6, 22.5) 0.180	Δ-30.2 (16.7, 43.7) **<0.001**
Cholesterol, mg *(E%)*	325.4±53.0 *(0.15)*	594.8±53.0 *(0.3)*	271.6±53.0 *(0.13)*	Δ269.4 (421.5, 117.3) **0.002**	Δ-53.8 (-98.3, 205.9) 0.470	Δ-323.2 (171.1, 475.3) **<0.001**
Omega-3, g *(E%)*	2.4±0.6 *(0.9)*	6.5±0.6 *(3.4)*	2.7±0.6 *(1.4)*	Δ4.1 (5.7, 2.5) **<0.001**	Δ0.3 (-1.9, 1.3) 0.710	Δ-3.8 (2.2, 5.4) **<0.001**
Omega-6, g *(E%)*	10.2±1.6 *(4.7)*	15.6±1.6 *(7.7)*	9.7±1.6 *(4.8)*	Δ5.4 (10.0, 0.7) **0.030**	Δ-0.5 (-4.1, 5.2) 0.810	Δ-5.9 (1.3, 10.6) **0.020**
Sugar, g *(E%)*	33.0±5.7 *(6.9)*	3.1±5.7 *(0.7)*	24.0±5.7 *(5.1)*	Δ-30.0 (13.2, 46.7) **0.001**	Δ-9.0 (-7.7, 25.8) 0.270	Δ20.9 (37.6, 4.1) **0.017**
Fiber, g *(E%)*	25.8±5.0 *(5.4)*	15.8±5.0 *(3.4)*	26.4±5.0 *(5.5)*	Δ-10.0 (-4.7, 24.6) 0.170	Δ0.6 (-15.4, 14.0) 0.930	Δ10.6 (-25.3, 4.1) 0.150

Data presented as estimated marginal means ± SEM. (W; week, E%; energy percent, CI; confidence interval, Δ; Mean difference between the timepoints)

Table 4. PAL and steps per day at the different timepoints and change over time

	Baseline (n = 9)	**W7** (n = 9)	**W13** (n = 8)	**Baseline to W7** Δ 95% CI p-value	**Baseline to W13** Δ 95% CI p-value	**W7 to W13** Δ 95% CI p-value
PAL	1.4±0.02	1.4±0.02	1.4±0.02	Δ-0.02 (-0.02, 0.06) 0.3	Δ-0.01 (-0.03, 0.05) 0.6	Δ0.01 (-0.05, 0.03) 0.6
Steps	5241.7±465.8	5359.3±465.8	5387.4±465.8	Δ117.7 (-803.0, 567.7) 0.7	Δ145.8 (-831.1, 539.6) 0.7	Δ28.1 (-713.5, 657.3) 0.9

Data presented as estimated marginal means ± SEM.
(W; week, PAL: physical activity level, CI; confidence interval, Δ; Mean difference between the timepoints)

Table 1: Body weight and composition and changes over time.

	Baseline (n = 9)	**W7** (n = 9)	**W13** (n = 8)	**Baseline to W7** Δ 95% CI p-value	**Baseline to W13** Δ 95% CI p-value	**W7 to W13** Δ 95% CI p-value
BW, kg	102.6±4.1	98.0±4.1	98.5±4.1	Δ-4.6 (3.2, 6.2) **<0.001**	Δ-4.1 (2.7, 5.6) **<0.001**	Δ0.5 (-2.0, 0.9) 0.430
(%WL)				(-4.5%±2.4)	(-4.0%±2.2)	(-0.6%±0.9)
BMI, kg/m^2	36.7±1.5	35.1±1.5	35.3±1.5	Δ-1.6 (1.2, 2.1) **<0.001**	Δ-1.4 1.0, 1.9) **<0.001**	Δ0.2 (-0.7, 0.3) 0.350
Waist circumference, cm	98.3±2.7	94.0±2.7	96.0±2.7	Δ-4.3 (2.8, 6.0) **<0.001**	Δ-2.3 (1.2, 4.4) **0.020**	Δ2.0 (-3.2, 0.04) 0.060
Hip circumference, cm	125.2±1.6	123.0±1.6	123.0±1.6	Δ-2.2 (1.3, 3.8) **0.010**	Δ-2.2 (1.0, 3.6) **0.010**	Δ0.0 (-1.5, 1.0) 0.700
Waist/hip ratio	0.8±0.02	0.8±0.02	0.8 ±0.02	Δ-0.02 (0.004, 0.04) **0.017**	Δ-0.01 (-0.01, 0.03) 0.300	Δ0.01 (-0.03, 0.004) 0.140

Thigh, cm	67.0±3.0	65.0±3.0	65.1±3.0	Δ-2.0 (-0.6, 3.6) 0.200	Δ-1.9 (-0.3, 4.0) 0.080	Δ0.1 (-1.8, 2.5) 0.730
Calf, cm	48.0±3.8	47.0±3.8	47.5±3.8	Δ-1.0 (0.1, 1.7) **0.030**	Δ-0.5 (-0.4, 1.2) 0.330	Δ0.5 (-1.3, 0.3) 0.180
FM, kg	47.8±3.1	46.4±3.1	46.3±3.1	Δ-1.4 (-0.5, 3.3) 0.140	Δ-1.5 (-0.5, 3.3) 0.140	Δ-0.1 (-1.9, 2.0) 0.970
FM, %	46.5±1.4	46.8±1.4	46.6±1.4	Δ0.3 (-2.2, 1.6) 0.740	Δ0.1 (-2.0, 1.8) 0.920	Δ-0.2 (-1.7, 2.1) 0.810
FFM, kg	54.3±1.7	51.9±1.7	52.0±1.7	Δ-2.4 (0.03. 4.7) **0.048**	Δ-2.3 (-0.04, 4.7) 0.060	Δ0.1 (-2.4, 2.3) 0.950
SMM, kg	30.1±1.0	28.7±1.0	29.0±1.0	Δ-1.4 (0.2, 2.7) **0.024**	Δ-0.2 (-0.01, 2.5) 0.051	Δ0.3 (-1.5, 1.0) 0.700
Body water, l	41.0±1.4	38.1±1.4	38.6±1.4	Δ-2.9 (-0.1, 5.0) 0.060	Δ-2.4 (-0.5, 4.6) 0.110	Δ0.5 (-3.0, 2.1) 0.750

Data presented as estimated marginal means ± SEM.

(W; week, BW; body weight, BMI; body mass index, FM; fat mass, FFM; fat free mass SMM; skeletal muscle mass, CI: confidence interval, Δ; Mean difference between the timepoints)

Table 5. Pain at the different timepoints and changes over time.

	Baseline (n = 9)	**W7** (n = 9)	**W13** (n = 8)	**Baseline to W7** Δ 95% CI p-value	**Baseline to W13** Δ 95% CI p-value	**W7 to W13** Δ 95% CI p-value
VAS	4.6±0.7	2.3±0.7	4.2±0.7	Δ-2.3 (0.4, 4.1) **0.018**	Δ-0.4 (-1.5, 2.2) 0.690	Δ1.9 (3.7, 0.1) **0.041**

Data presented as estimated marginal means ± SEM.
(W; week, VAS: visual analogue scale, CI; confidence interval, Δ; Mean difference between the timepoints)

Table 6. QoL scores at the different timepoints and changes over time.

	Baseline (n = 9)	**W7** (n = 9)	**W13** (n = 8)	**Baseline to W7** Δ 95% CI p-value	**Baseline to W13** Δ 95% CI p-value	**W7 to W13** Δ 95% CI p-value
QoL_GL	5.1± 0.6	6.1± 0.6	6.1± 0.6	Δ1.0 (2.0, 0.001) **0.050**	Δ1.0 (2.0, 0.001) **0.050**	Δ0.0 (-1.0, 1.0) 1.0
QoL_Fu	2.1±14.4	2.0±14.4	2.0±14.4	Δ-0.2 (-0.1, 0.5) 0.230	Δ-0.1 (-0.3, 0.4) 0.790	Δ0.0 (-0.5, 0.2) 0.35
QoL_BI	3.1±0.2	2.7±0.2	2.9±0.2	Δ-0.4 (0.2, 0.7) **0.030**	Δ-0.2 (-0.08, 0.5) 0.100	Δ0.2 (-0.5, 0.03) 0.080
QoL_S	2.8±0.2	2.3±0.2	2.5±0.2	Δ-0.5 (0.1, 1.0) **0.020**	Δ-0.3 (-0.1, 0.8) 0.100	Δ0.2 (-0.7, 0.3) 0.400
QoL_Fe	1.9±0.2	1.7±0.2	1.7±02.2	Δ-0.2 (-0.2, 0.6) 0.300	Δ-0.2 (-0.2, 0.6) 0.300	Δ0.01 (-0.4, 0.4) 1.000
QoL_T	11.0±1.05	9.9±1.05	10.0±1.05	Δ-1.1 (-0.7, 2.9) 0.200	Δ-1.0 (-0.8, 2.8) 0.300	Δ0.1 (-1.9, 1.7) 0.900

Data presented as estimated marginal means ± SEM.
(W; week, E%; energy percent, CI; confidence interval, Δ; Mean difference between the timepoints, QoL: quality of life. GL: general life quality. Fu: function. Bl: body image, S: symptoms. Fe: feelings. T: total.)

Table 7: Markers of glucose, lipid and electrolytes metabolism in the blood at different timepoints and changes over time

	Baseline (n = 9)	**W7** (n = 9)	**W13** (n = 8)	**Baseline to W7** Δ 95% CI p-value	**Baseline to W13** Δ 95% CI p-value	**W7 to W13** Δ 95% CI p-value
CRP (mg/L)	3.3±0.9	4.0±0.9	2.6±0.9	Δ0.6 (-2.5, 1.2) 0.500	Δ-0,7 (-1.2, 2.5) 0.440	Δ-1.3 (-0.5, 3.1) 0.150
Total cholesterol (mmol/L)	5.0±0.3	4.7±0.3	4.8±0.3	Δ-0.2 (-04, 0.8) 0.400	Δ-0.6 (-0.4, 0.8) 0.570	Δ0.08 (-0.7, 0.5) 0.790
HDL-cholesterol (mmol/L)	1.5±0.07	1.5±0.07	1.5±0.07	Δ0.01 (-0.2, 0.1) 0.810	Δ0.003 (-0.2, 02) 0.960	Δ-0.01 (-0.1, 0.2.) 0.840
LDL-cholesterol (mmol/L)	3.25±0.3	2.9±0.3	3.1±0.3	Δ-0.2 (-0.3, 0.7) 0.320	Δ-0.1 (-04, 06) 0.660	Δ0.1 (-0.6, 0.4) 0.560
Triglyceride (mmol/L)	1.1±0.1	0.7±0.1	1.1±0.1	Δ-0.4 (0.2, 0.6) **0.003**	Δ-0.03 (-0.2, 0.3) 0.800	Δ0.4 (-0.6, -0.1) **0.010**
Glucose (mmol/L)	3.2±0.3	2.9±0.3	3.1±0.3	Δ-0.2 (-0.7, 0.3) 0.320	Δ-0.1 (-0.6, 0.4) 0.660	Δ0.1 (-0.4, 0.6) 0.580
HbA1c (mmol/mol)	34.6±1.1	31.8±1.1	33.9±1.1	Δ-2.9 (-5.0, -0.7) **0.010**	Δ-0.8 (-2.9, 1.4) 0.470	Δ2.1 (-0.03, 4.2) 0.050
ALAT (U/L)	22.2±3.3	21.0±3.23	17.8±3.3	Δ-1.2 (-9.2, 6.8) 0.750	Δ-4,5 (-12.5, 3.6) 0.260	Δ-3.3 (-11.3, 0.8) 0.400

GT (U/L)	19.1±4.02	18.0±4.02	14.3±4.02	Δ-1.1 (-7.7, 5.4) 0.720	Δ-4.9 (-11.4, 0.66) 0.130	Δ-3.7 (-10.3, 2.8) 0.250
ALP (U/L)	73.4±5.3	66.7±5.4	74.4±5.4	Δ-6.7 (-11.9, -1.6) **0.010**	Δ1.0 (-4.2, 6.2) 0.700	Δ7.7 (2.5, 12.9) **0.010**
Natrium (mmol/L)	140.3±0.5	140.3±0.5	140.4±0.5	Δ0.08 (-1.2, 1.3) 0.890	Δ0.1 (-1.1, 1.4) 0.830	Δ0.04 (-1.2, 1.3) 0.940
Potassium (mmol/L)	4.1±0.07	4.0±0.07	4.03±0.07	Δ-0.11 (-0.3, 0.05) 0.170	Δ-0.04 (-0.12, 0.1) 0.620	Δ0.07 (-0.09, 0.2) 0.35

Data presented as estimated marginal means ± SEM.

(W; week, CRP; C-reactive protein, HDL; high-density lipoprotein, LDL; low-density lipoprotein, HbA1c; glycated haemoglobin, ALAT; alanine transaminase, GT; gamma-glutamyltransferase, ALP: alkaline phosphatase, CI: confidence interval, Δ; Mean difference between the timepoints)

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Figure 1. Timeline of data collection throughout the LIPODIET-study.