UiT The Arctic University of Norway

Faculty of health sciences

Effect of ketosis on pain and quality of life in women with lipedema

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Master's thesis in Clinical Nutrition [ERN-3900], 2021-2022

Abstract

Background: Lipedema is an adipose tissue condition in females and is characterized by immobility, pain, and reduced quality of life (QoL). Recent publications indicate that ketogenic diets may induce symptom relief in women with lipedema, and several mechanisms are hypothesized. The aim of this study was to investigate the impact of a low-energy ketogenic diet on pain and QoL in women with lipedema, compared to a low-energy non-ketogenic diet.

Methods: Females with lipedema aged between 18-75 years and body mass index (BMI) 30-45 kg/m^2 were randomized to either a low-energy ketogenic diet (keto) or a low-energy non-ketogenic diet (control) for eight weeks. Pain was measured by Brief Pain Inventory, QoL by RAND-36, Impact of Weight on Quality of Life-lite (IWQOL-Lite), and Lymphoedema Quality of Life (LYMQOL) at baseline and week 9. The paired samples t-test or Wilcoxon rank test, and multiple linear regression with 95% confidence intervals were used to assess change from baseline to week 9, and to compare effects between groups.

Results: 29 women with lipedema (age: 47.0 ± 11.2 years, BMI: 38.2 ± 5.5 kg/m^2) were recruited to the study. The keto group (n = 12) was ketotic with a diet of 1200 kcal, 15 E% carbohydrate, 24 E% protein, and 57 E% fat, and the control group (n = 12) remained non-ketotic with a diet of 1200 kcal, 60 E% carbohydrate, 18 E% protein, and 18 E% fat. The keto group had significantly larger weight loss compared to the control group (-9.5 ± 1.4% vs. -7.1 ± 2.9%, p = 0.017). In the keto group only, there was a significant reduction in strongest pain score (-2.0 ± 2.7, p = 0.020) and average pain score (-1.8 ± 2.1, p = 0.016). Pain relief was not associated with weight loss in the keto group (r = -0.082, p = 0.801). Both the keto- and control-group significantly improved the score of total QoL (11.6 ± 6.3, p = 0.002 vs. 6.8 ± 10.4, p = 0.046, respectively) and physical function (7.2 ± 5.7, p = 0.001 vs. 11.6 ± 18.5, p = 0.045, respectively) from IWQOL-Lite, and energy (16.4 ± 20.5, p = 0.024 vs. 8.8 ± 8.6, p = 0.005, respectively) from RAND-36. The keto group only, improved self-esteem score (9.8 ± 13.3, p = 0.026) from IWQOL-Lite. Nevertheless, there were no difference between groups in average pain, strongest pain, or any QoL variable from baseline to week 9.

Conclusion: In this randomized controlled trial, a ketogenic diet induced pain relief and improved QoL in women with lipedema. Larger clinical trials and longitudinal studies are needed to confirm these results and explore underlying biological mechanisms.

Acknowledgements

First and foremost, I would like to thank my supervisor Siren Nymo for initiating the project and for her expertise, guidance, and quick feedback throughout the whole period. I would also like to express my gratitude to my secondary supervisors Patrik Hansson and Ingvild Hansen Ivan, for their valuable suggestions and encouragement in this master's thesis. I am profoundly grateful for the academic deliberations and support through each step of the project.

I wish to show my sincere appreciation to the Obesity Research Center for the hospitality and including me in the research environment. A special thanks to Julianne Lundanes for her dedication and help with the data collection. I would also like to acknowledge the effort of several coworkers in this project: Hege Bjøru and Sissel Salater for training and assistance in blood draw. Ann Kristin De Soysa, Wilma Van de Veen, and Kari Hanne Gjeilo for their proficiency and insightful input. Master students Marte Solem and Oda Aakervik for the great teamwork. Also, many thanks to all participants for their commitment to the study and making this research possible.

Finally, I would like to thank my fellow students at the University of Tromsø, friends, and family for support and motivation throughout my years of study. This accomplishment would not have been possible without them. Thank you!

Trondheim, May 2022
Frida Huhta Sandnes

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Abbreviations

AcAc:	acetoacetate
BHB:	β-hydroxybutyrate
BIA:	bioelectrical impedance analysis
BL:	baseline
BMI:	body mass index
BPI:	brief pain inventory
CHO:	carbohydrate
E%:	energy percent
ECW:	extracellular body water
FFM:	fat free mass
FM:	fat mass
ICW:	intracellular body water
IWQOL-Lite:	impact of weight on quality of life-lite
KD:	ketogenic diet
LAT:	lipedema adipose tissue
LCHF:	low carbohydrate, high fat diet
LED:	low-energy diet
LYMQOL:	lymphoedema quality of life
MET:	metabolic equivalents of task
MUFA	monounsaturated fatty acids
PA:	physical activity
PAL:	physical activity level
PFD:	pre-coded food diaries
PUFA:	polyunsaturated fatty acids
QoL:	quality of life
RCT:	randomized controlled trial

ROS: reactive oxygen species

SFA: saturated fatty acids

SMM: skeletal muscle mass

TBW: total body water

Wk: week

1 Introduction

The adipose tissue disorder lipedema is characterized by bilateral and symmetrical accumulation of subcutaneous fat in the lower extremities and occasionally upper extremities (30%), sparing the feet and hands (1). Lipedema primarily affects females and typically appears during puberty, pregnancy, or menopause (2). Women with lipedema often report daily pain, tenderness, immobility and low quality of life (QoL) (3). Nevertheless, lipedema is little documented in medical literature and rarely recognized by general practitioners (1, 4). The lack of epidemiological studies and diagnostic code makes the prevalence of lipedema still uncertain (5, 6).

Etiology and pathogenesis in lipedema are not fully understood, but it is suggested that genetics, hormones, lymph- and vascular system, and inflammation are involved factors (7). There is no cure for lipedema, and current treatments primarily aim at relieving symptoms and preventing progression and complications (4). Compression therapy, manual lymph drainage, healthy diet, non-aerobic exercise, and surgical liposuction are the most common treatments for lipedema (2, 4). 62-88% of women with lipedema have comorbid obesity (8), making weight management critical as any weight gain seem to aggravate the condition (9-11). Lipedema adipose tissue (LAT) is thought to be resistant to conventional diet and exercise and result in weight loss only in the upper body (12). However, intervention studies on lifestyle-induced weight loss have been nearly non-existing in this patient group (2, 9).

Recently, Di Renzo et al. (13) showed reduced fat mass in the upper and lower limbs, as well as improved daily functioning in women with lipedema after four weeks of a modified Mediterranean diet. Furthermore, “The lipedema project”, by Seo and Keith, promote a ketogenic way of eating for women with lipedema, and has reported weight loss and pain relief in the affected areas (14). A case report by Cannataro et al. (15) correspondingly presented weight loss, pain relief, and improved QoL with a two-year ketogenic diet (KD) intervention. Moreover, the pilot study (16) of this present project proposed reduced pain, independent of weight loss, in women with lipedema with a seven-week KD. Detailed results from publications are presented in Appendix 1.

2 Theory

2.1 Lipedema

Lipedema was labeled by Dr. Allen and Hines Jr from the Mayo clinic in 1940 (17), but is referred to as both lipedema, lipoedema, lipalgia, adiposalgia, adiposis dolorosa, lipomatosis dolorosa of the legs, lipohypertrophy dolorasa, painful column leg lipedema, and painful lipedema syndrome (1, 5). Lipedema can be considered a condition along the spectrum of rare adipose disorders, which includes familial multiple lipomatosis, Madelung's disease, and Dercum's disease. Nevertheless, whether each of these conditions represents a single disorder or a variation of features in adipose tissue is still unknown (10). Lipedema is not registered in the International Classification of Diseases (ICD-10) by The World Health Organization (WHO). However, ICD-11 approved by WHO in 2019 includes the lipedema code EF02.2 (18).

Lipedema is recognized by clinical history, in addition to visual and physical examination, as there are no blood or urine biomarkers for the condition (1). Disproportional waist-to-hip ratio, "cut-off" signs at ankles and wrists, non-pitting edema, negative Kaposi Stemmer's sign (the ability to pinch and lift a skin fold of the second toe or middle finger), nodular tissue, pale and cool skin with presence of striae, varicose veins, and telangiectasias are common indications of lipedema (1, 10). In addition, the affected areas are often described as heavy, pressing, tender, and painful (4). The pain may appear spontaneously and randomly but tends to intensify throughout the day, and is often exaggerated by warm weather, exercise, air travel, and long periods of sitting or standing (2, 5, 9).

Lipedema can be classified into five types (Figure 1) (1, 19). Type 1: pelvis, buttocks, and hips. Type 2: buttocks to knees. Type 3: buttocks to ankles. Type 4: arms. Type 5: isolated lower leg. Type 1 to 3 are the most common, but a mix of types may be present. Lipedema exclusively in the arms is rare (3%) (1).

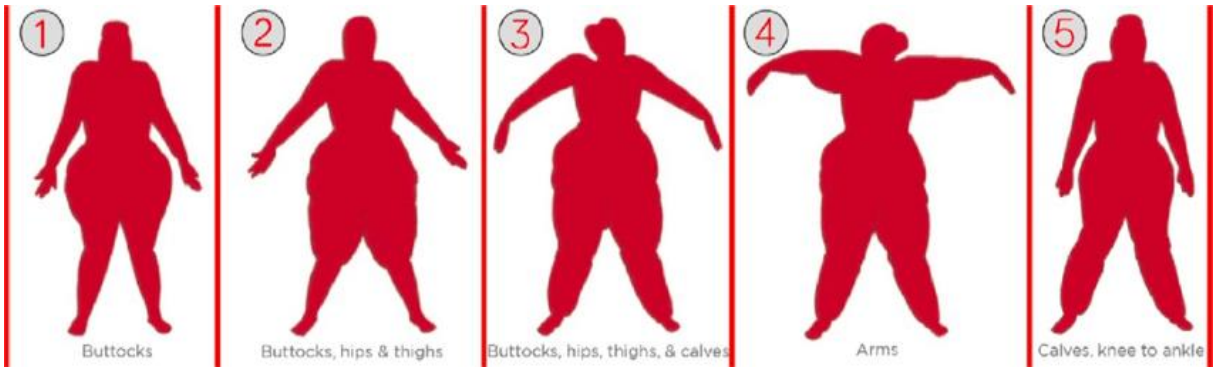

Figure 1 Types of lipedema (19). Copyright 2021 Medical Hypotheses.

The severity of lipedema can be mild and remain unchanged, or progress gradually or rapidly (11). The severity can be divided into four stages (Figure 2) (19). Stage 1: smooth skin surface with expanded SAT. Stage 2: irregular skin pattern with growth of nodules, lipomas or angiolipomas. Stage 3: large swelling of nodular fat causing serious deformations especially on the thighs and around the knees. Stage 4: Lipedema affects the lymphatic system and cause secondary lymphedema, also known as lipolymphedema (10). It is important to notice that these stages do not necessarily correspond with pain severity (8).

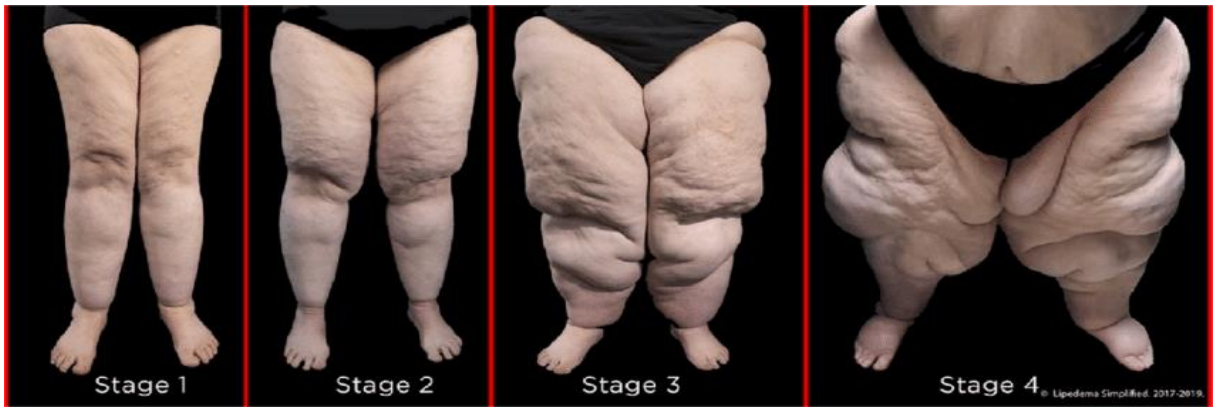

Figure 2 Stages of lipedema (19). Copyright 2021 Medical Hypotheses.

2.1.1 Etiology and pathogenesis

Lipedema is believed to be a genetic condition, and familial occurrence associated with a genetic component has been reported in up to 60% of lipedema cases (1, 5). Hormonal interference, particularly by estrogen, is suggested as lipedema affects almost exclusively women, who often find that the condition occurs or worsens during stress, surgery, puberty, pregnancy, menopause, or other times of hormonal fluctuation (2, 10). Men with lipedema are only mentioned in case reports and are often linked with male hypogonadism,

hyperestrogenemia, liver disease, or hormone therapy (1, 5, 9). Estrogen has a direct effect on white fat-cells via their estrogen receptors (ER), which are abnormally expressed. An unbalance between the subtypes ER-α and ER-β in LAT is hypothesized (6, 20).

In similarity with obesity, lipedema is considered an inflammatory condition (Figure 3) (8). Localized proliferation of LAT is a result of hypertrophy and hyperplasia of fat cells, which in turn may lead to hypoxia, thus adipocyte necrosis and other stress signals. These mechanisms stimulate recruitment of immune cells to the adipose tissue and result in an inflammatory state (5, 6, 8). This theory is supported by the discovery of an accumulation of sodium in the skin and subcutaneous fat of women with lipedema, which is considered a hallmark of inflammatory diseases (21). In addition, necrotizing adipocytes surrounded by infiltrating macrophages have been revealed in immunohistochemical analysis of LAT (22). Further, there was a higher level of macrophages in the adipose tissue of women with lipedema, both with and without obesity, compared to controls with obesity, suggesting inflammation in LAT may occur independently of obesity-induced inflammation (22).

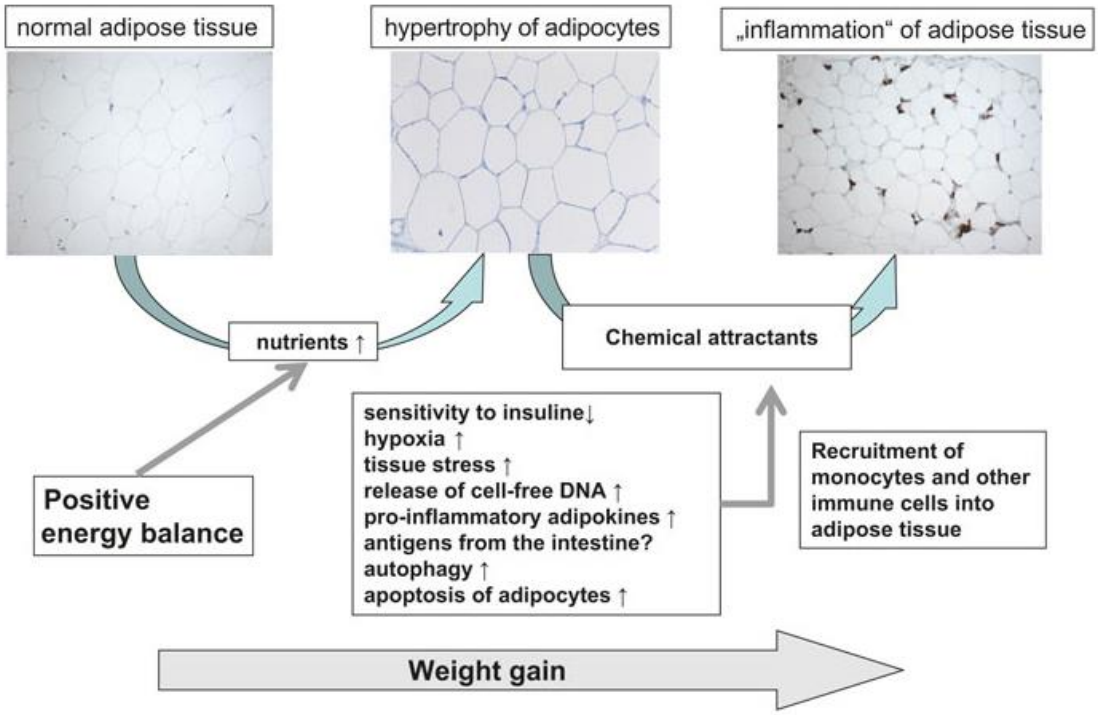

Figure 3 Mechanisms of adipose tissue dysfunction and inflammation (8) Copyright 2020, Georg Thieme Verlag KG

Capillaries in LAT are fragile and hyperpermeable, which explain the pale and cool skin, easy bruising, and telangiectasias commonly observed in lipedema (Figure 4) (10, 23). Protein molecules from the leaking capillaries may attract additional fluid into the intercellular space between fat cells, causing edema and increased hydrostatic pressure (1, 4, 24). As lipedema progresses, the surrounding lymphatic vessels become overloaded and start to stretch and dilate, forming microaneurysms (10). Concurrently, increasing fibrosis caused by chronic inflammation contribute to dysfunctional lymphatic drainage, and may lead to lipolymphedema (10, 23). However, it is discussed whether progressive obesity rather than lipedema cause additional lymphoedema (8).

Ninety percent of women with lipedema report daily pain in the affected areas (3). The pain can be explained by the consequences of hypoxia and inflammation associated with activation of surrounding nociceptors, tissue compression of nociceptors, and/or central sensitization (Figure 4) (22-26). In fact, several painful conditions have been associated with inflammation and hypersensitivity (25, 27). The excessive weight will also load the hips and knees, potentially resulting in joint pain and arthritis (1, 11). Consequently, a feedback loop occurs as joint problems may limit physical activity, and thereby induce weight gain and progression of lipedema (28).

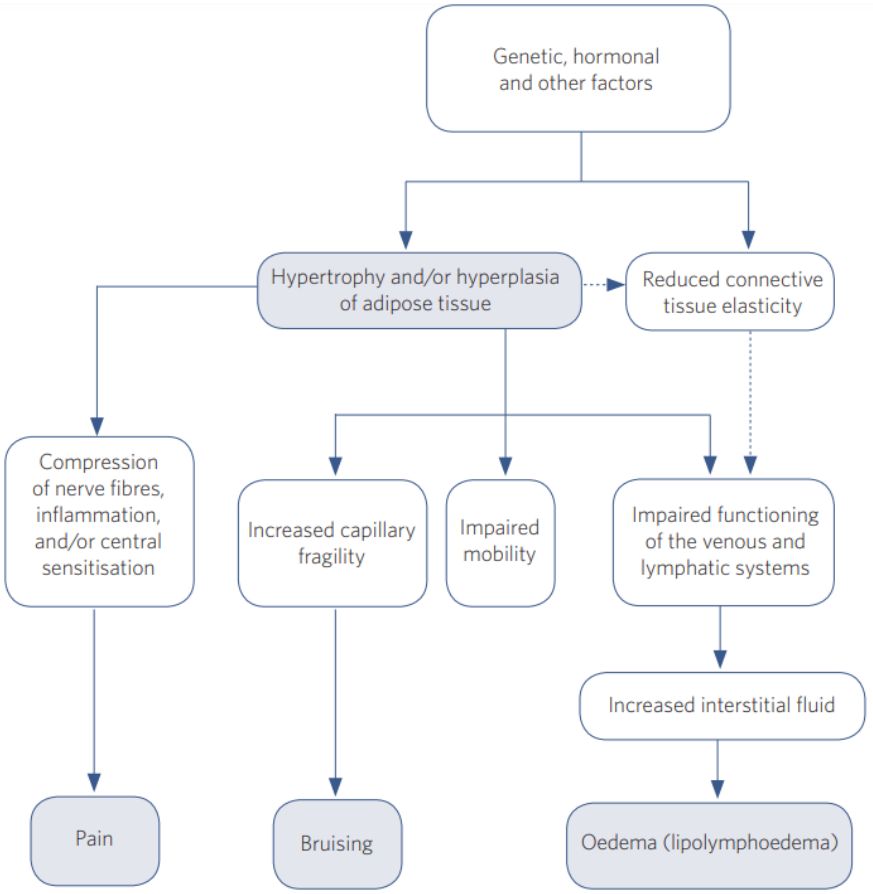

Figure 4 Possible pathophysiology of lipedema (23). Copyright 2017, OmniaMed Communications Ltd.

Chronic pain is one of the most common reasons for seeking medical care, immobility, use of opioids, long-term sick leave, depression, and reduced QoL (29, 30). Pain affects most domains of QoL, defined as a person's own perception of physical and mental health, social relationships, environment, and overall QoL (31-33). Results from the Lipedema UK survey (34) revealed that 87% of the respondents (n = 250) answered lipedema has a negative impact on their QoL. Additionally, 86% reported low self-esteem, 76% described lack of energy, 60% noted limitation of their social life, and 55% reported reduced mobility. Moreover, a feeling of hopelessness, depression, and eating disorders were also commonly reported (34). The results are consistent with those from a review from 2020 (35), including four observational studies using different tools to assess QoL in women with lipedema.

Chronic pain, decreased limb mobility, weight stigma, and unsuccessful therapy are proposed as factors that cause poor QoL in women with lipedema (34-36). On the other hand, mental stress seems to lower the pain threshold and lead to a significant reinforcement in pain

perception (8, 37). Depression and anxiety are also found to increase inflammatory markers that is unrelated to any underlying somatic disease (38). Consequently, a vicious cycle may occur with psychological symptoms intensifying the pain through inflammatory mediators, which in turn may increase mental stress (8, 36).

2.2 Ketogenic diet

Ketogenic diets, including very low-energy diets (< 800 kcal/day) and low-carbohydrate diets (ad libitum or energy restricted), induce the metabolic state ketosis when carbohydrate (CHO) and/or energy are sufficiently limited (39-41). The level of insulin decreases and the level of glucagon increases as a response to prevent low blood glucose concentrations (42). This results in increased glycolysis, gluconeogenesis, and lipolysis, while glycogenesis and lipogenesis decreases. After a few days, the glucose reserves become insufficient both for fat oxidation and for the supply of glucose to the central nervous system, and alternative energy sources are needed (42). Consequently, circulating fatty acids are transformed into the ketone bodies: acetoacetate (AcAc), β-hydroxybutyrate (BHB) and acetone, in the mitochondrial matrix of the liver (Figure 5) (42, 43).

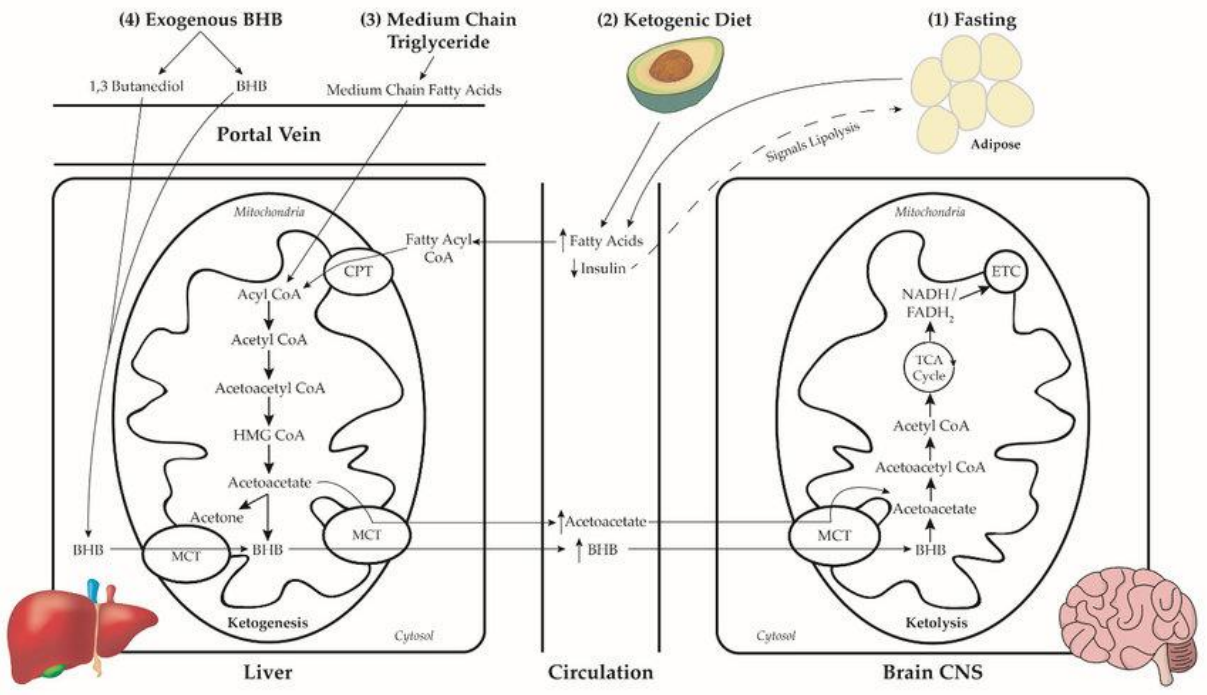

Figure 5 Mechanism of ketosis (43) Copyright 2019, Taylor MK, Swerdlow RH, Sullivan DK. The major mechanisms to induce ketosis. Licensed under CC BY 4.0

Ketone bodies can be used as oxidative fuel by many tissues, including the brain due to the ability to cross the blood-brain barrier (42, 43). The main ketone body is AcAc as it is easily metabolized and can be converted into BHB and acetone during high concentrations. However, the primary circulating ketone is BHB, and ketosis is often indicated by BHB levels ≥ 0.3 mmol/l in blood (42, 44).

2.2.1 Weight loss

Ketogenic diets have become a popular weight loss strategy in the recent years, and research provides strong evidence for their effectiveness (45, 46). The underlying biological mechanisms are still controversial, but hypotheses include: reduced appetite due to a higher satiety effect of proteins and fat, a direct and indirect appetite suppressant consequence of BHB, reduced lipogenesis and increased lipolysis induced by low CHO and insulin levels, improved fat oxidation in resting state, and enhanced energy expense of gluconeogenesis (42, 45-48). The rapid initial weight loss is however attributed to diuresis caused by depletion of glycogen storages in the liver and muscles, which contain large amounts of water (49).

2.2.2 Treatment for pain

Ketogenic diets have been used to treat epilepsy since the 1920's (50). In recent years, it has also been suggested that KD may be a potential nonpharmacological treatment of neurodegeneration, type 2 diabetes, cancer, metabolic disorders, and pain (26, 51, 52). Dietary interventions have been described as a promising treatment option for pain in the literature (53, 54), but the existence of clinical trials on KD is still limited.

A randomized controlled trial (RCT) in older adults with knee osteoarthritis pain (55), showed that the low-CHO diet group (ad libitum energy intake, < 20 g CHO/day) had significantly reduced functional pain, increased QoL, and lower oxidative stress biomarkers, compared to the low-fat diet group (1200 kcal, 60 E% CHO, and 20 E% protein, 20 E% fat) over a 12-week period. Likewise, a recent pilot RCT in patients with chronic musculoskeletal pain (56) proposed greater pain relief in the whole-food, KD group (ad libitum energy intake, 70 g CHO/day) compared to the whole-food, non-KD group over a period of 12 weeks, including a 3-week whole-food run-in diet. In addition, the KD group only, achieved significant improvement in pain interference, depression, anxiety, and inflammation (56). Moreover, animal studies have presented decreased sensitivity to pain and reduced neuropathy after KD

interventions (57-59). This suggests that a KD could relieve pain by targeting the pathways of oxidative stress, inflammation, and the nervous system.

Oxidative stress arises when the body's antioxidant defense systems no longer can cope with the amount of free radicals, like reactive oxygen species (ROS), leading to release of pro-inflammatory cytokines and chemokines, and eventually inflammation (27). Contrasted to the glucose metabolism, a ketone-based metabolism promotes lower levels of ROS (25). Moreover, a KD may induce anti-inflammatory effects attributed by the presence of BHBs and increased levels of specific polyunsaturated fatty acids (PUFA), which both decrease production of ROS and inflammatory components (60-64). Caloric restriction and weight loss may also be beneficial as excess energy result in increased adiposity which directly contributes to chronic inflammation through the release of pro-inflammatory cytokines (48, 62, 65).

2.2.3 Safety and side effects

Diet-induced ketosis is considered safe as the maximum levels of ketone bodies can only reach 7-8 mmol/l, leaving the blood pH unaffected (42, 66). Constipation, headache, bad breath, muscle cramps, fatigue, gastroesophageal reflux, hypoglycemia, hyperlipidemia, and diarrhea are common side effects of KD (67, 68). These side effects usually decrease after a few days to a few weeks on the diet, and can be alleviated with adequate consumption of fluid and electrolytes (66). More adverse side effects, such as hepatic steatosis, hypoproteinemia, kidney stones, and vitamin- and mineral deficiencies, may appear over time (69). Long-term studies on KD are mostly conducted on children with epilepsy, and very few studies have investigated the effects of KD in adults for more than one year (70).

2.3 Aim and hypotheses

The objective of this master's thesis was to investigate the impact of diets and weight loss on pain and QoL in women with lipedema.

- The main aim was to compare the effect of a low-energy KD and a low-energy non-KD on pain sensations over a period of eight weeks.
- Secondary aims were to assess changes in QoL before and after diet interventions and to compare differences in QoL between the groups.

A ketogenic diet is hypothesized to promote lipolysis in LAT by the ability to induce low levels of insulin and improve glycemic control (19). Reducing the amount of LAT may relieve pressure on surrounding capillaries and nerves, decrease the level of inflammation, and thus, alleviate pain (19). The dietary composition and metabolic influences of KD are also suggested to promote anti-inflammatory effects and relieve pain (16, 25, 60-64). Provided that a KD causes pain relief and weight loss, particularly in the affected areas, it is reasonable that the diet would improve physical and emotional functioning, as well as overall QoL in women with lipedema (36, 71, 72).

3 Method

3.1 Study design

This project is a part of the Norwegian Lipodiet Study, initiated by Nord-Trøndelag Hospital Trust and conducted in cooperation with the Center of Obesity Research (ObeCe) and the Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology (NTNU). The Lipodiet Study is a prospective, two-armed RCT, which investigates the impact of KD, independently of weight loss, on pain in women with lipedema. The eight-week intervention compares a low-energy KD to a low-energy non-KD (control group).

3.2 Study population

Inclusion criteria were women with lipedema and pain, aged 18-75 years with body mass index (BMI) 30-45 kg/m^2. The participants were recruited via announcement at obesity treatment facilities, social media, and posters in the region. Exclusion criteria were pregnancy or breast feeding, history of infectious diseases, medication known to affect obesity, bariatric surgery, and enrolment in any other obesity treatments. Further, they had to be weight stable over the last three months (± 2-3 kg), and not currently dieting to lose weight. Moreover, those with a history of psychological disorders, not mastering a Scandinavian language, having a malign disease, kidney disease, diabetes or any disease that leads to dietary advice that is inconsistent with the intervention were also excluded from the study.

3.3 Compliance

Diet, ketosis, weight loss, and side effects were evaluated at weekly follow-ups to enhance compliance and prevent dropouts (73). This also enabled necessary changes and adjustments in the diet within the limitations of calories and macronutrients during the intervention period.

Diet:

Dietary compliance were evaluated with daily food records (Appendix 2) and validated Pre-coded Food Diaries (PFD) (Department of Nutrition, Institute of Basic Medical Sciences, Oslo, Norway) (74) (Appendix 3). All participants were asked to fill out daily food records throughout the intervention period, which were analyzed for energy (kcal/day) and macronutrients (g/day, E%) using Kostholdsplanleggeren (Norwegian Food Safety Authority and Norwegian Directorate of Health, Oslo, Norway, 2021) (75) every consecutively week and discussed at the weekly follow-ups. The PFDs were completed with instructions and an illustrative booklet of

portion sizes (Department of Nutrition, Institute of Basic Medical Sciences, Oslo, Norway) (Appendix 4) for four days, including one weekend day, at baseline (BL), Week (Wk) 3, and Wk 8.

The Cardiff TeleForm version 10.5.1 software (Datascan Oslo, Norway) was used to scan the PFDs at the University of Oslo (Department of Nutrition, Institute of Basic Medical Sciences). The interpreted files were proofread, and open spaces were coded manually. The food database AE-18 and the diet calculation software system, Kostberegningssystem version 7.4 (Department of Nutrition, Institute of Basic Medical Sciences, University of Oslo), were used to calculate dietary intake. AE-18 is based on the Norwegian food composition table (Norwegian Food Safety Authority, www.matvaretabellen.no, 2020) (76), enlarged with values from additional databases and calculated recipes. Daily intake of energy (kcal/day) and macronutrients (g/day, E%) and changes over time were analyzed.

Ketosis:

Ketostix ® reagent test strips (Bayer Corp., Elkhart, IN, USA) were used in the weekly follow-ups to measure urinary ketone bodies (AcAc) (77). The participants received urine dipsticks along with a color chart (Appendix 5) and were asked to send pictures of the sticks at follow-ups performed via phone every other week. Cutoff level 0.5 mmol/l was used for negative ketostix. Moreover, whole blood finger-pricks were performed to measure BHB levels, Freestyle Precision Neo (Abbott, CA, USA) and Freestyle β-ketone reagent strips (Abbott, CA, USA) (78). The levels of BHB were evaluated every other week at ObeCe, and a level ≥ 0.3 mmol/l was considered ketotic.

Physical activity:

Physical activity (PA) may influence both the intervention and outcome variables. The participants were therefore instructed not to change their physical activity levels (PAL) throughout the intervention. To check for compliance, the participants were asked to wear a SenseWeare Armband (BodyMedia Inc., Pittsburgh, PA, USA) (79, 80) for a seven-day period at BL, Wk 3, and Wk 8. The participants received detailed instructions for using the activity monitor. More than 95% of the data over a 24-hour period for minimum four days, including at least one weekend day, needed to be available to be considered valid (81). Average metabolic

equivalents of task (METs, kcal/kg/hour), PA duration (min/day), PA intensity (sedentary, light, moderate, and vigorous), steps/day, and PAL value were analyzed.

3.4 Outcome variables

Figure 6 summaries the assessments during the study period. The participants were medically screened pre-BL and current treatments for lipedema were assessed. The study had two comprehensive test days during the intervention period (BL and Wk 9) at St. Olavs hospital, ObeCe. The participants were asked to have an overnight fast of twelve hours, not drink anything except water, avoid any vigorous PA for at least eight hours, and empty bladder before the testing (82). Furthermore, the study had weekly follow-ups, every other week was performed at ObeCe and the other weeks via phone calls.

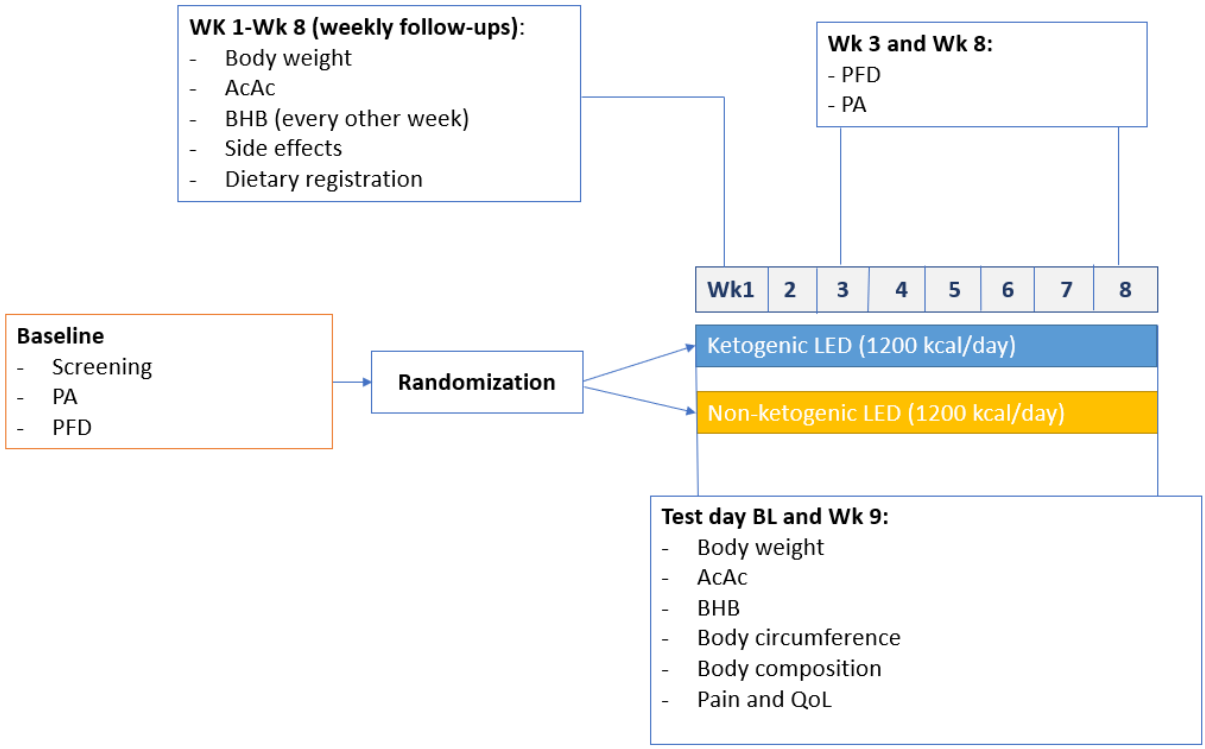

Figure 6 Overview of assessments in the study period. AcAc: acetoacetate, BHB: β-hydroxybutyrate, BIA: Bioelectrical Impedance Analysis, LED: Low Energy Diet, PA: Physical activity, PFD: Pre-coded food diaries, QoL: Quality of life, Wk: Week.

Anthropometry:

Anthropometric assessments were completed by standardized procedures (83). Height was measured to the nearest 0.1 cm with Seca 217 stadiometer (SECA, Hamburg, Germany) at BL. The participant had to stand straight with the head, shoulders, and buttocks against the stadiometer, without shoes, and look straight ahead. Weight was assessed to the nearest 0.1 kg with Seca 876 digital flat scale (SECA, Hamburg, Germany) at BL, Wk 9, and follow-ups at ObeCe. The measurements were performed standing and only wearing underwear.

Waist, hip, thigh, and leg circumferences were measured to the nearest 0.1 cm with a metric tape at BL and Wk 9. The participants were only wearing underwear during the assessments. The measurements were completed three times to calculate an average circumference. Moreover, the measuring point was marked on the participant and the length from the foot to the point was recorded while standing on a measuring board. Hip, thigh, and leg circumferences were measured at the widest part, while waist circumference was measured at the narrowest area looking from behind.

Body composition:

Fat mass (FM), fat free mass (FFM), skeletal muscle mass (SMM), total body water (TBW), intracellular body water (ICW), and extracellular body water (ECW), were assessed from Bioelectrical Impedance Analysis (BIA) (InBody 720 (BIA), Seoul, South Korea) (82, 84, 85) at BL and Wk 9. The measurements were performed standing barefoot with the soles, palms, and fingers in contact with the electrodes, and with a 15-degree angle formed between the arms and the body sides (86).

Pain:

The Norwegian version of Brief Pain Inventory (BPI) including a linear, 11-point Numeric Rating Scale (NRS) (87-89) was used for pain measurement. The medical questionnaire BPI assesses pain intensity (strongest pain, weakest pain, average pain, pain now), relief of pain treatment or medication, and pain interference on daily activity, mood, walking ability, work, social relations, sleep, and QoL (88). A pain severity score is calculated from the four items about pain intensity (90). Each item is rated from 0 = no pain, to 10 = worst imaginable pain, and contributes with the same weight to the final score. A pain interference score is computed based on the seven items on pain interference. These seven items are rated from 0 = no impact,

to 10 = completely affected, and contributes with the same weight to the final score. The item on pain treatment or medication do not contribute to the scoring (90). The questionnaire was self-reported by the participants at BL and Wk 9.

Quality of life:

The Norwegian version of RAND-36 survey (91-93) was utilized to assess health-related QoL at BL and Wk 9. The questionnaire was originally developed by RAND Corporation, USA, Medical Outcomes Study (94), and covers the following eight categories: physical functioning, role limitations due to physical health problems, role limitations due to personal or emotional problems, energy, mental health, social functioning, bodily pain, and general health perceptions (93). The participants were asked to pick the alternative best describing their perceived health for each item. Pre-coded values for each item were recoded before calculating an average score for each category, ranging from 0-100% of total possible score. A high score represented greater health-related QoL (95).

The Norwegian version of Impact of Weight on Quality of Life-Lite (IWQOL-Lite) questionnaire (96) was used to assess obesity-specific QoL at BL and Wk 9. The scheme is validated and consists of 31 questions that are divided into five categories: physical function, self-esteem, sexual life, public distress, and work (97). The participants were asked to select the alternative (numerated 1 to 5) best describing their experiences the past week; 1 = never, 2 = rarely, 3 = sometimes, 4 = usually, 5 = always. Each category gives an individual score, in addition to a total score from 0-100, with 100 reflecting the best QoL.

The Norwegian version of Lymphoedema Quality of Life (LYMQOL) questionnaire (98, 99) was utilized to measure QoL at BL and Wk 9. The validated questionnaire was originally developed for assessing QoL in women with limb lymphedema (98). Twenty-one questions are divided into the following four categories: symptoms, body image, function, and mood. The participants were asked to pick the most accurate alternative (numerated 0 to 4) for each question; 0 = Not applicable, 1 = not at all, 2 = a little, 3 = quite a bit, 4 = a lot. A total score for each category was calculated, with a high score representing low QoL. For the last question, the respondents were asked to grade their general QoL on a scale of 0 to 10 (0 = bad, 10 = excellent).

3.5 Dietary interventions

Block randomization was performed with BMI stratification (30-34.9, 35-39.9, and 40-44.9 kg/m^2). Participants were randomized into two groups and followed either a KD (keto) or a non-KD (control) for eight weeks. Both interventions were low-energy diets (1200 kcal/day). Table 1 presents the total energy content (kcal) and macronutrient composition in grams (g), kilocalories (kcal), and energy percent (E%) of the two diets.

Table 1 Composition of the diets in keto- and control-groups.

	Energy	**CHO (excl. fiber)**			**Protein**			**Fat**		
	Kcal	E%	Kcal	g	E%	Kcal	g	E%	Kcal	g
Low-energy KD	1200	25	300	75	20	240	60	55	660	73
Low-energy non-KD	1200	60	720	180	20	240	60	20	240	27
CHO: carbohydrate, E%: energy percent, Kcal: kilocalories, KD: ketogenic diet										

Standard dietary plans (Appendix 6 and 7) with conventional foods were conducted at BL with guidance from a master student in clinical nutrition for both groups. The dietary plans consisted of four main meals (250 kcal x 3, 400 kcal x 1) and one snack (50 kcal), with foods in line with the Nordic Nutrition Recommendations (NNR) 2012 (100). The dietary plans were adjusted with respect to food preferences, intolerances, and allergies. The participants were recommended to use a multivitamin and drink minimum two liters of fluid every day. Moreover, they were allowed free amounts of black coffee, tea, mineral water, and moderate amounts of foods/drinks with artificial sweeteners. The interventions were considered harmless for the short-term period, and participants received close follow-up of diet, ketosis, weight loss, and side effects from the master student.

3.6 Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics 28 (SPSS, Inc., Chicago, IL, USA) and statistical significance assumed below 5%. The data were analyzed for the presence of outliers and for normal distribution with histograms, QQ plots, and Shapiro-wilk test. Data is presented as mean ± standard deviation (SD) for consistency. To assess change Δ in the variables from BL to Wk 9 within groups, the paired samples t-test was used for normal

distributed data and the Wilcoxon rank test for skewed data. Multiple linear regression was utilized to compare Δ BL-Wk 9 between groups, with BL value and group (control = 0, keto = 1) as independent variables and Wk 9 value as dependent variable. Normal distribution of residuals was explored with histograms and residual plots to check if the model was suitable. Correlations were performed using Pearson correlation coefficient (r) or Spearman correlation coefficient (rho) when data was not normally distributed.

3.7 Power calculation

A power calculation for the Lipodiet Study was performed in collaboration with professor Turid Follestad from the Clinical Research Unit Central Norway. The pre-post study compares changes between two diet interventions. The primary outcome of the study is pain, and a difference in mean pain score of 2 units on a NRS ranging from 0-10 was considered clinically relevant. Based on the pilot study (16), SD was set to 3. Thus, 37 participants in each group are required to obtain 80% statistical power with a paired samples t-test. Given that a drop-out rate of 20% is commonly seen in this type of studies, 47 participants in each group would be necessary. Furthermore, adjusting for skewed data and requirement of non-parametric tests would demand 54 participants in each group. However, this master project applied to a smaller selection due to the limited study period.

3.8 Ethics

The Lipodiet Study was approved by the Regional Ethical Committee (REK 93888) and the Data Access Committee by Nord-Trøndelag Hospital Trust and registered in Clinicaltrials.gov (NCT04632810). Participation was voluntary, and the participants needed to sign a written informed consent form (Appendix 8) in line with the Helsinki declaration (101) before entering the study. Data and collected samples were handled without personal identification numbers, or other directly recognized information, by using a coding system specifically for this study. Only authorized study personnel were able to link participant data and collected samples. Data was saved in NTNU's file area for storing research data protected with two-factor authentication, and/or locked in an archive at St. Olavs Hospital. Information will be stored for five years after the study ends.

4 Results

4.1 Study population

Figure 7 shows a flow diagram of the study participants. 29 women met entry criteria and were included in the study with an average age of 47 ± 11.2 years and BMI 38.2 ± 5.5 kg/m^2. 13 participants were randomized to the keto group and 16 to the control group. Three participants in the control group were lost to follow-up, and one participant in each group were excluded from the analysis due to non-compliance. Finally, a total of 24 participants, 12 participants in each group, were included in the analysis. Baseline characteristics are presented in Table 2. Lipedema type and stage are shown in Table 3. The participants had lipedema type 1 (13.8%), type 2 (31.0%), and type 3 (55.2%). 44.8% also had an additional type 4 (arms). The disease severity was distributed as following: stage 1 (20.7%), stage 2 (62.1%), and stage 3 (17.2%).

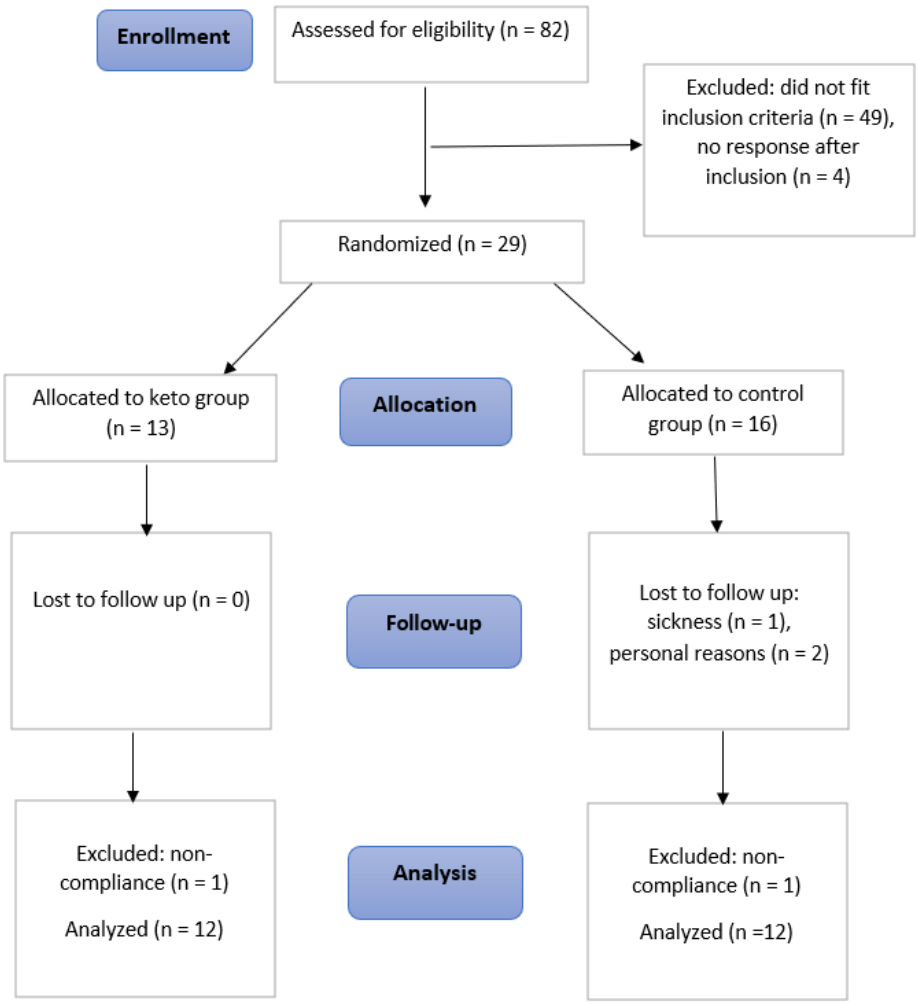

Figure 7 Flow diagram of study participants

Table 2 Baseline characteristics of all participants, keto- and control-groups

	All participants (n = 29)	Keto (n = 13)	Control (n = 16)
Age (years)	47.0 ± 11.2	49.1 ± 9.5	45.1 ± 12.4
Height (cm)	168.0 ± 5.3	167.9 ± 3.8	168.0 ± 6.4
BW (kg)	107.7 ± 16.1	105.7 ± 14.0	109.2 ± 17.8
BMI (kg/m^2)	38.2 ± 5.5	37.5 ± 4.6	38.7 ± 6.2
FM (kg)	54.1 ± 11.6	52.9 ± 10.2	55.2 ± 12.9
FM (%)	49.5 ± 4.2	49.3 ± 3.7	49.6 ± 4.6
FFM (kg)	54.0 ± 6.0	53.1 ± 4.6	54.7 ± 7.1
TBW (l)	40.2 ± 4.5	39.4 ± 3.5	40.9 ± 5.3
ICW (l)	24.6 ± 2.7	24.2 ± 2.1	25.0 ± 3.1
ECW (l)	15.6 ± 1.9	15.2 ± 1.4	15.9 ± 2.2

Data is presented as mean ± SD. BMI: body mass index, BW: body weight, ECW: extracellular water, FFM: fat free mass, FM: fat mass, ICW: intracellular water, l: liters, TBW: total body water.

Table 3 Lipedema type and stage of all participants, keto- and control-groups

	All participants (n = 29)	Keto (n = 13)	Control (n = 16)
Type	n (%)	n (%)	n (%)
1	4 (13.8%)	2 (15.4%)	2 (12.5%)
2	9 (31.0%)	4 (30.8%)	5 (31.3%)
3	16 (55.2%)	7 (53.9%)	9 (56.3%)
4	13 (44.8%)	7 (53.9%)	6 (37.5%)
5	0	0	0
Stage	n (%)	n (%)	n (%)
1	6 (20.7%)	3 (23.1%)	3 (18.8%)
2	18 (62.1%)	9 (69.2%)	9 (56.3%)
3	5 (17.2%)	1 (7.7%)	4 (25%)
4	0	0	0

4.2 Compliance

Ketosis

Table 4 shows compliance for ketosis in both groups during the intervention period, measured by the level of AcAc in urine and BHB in blood.

Table 4 Levels of acetoacetate and β-hydroxybutyrate in keto- and control- groups

	Keto					Control				
	BL	**Wk 3**	**Wk 5**	**Wk 7**	**Wk 9**	**BL**	**Wk 3**	**Wk 5**	**Wk 7**	**Wk 9**
BHB (mmol/l)	0.1 ± 0.1 (n = 13)	0.6 ± 0.4 (n = 7)	0.7 ± 0.5 (n = 11)	0.6 ± 0.3 (n = 4)	0.6 ± 0.3 (n = 12)	0.1 ± 0.1 (n = 16)	0.3 ± 0.3 (n = 8)	0.1 ± 0.1 (n = 11)	0.1 ± 0.1 (n = 3)	0.2 ± 0.1 (n = 12)
AcAc (mmol/l)	0.0 ± 0.1 (n = 12)	2.9 ± 3.1 (n = 12)	2.9 ± 3.2 (n = 12)	2.4 ± 2.4 (n = 12)	1.8 ± 2.9 (n = 12)	0.0 ± 0.0 (n = 16)	0.1 ± 0.2 (n = 14)	0.0 ± 0.0 (n = 12)	0.0 ± 0.0 (n = 10)	0.0 ± 0.0 (n = 12)

Data is presented as mean ± SD. AcAc: acetoacetate, BHB: β-hydroxybutyrate, BL: baseline, Wk: Week. Ketosis is considered BHB ≥ 3.0 mmol/l and AcAc ≥ 0.5 mmol/l.

Diet

The daily intake of energy, CHO, fiber, protein, and fat for each week during the intervention period is presented in Figure 8 and Table 5. The keto group had an average daily intake of 1178 ± 40 kcal, 43 ± 3 g CHO (15 E%), 25 ± 4 g fiber, 72 ± 6 g protein (24 E%), 75 ± 3 g fat (57 E%) throughout the intervention. The control group had an average daily intake of 1171 ± 70 kcal, 177 ± 12 g CHO (60 E%), 29 ± 6 g fiber, 52 ± 5 g protein (18 E%), 24 ± 4 g fat (18 E%).

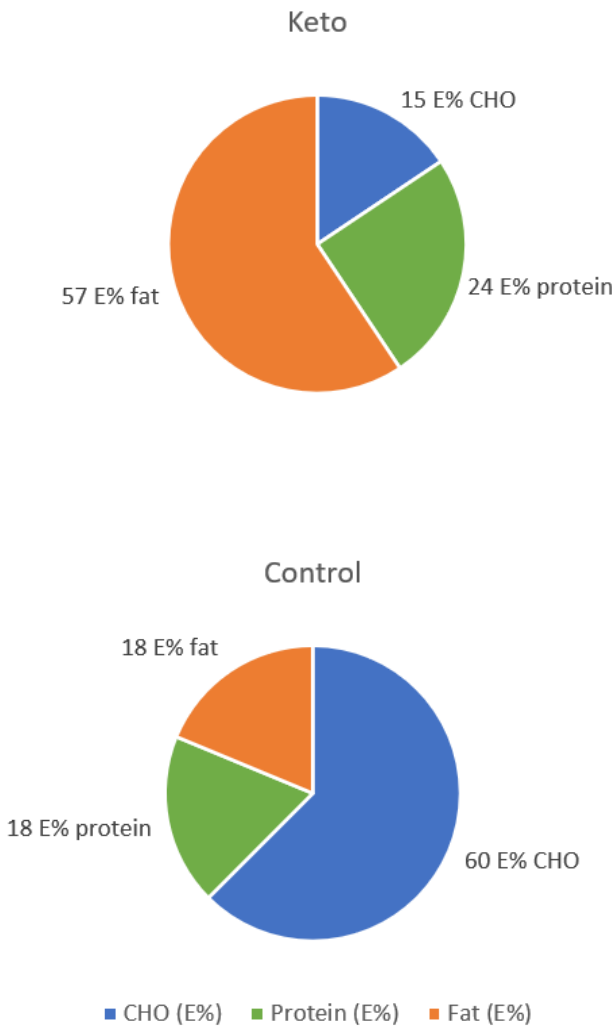

Figure 8 Dietary composition in keto- and control-groups

Table 5 Daily intake of energy and macronutrients in keto- and control-groups

	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Total
Energy (kcal)									
Keto	1220 ± 82	1167 ± 43	1199 ± 45	1174 ± 53	1145 ± 79	1177 ± 43	1195 ± 67	1175 ± 70	1178 ± 40
Control	1213 ± 95	1192 ± 51	1170 ± 115	1146 ± 182	1102 ± 208	1159 ± 187	1222 ± 62	1208 ± 33	1171 ± 70
CHO (g) (E%)									
Keto	46 ± 7 (15 E%)	44 ± 5 (15 E%)	47 ± 5 (16 E%)	44 ± 5 (15 E%)	40 ± 4 (14 E%)	42 ± 4 (14 E%)	42 ± 5 (14 E%)	41 ± 5 (14 E%)	43 ± 3 (15 E%)
Control	179 ± 10 (59 E%)	179 ± 9 (60 E%)	176 ± 19 (60 E%)	174 ± 28 (61 E%)	180 ± 34 (65 E%)	175 ± 27 (60 E%)	184 ± 12 (60 E%)	184 ± 8 (61 E%)	177 ± 12 (60 E%)
Fiber (g)									
Keto	28 ± 6	26 ± 6	26 ± 5	25 ± 6	22 ± 5	23 ± 4	23 ± 5	23 ± 6	25 ± 4
Control	29 ± 6	29 ± 6	29 ± 8	28 ± 8	27 ± 6	28 ± 6	29 ± 7	31 ± 5	29 ± 6

Protein (g) (E%)									
Keto	80 ± 10 (26 E%)	76 ± 7 (26 E%)	76 ± 8 (25 E%)	70 ± 7 (24 E%)	69 ± 10 (24 E%)	69 ± 8 (23 E%)	69 ± 9 (23 E%)	72 ± 9 (25 E%)	72 ± 6 (24 E%)
Control	53 ± 8 (17 E%)	51 ± 6 (17 E%)	52 ± 6 (18 E%)	49 ± 7 (17 E%)	50 ± 7 (18 E%)	49 ± 10 (17 E%)	53 ± 8 (17 E%)	52 ± 5 (17 E%)	52 ± 5 (18 E%)
Fat (g) (E%)									
Keto	73 ± 7 (54 E%)	69 ± 7 (53 E%)	74 ± 6 (56 E%)	76 ± 6 (58 E%)	75 ± 6 (59 E%)	78 ± 4 (60 E%)	79 ± 5 (59 E%)	77 ± 5 (59 E%)	75 ± 3 (57 E%)
Control	27 ± 7 (20 E%)	25 ± 3 (19 E%)	24 ± 5 (18 E%)	23 ± 8 (18 E%)	22 ± 6 (18 E%)	24 ± 7 (19 E%)	25 ± 5 (17 E%)	24 ± 5 (18 E%)	24 ± 4 (18 E%)

Data is presented as mean ± SD. Keto: n = 16, control: n = 13. BL: baseline, CHO: carbohydrate, E%: energy percent, Kcal: kilocalories, Wk: week.

Table 6 presents daily intake of energy, CHO, fiber, protein, fat, saturated fatty acids (SFA), monounsaturated fatty acids (MUFA), polyunsaturated fatty acids (PUFA), and omega-6/omega-3 ratio at BL, Wk 3, and Wk 8. In both groups, there was a significant decrease in energy intake (kcal/day) from BL (keto: 2079 ± 445, control: 2365 ± 836) to Wk 3 (keto: 1119 ± 381, $p = 0.011$, control: 1107 ± 260, $p = 0.013$) and Wk 8 (keto: 1410 ± 563, $p = 0.047$, control: 1297 ± 239, $p = 0.007$). In the keto group only, intake of CHO decreased significantly from BL to Wk 3 and Wk 8. In both groups, protein intake decreased significantly from BL to Wk 8. In the control group only, there was a significant decrease in intake of fat, SFA, MUFA, and PUFA, from BL to Wk 3 and Wk 8. Omega-6/omega-3 ratio remained unchanged in both groups from BL to Wk 8.

Table 6 Daily intake of energy and macronutrients and changes over time in keto- and control-groups

	BL	Wk 3	Wk 8	Δ BL-Wk 3	P-value	Δ BL-Wk 8	P-value	Δ Wk 3-Wk 8	P-value
Energy (kcal)									
Keto	2079 ± 445	1119 ± 381	1410 ± 563	-897 ± 631	0.011*[S]	-646 ± 806	0.047*[S]	154 ± 249	0.386[S]
Control	2365 ± 836	1107 ± 260	1297 ± 239	-1124 ± 631	0.013*[S]	-1259 ± 672	0.007**[S]	229 ± 642	0.288
CHO (g) (E%)									
Keto	200 ± 40 (38 E%)	91 ± 38 (33 E%)	107 ± 91 (30 E%)	-96 ± 55	0.008**[S]	-87 ± 94	0.017*[S]	16 ± 104	0.959[S]
Control	211 ± 82 (36 E%)	151 ± 46 (55 E%)	170 ± 42 (53 E%)	-53 ± 109	0.139[S]	-59 ± 82	0.074[S]	10 ± 45	0.515[S]
Fiber (g)									
Keto	21 ± 5	17 ± 4	19 ± 6	-2 ± 6	0.287	-2 ± 7	0.497	1 ± 4	0.610
Control	18 ± 9	19 ± 4	23 ± 6	2 ± 9	0.591	3 ± 8	0.227	5 ± 7	0.079

Protein (g) **(E%)**									
Keto	83 ± 19 (16 E%)	65 ± 20 (23 E%)	62 ± 16 (18 E%)	-14 ± 27	0.139[S]	-21 ± 26	0.037*[S]	-2 ± 31	0.878[S]
Control	89 ± 35 (16 E%)	46 ± 8 (17 E%)	54 ± 11 (17 E%)	-37 ± 38	0.012*	-41 ± 29	0.007**[S]	8 ± 12	0.173[S]
Fat (g) **(E%)**									
Keto	93 ± 28 (40 E%)	51 ± 22 (41 E%)	78 ± 45 (50 E%)	-42 ± 37	0.021*[S]	-16 ± 62	0.443	19 ± 39	0.139[S]
Control	118 ± 45 (45 E%)	30 ± 9 (24 E%)	39 ± 5 (27 E%)	-79 ± 45	< 0.001**	-88 ± 37	< 0.001**	8 ± 5	0.002**
SFA (g) **(E%)**									
Keto	39 ± 13 (17 E%)	18 ± 8 (14 E%)	28 ± 14 (18 E%)	-20 ± 19	0.012*	-12 ± 24	0.139[S]	9 ± 11	0.047*[S]
Control	50 ± 20 (19 E%)	14 ± 4 (11 E%)	18 ± 3 (12 E%)	-35 ± 23	0.001**	-36 ± 18	0.005*[S]	4 ± 3	0.008**[S]

MUFA (g) (E%)									
Keto	32 ± 9 (14 E%)	18 ± 7 (14 E%)	30 ± 23 (19 E%)	-15 ± 13	0.007**	-2 ± 27	0.819	7 ± 19	0.231
Control	41 ± 17 (16 E%)	9 ± 3 (7 E%)	12 ± 2 (8 E%)	-29 ± 15	<0.001**	-33 ± 14	<0.001**	3 ± 3	0.012*
PUFA (g) (E%)									
Keto	15 ± 6 (6 E%)	11 ± 5 (9 E%)	13 ± 13 (8 E%)	-4 ± 6	0.078	-1 ± 15	0.333^{S}	1 ± 12	0.508^{S}
Control	16 ± 9 (6 E%)	3 ± 2 (2 E%)	4 ± 1 (3 E%)	-10 ± 6	<0.001**	-13 ± 8	<0.001**	1 ± 2	0.581
Omega-6/omega-3 ratio									
Keto	5 ± 2	3 ± 2	5 ± 1	-2 ± 1	0.002*	0 ± 3	0.928	1 ± 3	0.168
Control	5 ± 3	4 ± 1	4 ± 2	-2 ± 3	0.156	0 ± 2	0.760	1 ± 2	0.244

Data is presented as mean ± SD. Δ BL-Wk 9 in each group were analyzed by the paired samples t-test for normal distributed data and the Wilcoxon test (^{S}) for skewed data. Statistical significance was attributed as * $p < 0.05$, ** $p < 0.01$. Keto: n = 10 (BL), n = 11 (Wk 3), n = 11 (Wk 8), Control: n = 11 (BL), n = 11 (Wk 3), n = 10 (Wk 8). BL: baseline, CHO: carbohydrate, E%: energy percent, Kcal: kilocalories, MUFA: monounsaturated fatty acids, PUFA: polyunsaturated fatty acids, SFA: saturated fatty acids, Wk: week.

Physical activity

Physical activity levels over time can be seen in Appendix 9. No significant difference in MET, steps/day, PA duration or PA intensity were found in neither the keto group nor the control group. However, the keto group had a significant decrease in PAL from BL to Wk 3 ($p = 0.046$) and Wk 8 ($p = 0.026$).

4.3 Pain

Pain intensity and pain interference scores at BL and Wk 9 are presented in Figure 9 and Table 7. In the keto group only, there was significant reduction in the score of strongest pain (5.5 ± 1.9 vs. 3.4 ± 2.6, $p = 0.020$), average pain (5.2 ± 1.2 vs. 3.4 ± 2.3, $p = 0.016$), pain now (4.1 ± 1.9 vs. 2.1 ± 1.7, $p = 0.011$), total pain severity (4.3 ± 1.5 vs. 2.5 ± 1.7, $p = 0.008$), and pain interference on mood (3.8 ± 2.8 vs. 2.2 ± 2.2, $p = 0.041$) from BL to Wk 9. There was also a trend of improved score of pain interference on QoL in the keto group (3.7 ± 2.7 vs. 2.3 ± 2.7, $p = 0.076$). Moreover, the reduction in pain now and pain severity score were significantly greater in the keto group compared to the control group ($p = 0.004$, $p = 0.010$, respectively).

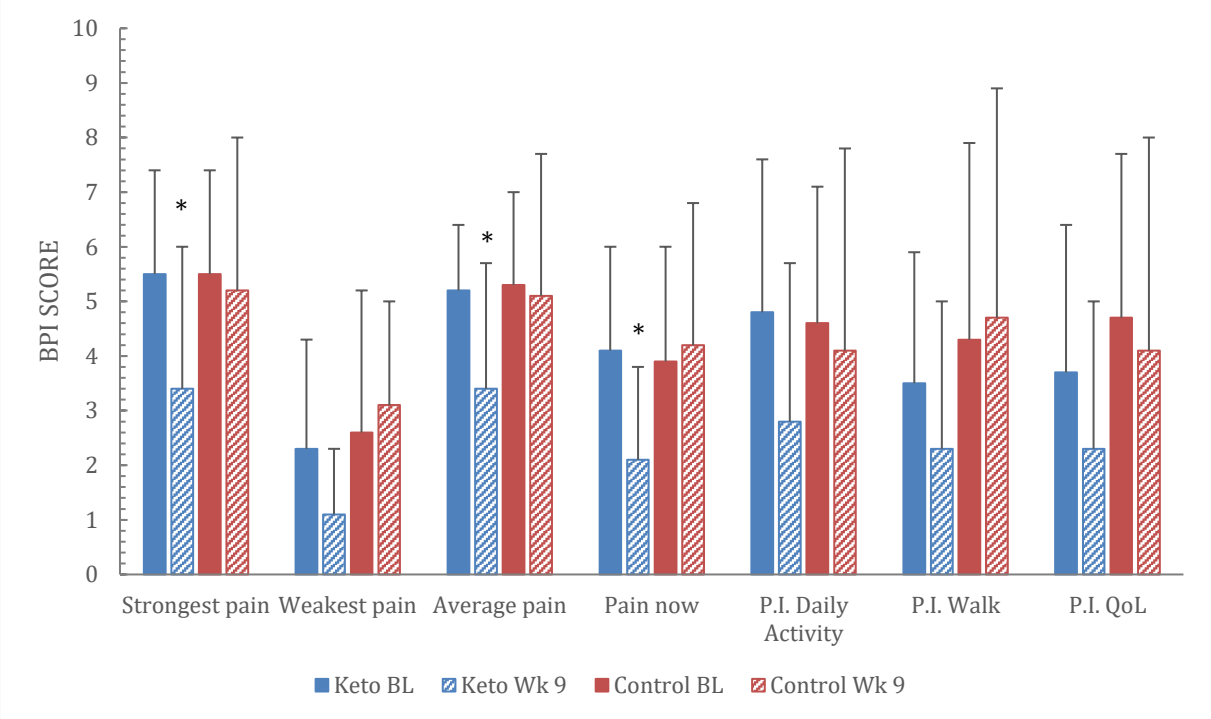

*Figure 9 Pain scores at baseline and week 9 in keto- and control-groups. Data is presented as mean ± SD. Statistical significance was attributed as * $p < 0.05$. BL: baseline, BPI: Brief Pain Inventory, P.I.: Pain Interference, QoL: quality of life, Wk: week.*

Table 7 Pain scores and changes over time in keto- and control-groups

	Keto			**Control**			**Δ BL - Wk 9**		
	BL (n = 13)	Wk 9 (n = 12)	P-value	BL (n = 16)	Wk 9 (n = 12)	P-value	Keto (n = 12)	Control (n = 12)	P-value
Pain intensity									
Strongest pain	5.5 ± 1.9	3.4 ± 2.6	0.020*[S]	5.5 ± 1.9	5.2 ± 2.8	0.504	-2.0 ± 2.7	-0.3 ± 1.7	0.083
Weakest pain	2.3 ± 2.0	1.1 ± 1.2	0.084[S]	2.6 ± 1.9	3.1 ± 1.9	0.474	-0.8 ± 1.6	0.3 ± 1.6	0.012*
Average pain	5.2 ± 1.2	3.4 ± 2.3	0.016*[S]	5.3 ± 1.7	5.1 ± 2.6	0.293	-1.8 ± 2.1	-0.5 ± 1.6	0.140
Pain now	4.1 ± 1.9	2.1 ± 1.7	0.011*	3.9 ± 2.1	4.2 ± 2.6	0.239	-1.8 ± 2.1	0.6 ± 1.6	0.004**
Pain severity score	4.3 ± 1.5	2.5 ± 1.7	0.008**	4.3 ± 1.6	4.4 ± 2.2	0.943	-1.6 ± 1.7	0.0 ± 1.0	0.010*
Relief pain medication (%)	43.1 ± 35.4	41.0 ± 32.1	0.566[S]	32.0 ± 34.9	7.3 ± 15.6	0.034*[S]	-2.2 ± 46.2	-23.6 ± 34.4	0.013*

Pain interference

Daily activity	4.8 ± 2.8	2.8 ± 2.9	0.141[S]	4.6 ± 2.5	4.1 ± 3.7	0.212[S]	-2.0 ± 4.4	-0.8 ± 2.3	0.352
Mood	3.8 ± 2.8	2.2 ± 2.2	0.041*[S]	4.2 ± 2.6	3.6 ± 3.4	0.504[S]	-1.3 ± 2.6	-0.6 ± 3.0	0.253
Walk	3.5 ± 2.4	2.3 ± 2.7	0.395[S]	4.3 ± 3.6	4.7 ± 4.2	0.473[S]	-1.1 ± 3.3	0.2 ± 3.4	0.259
Work	3.0 ± 2.2	2.3 ± 2.6	0.675[S]	5.2 ± 2.4	4.3 ± 3.7	0.473[S]	-0.6 ± 2.8	-0.7 ± 2.3	0.855
Relations	2.9 ± 2.2	1.8 ± 2.0	0.238[S]	4.4 ± 2.5	3.2 ± 4.1	0.283[S]	-1.2 ± 3.2	-1.3 ± 4.2	0.431
Sleep	4.4 ± 2.7	2.8 ± 2.8	0.151[S]	5.5 ± 3.1	4.7 ± 4.0	0.210[S]	-1.3 ± 3.3	-1.0 ± 2.6	0.492
QoL	3.7 ± 2.7	2.3 ± 2.7	0.076[S]	4.9 ± 3.0	4.0 ± 3.9	0.203[S]	-1.5 ± 2.4	-1.0 ± 2.5	0.439
Pain interference score	3.7 ± 1.7	2.3 ± 2.3	0.126[S]	4.7 ± 2.1	4.1 ± 3.7	0.307[S]	-1.3 ± 2.6	-0.8 ± 2.1	0.596

Data is presented as mean ± SD. Δ BL-Wk 9 in each group were analyzed by the paired samples t-test for normal distributed data and the Wilcoxon test ([S]) for skewed data. Multiple linear regression was used to compare Δ BL-Wk 9 between groups. Statistical significance was attributed as * $p < 0.05$, ** $p < 0.01$. BL: baseline, BPI: Brief Pain Inventory, QoL: quality of life, Wk: week

4.4 Quality of life

The quality-of-life scores at BL and Wk 9 from questioners are presented in Figure 10-11 and Table 8. A high score represents great QoL in RAND-36, IWQOL-Lite, and general QoL in LYMQOL, while a high score represents low QoL in the remaining subcategories in LYMQOL. In the keto group, there was a significant improvement in the score of role limitations due to physical problems (56.3 ± 37.1 vs. 80.8 ± 26.1, p = 0.017) from RAND-36, physical functioning (67.6 ± 16.3 vs. 74.3 ± 16.7, p = 0.001) and self-esteem (49.2 ± 23.0 vs. 60.4 ± 24.0, p = 0.026) from IWQOL-lite. The control group had a significant increase in physical functioning score (50.7 ± 20.7 vs. 59.7 ± 24.26, p = 0.045) from IWQOL-Lite and a significant decrease in function score (2.4 ± 0.7 vs. 2.7 ± 0.5, p = 0.026) from LYMQOL, as a high score represents low function. The scores of total QoL from IWQOL-Lite and energy from RAND-36 were significantly improved in both the keto group (67.9 ± 15.3 vs. 75.7 ± 15.6, p = 0.002, and 42.5 ± 28.4 vs. 64.2 ± 26.6, p = 0.024, respectively) and the control group (55.0 ± 18.4 vs. 62.1 ± 20.4, p = 0.046, and 39.1 ± 23.0 vs. 48.8 ± 24.5, p = 0.005, respectively). However, no significant difference between groups in any of the QoL variables from BL to Wk 9 was found.

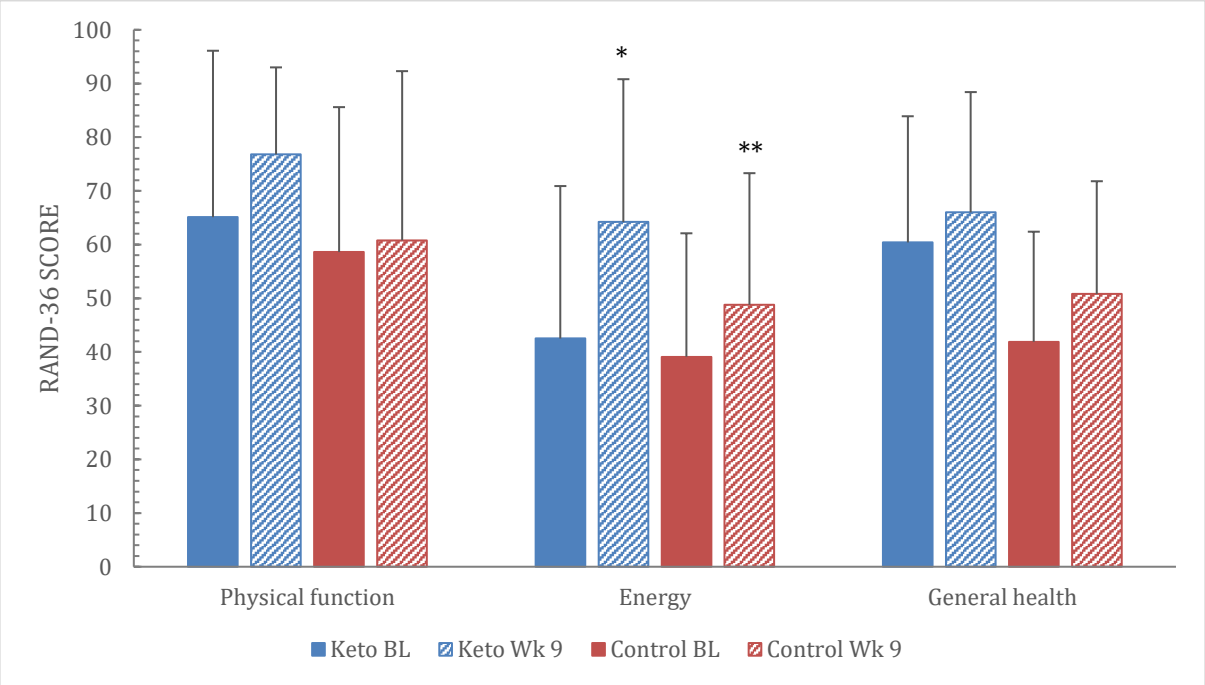

*Figure 10 Quality of life scores at baseline and week 9 in keto- and control-groups. Data is presented as mean ± SD. Statistical significance was attributed as * p < 0.05 and ** p < 0.01. BL: baseline, Wk: week.*

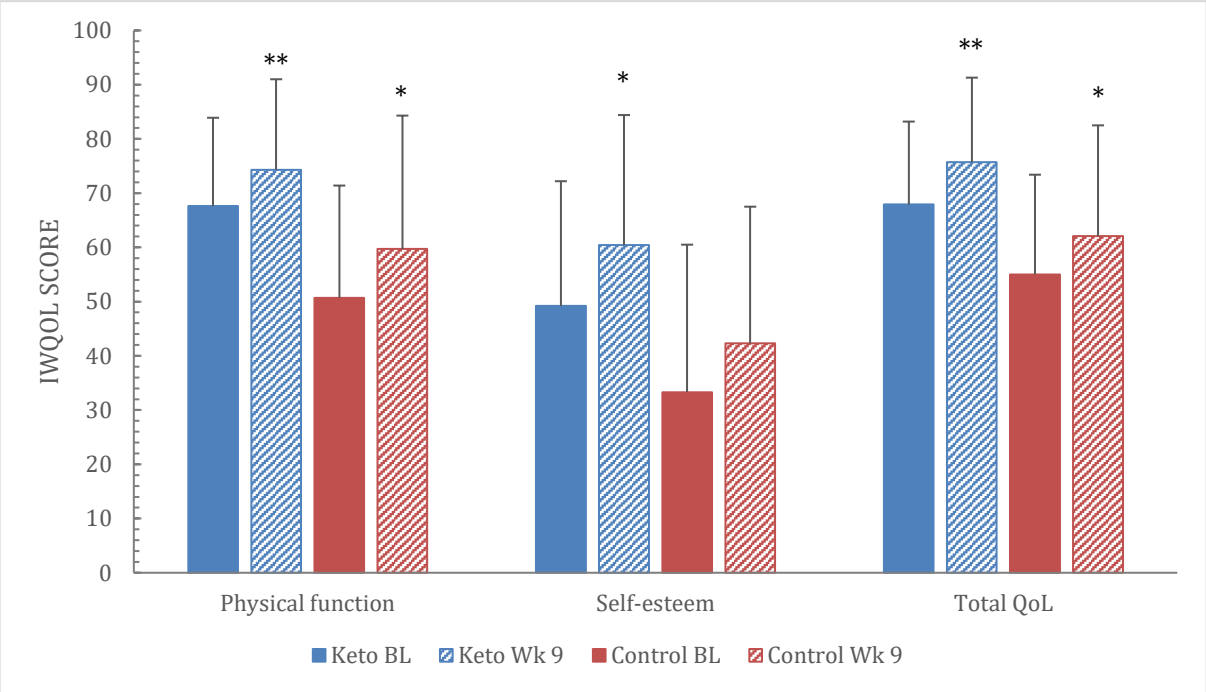

*Figure 11 Quality of life scores at baseline and week 9 in keto- and control-groups. Data is presented as mean ± SD. Statistical significance was attributed as * $p < 0.05$ and ** $p < 0.01$. BL: baseline, IWQOL: Impact of Weight on Quality of Life-Lite, QoL: quality of life, Wk: week*

Table 8 Quality of Life scores and changes over time in keto- and control-groups

	Keto			Control			Δ BL - Wk 9		
	BL (n = 13)	Wk 9 (n = 12)	P-value	BL (n = 16)	Wk 9 (n = 12)	P-value	Keto (n = 12)	Control (n = 12)	P-value
RAND-36									
Physical functioning	65.1 ± 31.0	76.8 ± 16.2	0.117[S]	58.6 ± 27.0	60.8 ± 31.5	0.649	15.4 ± 30.3	2.7 ± 19.3	0.109
Role limitations, physical	56.3 ± 37.1	80.8 ± 26.1	0.017*[S]	40.6 ± 40.7	52.1 ± 44.5	0.608[S]	26.8 ± 25.7	6.3 ± 45.4	0.063
Role limitations, emotional	77.8 ± 41.0	86.1 ± 26.4	0.273[S]	58.3 ± 39.4	66.7 ± 42.6	0.344[S]	9.1 ± 33.6	2.8 ± 26.4	0.347
Energy	42.5 ± 28.4	64.2 ± 26.6	0.024*	39.1 ± 23.0	48.8 ± 24.5	0.005**	16.4 ± 20.5	8.8 ± 8.6	0.192
Mental	66.3 ± 26.2	77.3 ± 18.3	0.191[S]	69.3 ± 20.3	71.7 ± 19.6	0.503[S]	10.2 ± 26.5	2.7 ± 12.1	0.352
Social	78.1 ± 18.6	81.0 ± 15.4	0.436[S]	54.7 ± 30.6	62.5 ± 29.7	0.389	3.1 ± 22.5	8.3 ± 25.2	0.474
Pain	49.2 ± 19.7	66.0 ± 23.0	0.124	36.7 ± 21.0	42.7 ± 25.7	0.341	14.3 ± 28.3	5.8 ± 20.3	0.144
General health	60.4 ± 23.5	66.0 ± 22.4	0.161	41.9 ± 20.5	50.8 ± 21.0	0.152[S]	5.7 ± 12.5	5.8 ± 12.6	0.620

IWQOL-Lite									
Physical function	67.6 ± 16.3	74.3 ± 16.7	0.001**	50.7 ± 20.7	59.7 ± 24.6	0.045*[S]	7.2 ± 5.7	11.6 ± 18.5	0.860
Self esteem	49.2 ± 23.0	60.4 ± 24.0	0.026*	33.3 ± 27.2	42.3 ± 25.2	0.181	9.8 ± 13.3	6.5 ± 15.9	0.318
Sexual life	76.4 ± 20.0	82.3 ± 19.7	0.031*[S]	65.2 ± 33.7	71.4 ± 28.5	0.574[S]	6.3 ± 9.6	3.7 ± 19.9	0.364
Public distress	73.9 ± 19.3	82.5 ± 17.9	0.100[S]	73.8 ± 22.0	74.6 ± 22.8	0.932[S]	7.5 ± 18.5	0.0 ± 10.4	0.200
Work	86.1 ± 19.5	91.1 ± 12.9	0.059[S]	71.5 ± 33.5	78.7 ± 23.0	0.407[S]	5.7 ± 8.6	5.7 ± 23.0	0.182
Total QoL	67.9 ± 15.3	75.7 ± 15.6	0.002**	55.0 ± 18.4	62.1 ± 20.4	0.046*[S]	11.6 ± 6.3	6.8 ± 10.4	0.513
LYMQOL									
Function	2.0 ± 0.6	2.1 ± 0.8	0.286[S]	2.4 ± 0.7	2.7 ± 0.5	0.026*[S]	0.2 ± 0.5	0.4 ± 0.5	0.075
Body image	2.7 ± 0.7	2.2 ± 0.9	0.333[S]	3.0 ± 0.5	3.0 ± 0.7	0.790[S]	-0.3 ± 0.8	0.1 ± 0.8	0.095
Symptoms	2.8 ± 0.3	2.3 ± 0.9	0.281[S]	3.1 ± 0.5	3.0 ± 0.6	0.798[S]	-0.3 ± 0.8	-0.1 ± 0.6	0.115
Mood	1.8 ± 0.9	1.7 ± 0.9	0.857	2.0 ± 0.7	2.0 ± 0.6	0.929[S]	-0.0 ± 0.5	0.0 ± 0.6	0.723
General QoL	5.0 ± 1.6	6.0 ± 2.1	0.558[S]	5.1 ± 1.9	5.0 ± 2.6	0.147[S]	0.8 ± 1.9	0.0 ± 1.5	0.139

Data is presented as mean ± SD. Δ BL-Wk 9 in each group were analyzed by the paired samples t-test for normal distributed data and the Wilcoxon test ([S]) for skewed data. Multiple linear regression was used to compare Δ BL-Wk 9 between groups. Statistical significance was attributed as * $p < 0.05$, ** $p < 0.01$. BL: baseline, IWQOL-Lite: Impact of Weight on Quality of Life-Lite, LYMQOL: Lymphoedema Quality of Life, Wk: week. A high score (RAND-36, IWQOL-Lite, *General QoL* in LYMQOL) represents great QoL. A high score (LYMQOL, ex. *General QoL*) represents low QoL.

4.5 Body weight and body composition

Table 9 shows body weight and body circumferences at BL and Wk 9. In both groups, there was a significant decrease in body weight (kg and %), BMI, and circumferences of the hip, waist, and thigh from BL to Wk 9. In the keto group, leg circumference decreased significantly, while a trend of reduced leg circumference was found in the control group. Waist/hip ratio remained unaffected in both groups. The keto group had significantly larger weight loss compared to the control group, both in kg (-9.9 ± 1.6 vs. -7.6 ± 3.2, $p = 0.030$) and % (-9.5 ± 1.4 vs. -7.1 ± 2.9, $p = 0.017$), as well as BMI (-3.5 ± 0.6 vs. -2.1 ± 1.2, $p = 0.041$).

Table 10 presents body composition variables of the participants at BL and Wk 9. One participant in the control group was excluded from this analysis due to measurement errors. In both the keto- and control-group, there was a significant reduction in FM kg (-7.3 ± 1.4, $p < 0.001$ vs. -4.9 ± 4.5, $p = 0.005$, respectively) and FM% (-2.7 ± 1.2, $p = 0.002$ vs. -1.7 ± 2.1, $p = 0.026$, respectively) from BL to Wk 9. Skeletal muscle mass and body water (TBW, ICW, and ECW) also decreased significantly in both groups. Fat free mass was significantly reduced in the keto group only. However, no significant difference between groups in any of the variables from BL to Wk 9 was found.

Table 9 Body weight and body circumferences and changes over time in keto- and control-groups

	Keto			Control			Δ BL-Wk 9		
	BL (n = 13)	Wk 9 (n = 12)	P-value	BL (n = 16)	Wk 9 (n = 12)	P-value	Keto (n = 12)	Control (n = 12)	P-value
Body weight (kg)	105.7 ± 14.0	95.6 ± 13.8	< 0.001**	109.2 ± 17.8	102.0 ± 20.0	< 0.001**	-9.9 ± 1.6	-7.6 ± 3.2	0.030*
Weight loss (%)							-9.5 ± 1.4	-7.1 ± 2.9	0.017*
BMI (kg/m^2)	37.5 ± 4.6	33.9 ± 4.6	0.002**	37.7 ± 7.8	36.9 ± 6.7	0.002**	-3.5 ± 0.6	-2.1 ± 1.2	0.041*
Hip (cm)	128.7 ± 7.3	119.2 ± 8.5	< 0.001**	128.8 ± 15.4	124.9 ± 15.3	0.002**^{S}	-9.2 ± 4.7	-5.9 ± 1.7	0.080
Waist (cm)	102.0 ± 13.5	95.5 ± 10.3	0.034*^{S}	105.0 ± 14.5	104.2 ± 16.7	0.023*^{S}	-5.8 ± 9.3	-3.6 ± 4.8	0.084
Waist/hip ratio	0.8 ± 0.1	0.8 ± 0.1	0.814	0.8 ± 0.1	0.8 ± 0.1	0.510	0.0 ± 0.0	0.0 ± 0.0	0.802
Thigh (cm)	69.4 ± 9.6	64.0 ± 8.6	0.004**	67.7 ± 8.7	64.0 ± 6.9	0.003**	-5.9 ± 5.6	-3.1 ± 2.9	0.218
Leg (cm)	47.5 ± 5.2	45.1 ± 5.4	< 0.001**	48.9 ± 4.3	47.9 ± 4.3	0.067	-2.7 ± 1.2	-1.1 ± 1.9	0.012*

Data is presented as mean ± SD. Δ BL-Wk 9 in each group were analyzed by the paired samples t-test for normal distributed data and the Wilcoxon test (^{S}) for skewed data. Multiple linear regression was used to compare Δ BL-Wk 9 between groups. Statistical significance was attributed as * $p < 0.05$, ** $p < 0.01$. BL: baseline, BMI: body mass index, Wk: week

Table 10 Body composition and changes over time in keto- and control-groups

	Keto			Control			Δ BL-Wk 9		
	BL (n = 13)	Wk 9 (n = 12)	P-value	BL (n = 15)	Wk 9 (n = 11)	P-value	Keto (n = 12)	Control (n = 11)	P-value
FM (kg)	52.8 ± 10.2	45.3 ± 10.4	< 0.001**	55.1 ± 12.9	51.6 ± 13.7	0.005**	-7.3 ± 1.4	-4.9 ± 4.5	0.077
FM (%)	49.3 ± 3.7	46.3 ± 4.6	0.002**^{S}	49.6 ± 4.6	48.9 ± 4.4	0.026*	-2.7 ± 1.2	-1.7 ± 2.1	0.208
FFM (kg)	53.1 ± 4.6	51.3 ± 4.5	0.012*	54.7 ± 7.1	52.9 ± 7.5	0.344^{S}	-1.8 ± 2.1	-0.9 ± 3.1	0.367
SMM (kg)	29.5 ± 2.8	28.1 ± 2.7	0.002**^{S}	30.6 ± 4.1	29.2 ± 4.3	0.012*	-1.4 ± 0.5	-1.0 ± 1.1	0.149
TBW (l)	39.4 ± 3.5	37.7 ± 3.4	0.002**^{S}	40.9 ± 5.3	38.9 ± 5.5	0.006**	-1.8 ± 0.6	-1.5 ± 1.5	0.427
ICW (l)	24.2 ± 2.1	23.1 ± 2.0	0.002**^{S}	25.0 ± 3.1	23.9 ± 3.3	0.013*	-1.1 ± 0.4	-0.8 ± 0.9	0.175
ECW (l)	15.2 ± 1.4	14.6 ± 1.4	0.002**^{S}	15.9 ± 2.2	15.0 ± 2.2	0.003**	-0.7 ± 0.3	-0.8 ± 0.6	0.880

Data is presented as mean ± SD. Δ BL-Wk 9 in each group were analyzed by the paired samples t-test for normal distributed data and the Wilcoxon test (^{S}) for skewed data. Multiple linear regression was used to compare Δ BL-Wk 9 between groups. Statistical significance was attributed as * $p < 0.05$, ** $p < 0.01$. BL: baseline, ECW: extracellular water, FFM: fat free mass, FM: fat mass, ICW: intracellular water, l: liters, SE: standard error, SMM: skeletal muscle mass, TBW: total body water, Wk: week

4.6 Correlations

Scatterplots for correlations are presented in Figure 12-14. In the control group, there was a significant strong, negative correlation between weight loss and change in average pain (r = -0.784, p = 0.003), but not in the keto group (r = -0.082, p = 0.801) (Figure 12). No significant correlations were found between change in FM, TBW, ECW, or ICW and change in average pain in neither group.

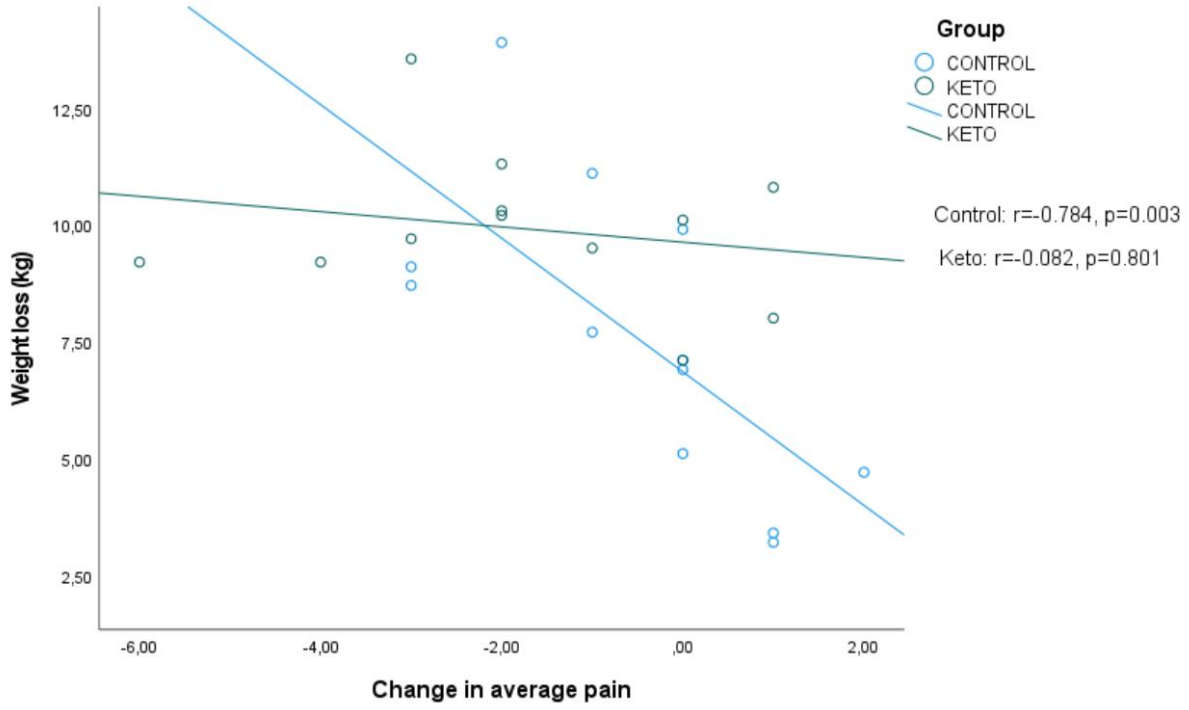

Figure 12 Scatterplot for correlation between weight loss and change in average pain in keto- and control-groups

In the keto group, there was a significant moderate, negative correlation between change in average pain and change in general health from RAND-36 (r = -0.629, p = 0.038), but not in the control group (r = -0.069, p = 0.831) (Figure 13). No significant correlations were found between change in average pain and change in physical function from neither three questionnaires, nor general QoL from IWQOL-Lite and LYMQOL.

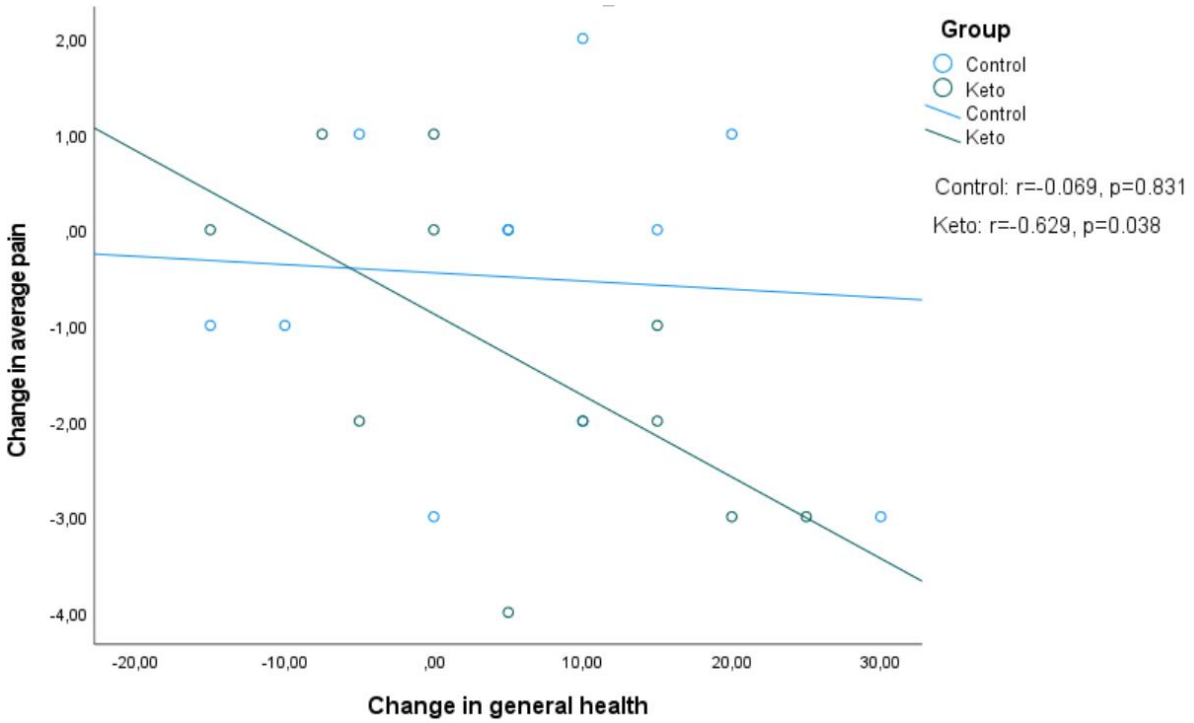

Figure 13 Scatterplot for correlation between change in average pain and change in general health (RAND-36) in keto- and control-groups

In the keto group only, there was a significant positive, moderate correlation between weight loss and change in general health from RAND-36 (r = 0.662, p = 0.042). In both the keto- and control-group, there was a significant positive, moderate correlation between weight loss and change in physical function from RAND-36 (rho = 0.657, p = 0.039, rho = 0.662, p = 0.026, respectively) (Figure 14). No significant correlations were found between weight loss and change in physical function or general QoL from IWQOL-Lite and LYMQOL.

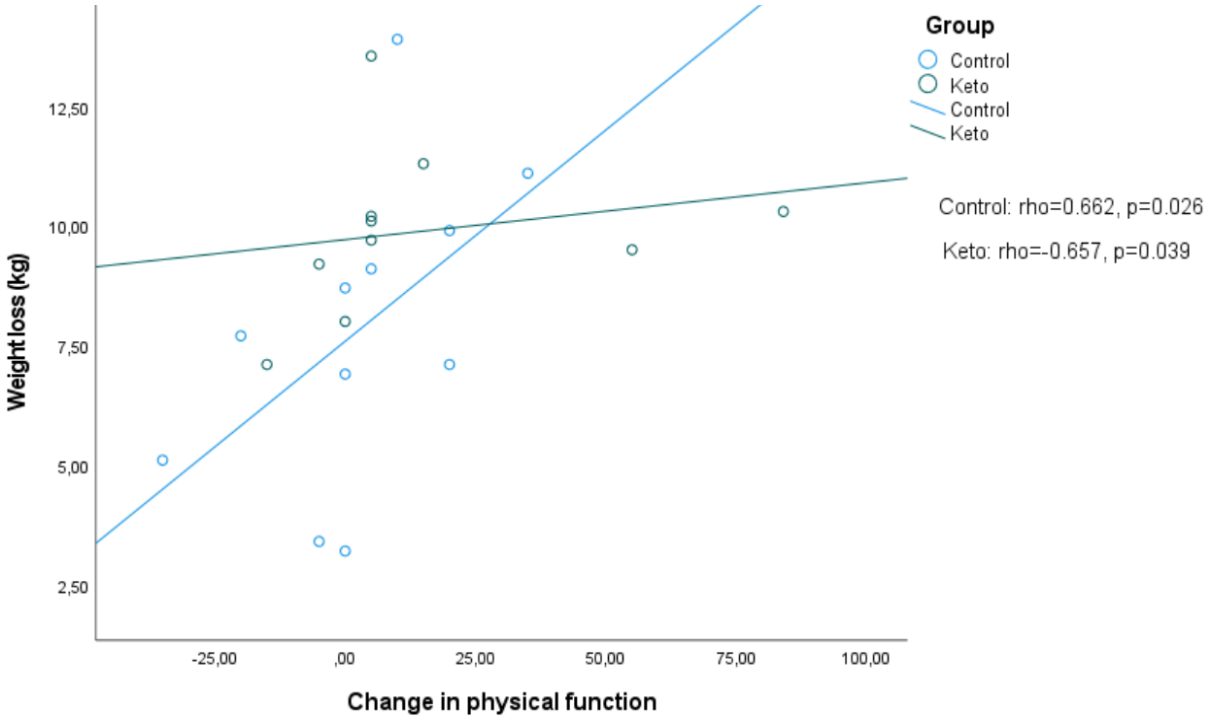

Figure 14 Scatterplot for correlation between weight loss and change in physical function (RAND-36) in keto- and control-groups

5 Discussion

The aim of this master's thesis was to investigate the impact of a low-energy KD on pain and QoL in women with lipedema, compared to a low-energy non-KD. The hypothesis was that a KD reduces pain and improves QoL, independently of weight loss.

The main finding was that the keto group only, achieved decreased pain severity scores from BL to Wk 9. Both groups improved the scores of total QoL and physical function from IWQOL-lite, and energy from RAND-36. The keto group only, increased self-esteem score from IWQOL-lite. However, there were no difference between groups in strongest pain, average pain, or any QoL subcategory from BL to Wk 9. The keto group had larger weight loss than the control group, but weight loss only correlated with pain relief in the control group. In the keto group, both weight loss and pain relief correlated with improved general health from RAND-36. In both groups, there was a correlation between weight loss and improved physical function from RAND-36.

5.1 Compliance

The level of ketone bodies, both in urine and blood, indicate that the participants had overall good compliance to the interventions. However, individual adjustments of the dietary plans were necessary to achieve ketosis in the keto group and avoid ketosis in the control group. The KD was originally constructed with 75 g CHO (25 E%) due to the combined energy restriction. Yet, a CHO level less than 50 g was necessary for most participants in the keto group to reach ketosis. On the other hand, some of the participants in the control group needed to increase the CHO level from 180 g up to 200 g to avoid ketosis. The intended protein intake of 60 g consequently increased to approximately 70 g in the keto group and decreased to approximately 50 g in the control group to maintain the energy restriction of 1200 kcal. The protein level in the keto group may partially explain why some participants were only borderline ketotic, as glucogenic amino acids can be converted into glucose through gluconeogenesis (49).

Despite dietary modifications, one participant in each group remained non-compliant with respect to the level of ketone bodies and were therefore excluded from the analyses. This could be attributed to individual variance, such as basal metabolic rate, BMI, and body fat percentage (66, 102). Moreover, the diets were not based on individual energy requirements, and variance in energy deficit may also be an explanation. Adjustments regarding meal frequency were also

necessary to enhance compliance during the intervention period. The amount of food was challenging for some participants, and they needed to split the meals into several small portions throughout the day. Others preferred to merge some meals as they found it difficult to manage five meals a day.

5.2 Pain

In this study, the keto group achieved a reduction in pain severity, while the control group did not attain any pain relief. Providers mostly evaluate average pain, but strongest pain is also considered of high value in pain intensity assessments (103). These two variables will therefore be emphasized in the discussion of the results. In the keto group, the mean difference in average pain and strongest pain was -1.8 and -2.0, respectively. This corresponds to a reduction of approximately 30%, which is considered clinically relevant (104), as stated in the power calculation. However, the results have low statistical power due to the small sample size and p-values higher than 0.01. In addition, there were no difference between groups in these two pain variables from BL to Wk 9. Nonetheless, other recent publications have also proposed pain relief in women with lipedema following KDs.

“The lipedema project”, a non-profit organization by Seo and Keith (14), encourages a ketogenic low-CHO, high-fat (LCHF) diet through online and physical classes and support groups for women with lipedema all over the world. They recommend consuming meat, dairy products, and eggs, supplemented with non-starchy vegetables. Fruits and berries are limited, while grains and sugar are excluded from the diet. These women report reduced or eliminated pain and improved QoL, along with weight loss and decreased body circumferences after implementing the diet (14). However, a clinical controlled trial is not yet initialized by this research group, thus, no specific intervention or objective outcome measures can be compared.

A case report by Cannataro et al. (15) presents a subject with lipedema, who achieved weight loss of -41 kg, -20% FM, decreased body circumferences in upper and lower limbs, reduced pain of 67% (9.2 vs. 3.0, assessed by visual analog scale), and improved QoL, after 22 months of KD (1300 kcal, 4 E% CHO, 30 E% protein, 66 E% fat) (15). The long-term intervention indicates continual symptom relief over time with sustained diet and BHB levels higher than 0.8 mmol/l. However, pain was only assessed with a single-item scale, and the results consider only one participant with exceptional compliance and weight loss.

Results from the pilot study (16) of this present project indicate that a KD may induce pain relief independent of weight loss. The study of nine women with lipedema presented pain relief (4.6 ± 0.7 vs. 2.3 ± 0.7, $p = 0.018$) with an eucaloric KD (5-10 E% CHO, 20 E% protein, 70-75 E% fat) over a period of seven weeks. No correlation was found between weight loss and pain relief. After a six-week isocaloric diet based on NNR (100), pain returned to prior levels, although weight loss was maintained (16). Nevertheless, this was a short-term intervention with a small sample size and no control group, only assessing pain with a one-item scale.

In our study, the keto group had larger weight loss compared to the control group. Nonetheless, weight loss was not associated with pain relief in the keto group. This supports the statement in the pilot study (16) of KD providing pain relief independent of weight loss. However, weight loss is believed to have some impact on symptom management as well, as proposed by the association between weight loss and pain relief in the control group. This could be a result of reduced non-lipidemic fat and inflammation, or decreased progression of lipedema (105). Yet, progression of lipedema would probably not be detected in such short-term intervention study. In case of general weight loss, energy deficit is the most central aspect as there does not appear to be a significant difference between diets based on diverse macronutrient composition on long-term weight loss (> 6 months) (46). Nevertheless, KDs have been reported to suppress the feeling of hunger and may therefore be helpful during energy restriction and enhance dietary compliance (42). This could explain why the keto group had larger weight loss with less variance compared to the control group.

One of the hypotheses considering the potential mechanism of KD-induced pain relief is the ability to induce low insulin levels and lipolysis, and thereby reduce the amount of LAT, edema, and inflammation (19). This theory is reinforced by the results of greater decrease in leg circumference and a trend of larger reduction in FM in the keto group compared to the control group. On the other hand, reduction in body water did not differ between the groups, and neither decreased FM nor body water correlated with pain relief in the keto group. To date, no dietary intervention study has assessed the direct influence on LAT. It thus remains unclear whether LAT is resistant to diet, and if a KD would be more effective than other diets.

As weight loss or change in body composition were not associated with pain relief in the keto group, it is reasonable to hypothesize that the potential effect of KD may be attributed to the

diet per se. The pathogenesis of lipedema is, in similarity with several other painful conditions, linked to inflammatory processes (8, 25, 27). The modern western diet, characterized by processed meat, refined sugar, and low intake of fruits and vegetables causes production of pro-inflammatory mediators and yields fewer anti-inflammatory mediators (106). In fact, several women have reported that especially highly processed foods tend to aggravate leg swelling and discomfort (4). A general dietary change with higher intake of anti-inflammatory nutrients and less refined products is therefore suggested to minimize pain.

Results from a recent study (13) of Italian Caucasian females support that such diet with anti-inflammatory characteristics could be appropriate for women suffering from lipedema. The study included 29 subjects, 14 women with lipedema and 15 controls, who followed a modified Mediterranean diet (20% caloric restriction, 40-45 E% CHO, 25-30 E% protein, 25-30 E% fat) for four weeks. The diet was rich in fruit, vegetables, legumes, nuts, whole grains, extra virgin olive oil, fish, and low-fat dairy products. Preserved and processed foods and high-glycemic CHO were excluded from the diet. The intervention resulted in decreased FM in arms and legs and improved QoL. However, pain severity was not significantly relieved after the intervention ($p = 0.750$). The Fibromyalgia Assessment Tool, the small sample size, or the intervention period of only four weeks, could be possible explanations.

In similarity with the modified Mediterranean diet, both groups in our study had low intake of processed foods and CHO sources were mostly fruits, vegetables, berries, and whole grains, which are rich in fiber and antioxidants like vitamin C, vitamin E, beta-carotene, polyphenols, and flavonoids. Still, the control group in our study and participants following the modified Mediterranean diet (13) did not achieve pain relief. This could be attributed to the general CHO intake which was higher compared to the KD in this study, the pilot study (16) and the case study by Cannataro et al. (15). It should also be noted that the keto group and participants in the pilot study (16) had lower CHO intake during the KD period compared to BL, while CHO intake in the control group and participants following the modified Mediterranean diet (13) was unchanged from BL. Because of the substantial influence CHO have on ROS production, low-CHO diets have been suggested to decrease oxidative stress and inflammation, and potentially relieve pain perception (25). Moreover, studies and clinical trials so far are inconclusive in whether dietary antioxidants improve the body's antioxidant defense system and thus reduce oxidative stress and inflammation (25).

In addition to limiting CHO intake, the dietary composition of KD also allows for higher intake of PUFA, provided consumption of foods rich in unsaturated fat rather than saturated fat. Omega-3 and omega-6 are the two main groups of PUFAs. Omega-3 PUFAs are found in flaxseed, chia seeds, walnuts, and fatty fish, while omega-6 PUFAs are found in a variety of animal products and vegetable oils. It is however the ratio between these fatty acids that seems particularly important with respect to inflammation, as the omega-3 docosahexaenoic acid (DHA) and eicosatetraenoic acid (EPA), promote anti-inflammatory effects, and the omega-6 arachidonic acid (ARA) stimulates production of pro-inflammatory mediators through the same metabolic pathways (62, 107). A shift in this metabolic pathway from pro-inflammatory ARA to anti-inflammatory DHA and EPA is therefore thought to relieve pain in inflammatory conditions (108). The precise omega-6/omega-3 ratio promoting inflammation is unknown, but ratios of 4-5:1 or less are generally recommended and considered the optimal dietary intake (109, 110). Both the keto- and control-group had ratios of 5:1 at BL and were not changed to Wk 8 in neither group. The keto group did however reduce the ratio to 3:1 at Wk 3, approximately the same level as the modified Mediterranean diet (13). Based on these marginal data, it seems that CHO is the macronutrient with the most impact on pain in lipedema.

The result of the macronutrient composition and energy restriction in KD is the metabolic state, ketosis. The increased level of BHB is thought to decrease ROS production and inhibit the release of pro-inflammatory cytokines, and thereby reduce the level of inflammation (62, 111). Looking at individual changes in pain severity in the keto group, two participants had highly reduced pain with a difference of 6-7 BPI units, of which one had 8.0 mmol/l AcAc the whole intervention period and 0.7 mmol/l BHB at Wk 9. Two participants in the keto group experienced no change in pain, of which one was borderline ketotic during the intervention period. Thus, the level of ketosis could partially explain the difference in pain relief in these participants.

It is likely that the potential influence of KD is induced by multiple anti-inflammatory properties rather than one single mechanism (62). Nevertheless, there are currently no consensus of KD acting through anti-inflammatory mechanisms or studies exploring the concentration of ketone bodies or dietary composition required to achieve a clinical effect in inflammatory and painful conditions.

5.3 Quality of life

In this present project, both the keto- and control-group improved total QoL and physical function from IWQOL-lite. Similar results were found in the study of women with lipedema following a modified Mediterranean diet for four weeks (13) (European Quality of Life questionnaire, total QoL score: 8.3 ± 1.8 vs. 6.9 ± 1.4, $p < 0.05$), highlighted by increased ability to perform daily physical activities. In similarity with our study, Cannataro et al. (15) assessed QoL with RAND-36 in the subject following a KD for 22 months. They found improvement in all RAND-36 variables, while our study only found increased energy in both groups and improved role limitations due to physical health in the keto group. Moreover, while the pilot study (16) of this project showed improved body image (3.1 ± 0.2 vs. 2.7 ± 0.2, $p = 0.030$), symptoms (2.8 ± 0.2 vs. 2.3 ± 0.2, $p = 0.020$), and general QoL (5.1 ± 0.6 vs. 6.1 ± 0.6, $p = 0.050$) from LYMQOL in the LCHF period, our study did not find any improvements in QoL with this questionnaire. This could be explained by higher variance in the LYMQOL scores in our study, as the mean values and differences in the keto group were quite similar those in the pilot study. It is also noteworthy that some participants in our study obtained maximum QoL scores at BL. This ceiling effect involves that the true impact of the interventions cannot be determined, and a potential improvement will then be interpreted as unchanged.

A long-term intervention period may allow for larger weight loss and greater pain relief, as shown in the case study by Cannataro et al. (15), which are important factors in optimizing QoL in women with lipedema (34-36). The impact of pain on QoL is in fact universal, and a wide spectrum of pain has shown to be strongly associated with poor QoL (71). Most domains of QoL, including physical, emotional, and social functioning, are also sensitive to effective pain relief treatment. This substantiates the trend of improved pain interference on QoL and the association between pain relief and improved general health in the keto group. On the other hand, most pain interference scores from BPI were not altered and no other QoL category correlated with pain relief. Thus, it should be noted that pain is only one of several factors influencing QoL, and pain relief is not equivalent to improved QoL (71, 112). This dose-response relationship is also influenced by the duration and intensity of pain, comorbidity, individual characteristics, social support, and coping mechanisms (71, 112). The causality between pain and QoL was however not determined in this study.

Weight loss was associated with improved physical function in both groups and general health in the keto group. Obesity has a direct negative impact on QoL by reducing the ability to perform daily activity and impairing the mental health (72, 113). Weight loss and reduced BMI are associated with improved QoL in individuals with obesity, and the positive effects are greater for those with BMI ≥ 30 kg/m^2 (72, 114, 115). The significant weight loss in both the keto- and control-group may explain why QoL from BL to Wk 9 did not differ between the groups. The similarities in QoL between the groups could also be a result of their gratefulness for being included in the study and receiving close follow-up during the whole intervention period. Conversely, diet interventions require considerable motivation and effort, including daily planning, dietary restrictions, and social difficulties.

5.4 Assessment methods

Ketosis

The level of ketone bodies was measured both in capillary blood with ketone meter and in urine with ketostix. Assessing the level of BHB in blood is an objective, rapid, and quantitative measurement with high accuracy (77). Urinary ketone bodies (AcAc) are only a surrogate marker of the clinically relevant BHB and is not recommended for detecting mild ketosis (≥ 0.3 and ≥ 0.5 mmol/l) induced by diet interventions due to the low sensitivity (116). Ketostix is also a visual, semi-quantitative method which only provides the presence of trace, small, moderate, or large concentrations of ketone bodies, and may result in user variety in the subjective interpretation of color change. Hydration status and air exposure of the urinary dipsticks have also shown to affect the results (77). On the other hand, ketostix is non-invasive, less expensive, and more user-friendly than ketone meter, and thus more appropriate for evaluations outside ObeCe.

Diet

Prospective food diaries are appropriate dietary assessment methods in clinical trials and are often considered a reference method due to the high validity and precision (117). The accuracy of PFDs in unconventional diets, such as KDs, may however be reduced. Compared to retrospective methods, PFDs do not require memory as the food registration is completed concurrently with consumption. Because estimating the quantity of consumed food may be challenging, instructions and an illustrative booklet of portion sizes were distributed for additional accuracy. On the other hand, self-reported food diaries are time consuming and

registration over long periods may result in simplified completion with reduced quality. It is also an expensive method with subsequent coding and analyzing of data (117). Therefore, the PFDs were only distributed for four days at BL, Wk 3, and Wk 8. To still ensure dietary compliance, abbreviated food records were assessed daily throughout the study period. These food records only involved registering the meal number from the dietary plans and commenting eventual deviations. Nevertheless, most meals and recipes included specific food measures, thus requiring weighing the food. Weighted food records provide precise diet assessments, but this method also involves a high risk of participants simplifying the records and thus inducing inaccurate data, which are important limitations of self-reported methods.

Pain

Pain is a subjective experience and pain measurements should rely on self-reported methods (118). The Brief Pain Inventory is a validated, simple method to assess pain intensity, which is considered one of the most important clinical dimensions of pain perception (119). Unlike traditional unidimensional scales, BPI evaluates several aspects like strongest, weakest, and average pain intensity over the past 24 hours with a NRS scale (120). Moreover, each NRS is sensitive and is also associated with better compliance compared to the visual analogue scale (119). Compared to one-item scales, the BPI additionally measures how pain influence daily function capacity, nevertheless, the validity of the pain interference items have been questioned (119). Another limitation with BPI is the inability to distinguish various types of clinical pain. Because comorbidities like fibromyalgia, migraine, and rheumatic diseases are often seen in women with lipedema (121), BPI might not identify and assess the specific pain related to lipedema in these subjects.

Quality of Life

Quality of life is a complex, dynamic concept which require assessment tools able to detect multiple dimensions such as physical health, psychological state, and social relationships. Questionnaires can be generic, which assess overall functioning in any population, or specific, which measure challenges commonly experienced by a definite group (122). It is recommended to use a combination of specific and generic tools to both address clinically important changes and compare different types of interventions and diseases (123). The choice of instruments should further depend on the aim of the study and the characteristics of the study group (122, 124).

The generic tool in this study was RAND-36, one of the most widely used standard health-related QoL survey instruments (93). Considering that obesity often co-occurs with lipedema and both interventions were low-energy diets, the IWQOL-Lite was used to detect the aspect of overweight upon QoL (97, 125). Since there is not yet developed a specific QoL assessment tool for persons suffering from lipedema, the LYMQOL questionnaire (98) was supplemented as symptoms of limb lymphedema are quite similar to those of lipedema. Despite that these three questionnaires have some overlapping items, they are designed and formulated of various interest and may have different sensitivity to the study group and interventions.

Body weight and composition

Measurement errors of body weight, circumferences, and composition were minimalized with standardized procedures. The assessments were completed by the same student for the same participant, and with identical equipment for all participants at BL and Wk 9.

Bioelectrical Impedance Analysis is an easy, mobile, non-invasive, and relatively inexpensive method for analyzing body composition. It has shown to be an appropriate instrument with high accuracy when specific BIA equations and standardized procedures are fulfilled (85, 126). The BIA algorithm has not been validated in subjects with BMI > 34 kg/m^2 or with abnormal hydration (127). The accuracy is thus reduced as most participants in our study exceeded this BMI limit, and it has been indicated that women with lipedema have higher levels of ECW compared to controls without lipedema (24). Simultaneously, the assessment of changes in ECW and ICW requires further research using a valid model that assures that fluctuations in these compartments do not disturb each other (82, 84).

A proper alternative method for assessing body composition in this patient group is the reference method, DEXA, which provides regional estimates (head, trunk, arms, legs) of FM, FFM, and bones (128). Magnetic resonance imaging or computer tomography scanning are even more precise as they provide a quantitative and qualitative assessment of subcutaneous adipose tissue (129), which is particularly relevant in lipedema. However, expenses, availability, technical expertise, and contraindications to these methods are important limitations.

5.5 Statistical considerations

This was an explorative project with a small sample size, thus simple statistical methods were used and only adjusted for BL value. No covariates were included in the linear regression model as they did not correlate with the dependent variable. However, an intention-to-treat analysis with linear mixed models could have been an appropriate method to assess the effect of time, group, and interactions, as well as accommodating missing values (130, 131).

The comprehensive scope on pain and QoL and the number of analyzes could have led to random significant results (Type 1 error). A post hoc analysis with a lower p-value could therefore have been proper to reduce the chance of committing a Type 1 error. However, this would make it less likely to detect accurate significant results (Type 2 error), which could be unfortunate as the risk of Type 2 error is already increased with a small sample size and weak statistical power (132).

5.6 Strengths and limitations

This study was a prospective RCT, known as the gold standard among study designs (133). Despite the small sample size, the group of participants had a wide range in age and BMI. All participants were diagnosed with lipedema before entering the study, mostly by specialized physiotherapists. However, the examination may have differed between practitioners as there are no standardized procedures or criteria for lipedema. Type and stage of lipedema were re-evaluated by study personnel at ObeCe with guidance of Wilma Van De Veen, specialized physiotherapist.

The intervention period only lasted eight weeks, thus long-term effects remain unclear. Nevertheless, longer study duration could induce larger dropout rates, reduced compliance, and higher costs (134). The control group made it possible to explore the effect of KD independent of weight loss, but both groups included women with lipedema. The results may thus reflect the influence of being included in the study itself. Moreover, this was an open-label study, which may have biased the results with expectations of KD being the most effective diet.

An important strength of this study is the dietary compliance, which is likely attributed to the close follow-ups and diet interventions with wide variety in food choices and no exclusion of food categories. Yet, most participants in the keto group experienced negative ketone tests and participants in the control group had positive ketone tests at least once during the study period.

The necessary individual adjustments throughout the intervention resulted in a large variation within groups in diet composition and meal frequency.

Because of travel time, covid-19 restrictions, or other reasons, many participants were not able to meet for physical follow-ups at ObeCe as often as planned. This resulted in fewer measurements of BHB in blood and evaluations were completed via phone. Furthermore, the physical activity analyses had a high proportion of missing data as several activity monitors were lost in the mail, and others did not have enough available data to be considered valid. The results may therefore not be representable for the whole study population. However, analyses on pain and QoL had little missing values as the questionnaires were proofread consecutively on the test days.

5.7 Clinical relevance and practical implications

The prevalence of lipedema is still unclear, but many cases are likely unidentified due to the lack of knowledge among health care providers (1, 4). Increasing the awareness of the condition and implementing physical examinations in outpatient clinics may result in several women with lipedema in the next years. Assuring proper diagnosis and treatment at an early stage are important to prevent many years of unnecessary physical and mental suffering (4). It has been assumed that lipedema is resistant to lifestyle interventions and result in weight loss only in the upper body. Nevertheless, this present study and several recent publications indicate the opposite. It should be noted that these interventions involved close follow-up, which may be particularly decisive for dietary compliance in this patient group.

To date, there is no evidence that a specific diet is more appropriate than others for women with lipedema. However, weight maintenance seems crucial to prevent further progression and complications of lipedema (105). It should also be kept in mind that comorbid obesity is common, thus weight loss of 5-10% will provide beneficial health effects in any case (135). In addition, diet interventions may be important for optimizing other concomitant treatment. For instance, physical activity can be challenging for women with late-stage lipedema or those with significant pain and result in immobility and lifestyle-induced obesity (10). Many also wish to undergo liposuction, a procedure to reduce pathological subcutaneous fat in legs and arms (2, 4). Criteria of liposuction involve an acceptable BMI and waist circumference to minimize the

risk of complications (135), making diet an important factor. Weight maintenance afterwards is also decisive for optimal results (28).

Regardless, the Nutrition Care Process should be a central concept in outpatient clinics. A thorough assessment exploring the individual experience of lipedema, potential comorbidities, weight history, nutritional status, previous interventions, and the patient's wish is central in developing a feasible and realistic treatment (136).

5.8 Future research

There is a knowledge gap in the pathogenesis and etiology of lipedema, making an optimal treatment absent. The dietary role in symptomatic treatment appears to be more important than previously thought, although the existing data is still limited. Larger diet interventions compared to a control group are needed for further investigation of the potential influence on pain management. Longitudinal studies are also necessary for evaluating prolonged effects. To explore underlying mechanisms of diet, future studies should perform biological measurements of the inflammatory and oxidative status of the participants, as well as accurate assessments of subcutaneous adipose tissue.

6 Conclusion

In this randomized controlled trial, a KD induced pain relief and improved QoL in women with lipedema. There was a clinically relevant reduction in pain in the keto group following a low-energy KD for eight weeks, and no change in the control group following a low-energy non-KD. The keto group achieved larger weight loss than the control group, however, pain relief was not associated with weight loss in the keto group. This suggests that a KD may reduce pain, independent of weight loss. Quality of life improved in both groups, but self-esteem increased in the keto group only. Both weight loss and pain relief were associated with improved QoL. However, this was a short-term study with a small sample size, high variability, and weak statistical power. Larger clinical trials and longitudinal studies are needed to confirm these results and to explore underlying biological mechanisms.

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Appendix 1: Table of publications on dietary interventions in women with lipedema

Authors, year, origin	Study design	Study population	Diet intervention	Follow-up and compliance	Outcome measures	Summary of findings
Seo and Keith (14), 2016-21, USA	Patient reports from "The lipedema project"	Women with lipedema worldwide	Ketogenic LCHF	Online and physical programs	Not specified	Subjective reports of weight loss, decreased body circumference, reduced swelling, pain relief, and improved QoL
Cannataro et al. (15), 2021, Italy	Case report	Woman with lipedema type 3 and 4, stage 2-3 (age 32 years)	22 months with ketogenic diet: 1300 kcal 4 E% CHO 30 E% protein 66 E% fat	Continuous support via phone. Physical follow-up every month in the laboratory. AcAc (ketostix) every week BHB (Glu/Ket blood glucose meter) every month	Body weight, body composition (BIA), body circumferences, pain (VAS), QoL (RAND-36, WOMAC, SQS)	**BHB** > 0.8 mmol/l every assessment **Weight loss:** - 41 kg **BIA:** -20% FM **Body circumferences:** hips (- 37.5 cm), waist (- 23.9 cm), arms (- 10.5 cm left, - 11.5 cm right), forearms (- 6.5 cm both), knees (- 8.5 cm both), calves (- 9 cm left, - 8.5 cm right), ankles (- 2.5 cm left, - 3 cm right) **Pain:** 9.2 vs. 3.0 (- 67.4%) **QoL:** WOMAC: 45 vs. 21 (- 53.3%), SQS: 37 vs. 19 (- 48.7%), all variables from RAND-36 improved (physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy, mental well-being, social functioning, pain, general health) (Figure 3)
Sørlie et al. (16), 2021, Norway	Prospective, repeated measures study. Pilot study of the Norwegian Lipodiet Study	9 Norwegian women with lipedema, including all types and stages affecting the legs	7 weeks with eucaloric, ketogenic LCHF diet: 5-10 E% CHO 20 E% protein 70-75 E% fat	30-minutes weekly follow-up with dietitian Daily food records, AcAc (ketostix) every week	Body weight, body composition (BIA), body circumferences, pain (VAS), QoL (LYMQOL)	*LCHF period:* **AcAc:** > 0.05-8 mmol/l **Weight loss:** - 4.6 ± 0.7 kg, $p < 0.001$ **Body composition:** FM (- 1.4 kg, $p = 0.140$), FFM (- 2.4 kg, $p = 0.048$), SMM (- 1.4 kg, $p = 0.024$), TBW (- 2.9 l, $p = 0.060$)

		(Age: 46.9 ± 7 years, BMI: 36.7 ± 4.5 kg/m^2)	6 weeks with isocaloric diet based on NNR			**Body circumferences:** waist (- 4.3 cm, p < 0.001), hip (- 2.2 cm p = 0.010), waist/hip ratio (- 0.02, p = 0.017), thigh (- 2.0 cm, p = 0.200), calf (- 1.0 cm, p = 0.030) **Pain:** 4.6 ± 0.69 vs. 2.3 ± 0.69, p = 0.018 **QoL:** General QoL (1.0 , p = 0.050), function (- 0.2, p = 0.230), body image (- 0.4, p = 0.030), symptoms (- 0.5, p = 0.020), mood (- 0.2, p = 0.300), total (- 1.1, p = 0.200) No correlation between weight loss and pain relief at week 7 (r = 0.283, p = 0.460) *NNR period:* **AcAc:** < 0.03 mmol/l **Body weight:** 0.3 ± 0.7 kg, p = 0.430 **Body composition:** FM (- 0.1 kg, p = 0.970), FFM (0.1 kg, p = 0.950), SMM (0.3 kg, p = 0.700), TBW (0.5 l, p = 0.750) **Body circumference:** waist (2.0, p =0.060), hip (0.0 , p = 0.700), waist/hip ratio (0.01, p = 0.140), thigh (0.1 cm, p = 0.730), calf (0.5 cm, p = 0.180) **Pain:** 2.3 ± 0.7 vs. 4.2 ± 0.7, p = 0.041 **QoL:** General QoL (0.0, p = 1.000), function (0.0, p = 0.350), body image (0.2, p = 0.080), symptoms (0.2, p = 0.400), mood (0.01, p = 1.000), total (0.1, p = 0.900)
Di Renzo et al. (13), 2021, Italy	Prospective clinical trial	29 Italian Caucasian females (age > 18 years) 14 women with lipedema (35.5 ± 12.2 kg/m^2), including all stages	4 weeks with modified Mediterranean diet: 20% caloric restriction 40-45 E% CHO 25-30 E% protein 25-30 E% fat	Weekly follow-ups with 48-hour dietary recall via phone 3 days diet record x 3 weeks (total 9 days). Weekly food frequency questionnaire	Body weight, body composition (DXA, BIA), body circumferences, pain (FAS tool), QoL (EQ-5D)	*Lipedema group:* **Body weight:** - 3.04 ± 4.75 kg, p = 0.025 **Body composition:** FM arms (4.1 ± 1.9 kg vs. 3.7 ± 1.5 kg, p = 0.048), FM legs (18.2 ± 8.5 kg vs. 15.9 ± 7.0 kg, p = 0.007), TBW (- 0.5 ± 3.7 l, p = 0.396), ECW (- 2.5 ± 13.0 l, p = 0.433) **Body circumferences:** Hip (- 0.95 ± 3.9 cm, p = 0.250), waist (- 1.7 ± 3.8 cm, p = 0.115), Waist/hip ratio (- 0.6 ± 5.2, p = 0.612) **Pain:** p = 0.750

		15 controls without lipedema (BMI: 27.5 ± 5.2 kg/m^2)				**QoL:** Improved EQ-5D total score 8.3 ± 1.8 vs. 6.9 ± 1.4, $p < 0.05$. *Control group:* **Body weight:** - 4.37 ± 3.94 kg, p = 0.001 **Body composition:** FM arms (3.2 ± 1.0 kg vs. 3.0 ± 1.0 kg, p = 0.046), FM legs (11.0 ± 3.7 kg vs. 10.2 ± 3.2 kg, p = 0.004), TBW (- 1.4 ± 2.8 l, p = 0.800), ECW (1.5 ± 8.0 l, p = 0.522) **Body circumferences:** Hip (- 2.6 ± 2.6 cm, p = 0.002), waist (- 5.4 ± 4.3 cm, p = 0.003), Waist/hip ratio (- 3.0 ± 4.4, p = 0.040) **Pain and QoL:** No significant results (data not shown)
AcAc: Acetoacetate, BHB: β-hydroxybutyrate, BIA: bioelectrical impedance analysis, BMI: body mass index, CHO: carbohydrate, ECW: extracellular water EQ-5D: European Quality of Life, E%: energy percent, FAS: Fibromyalgia Assessment Status, FFM: fat free mass, FM: fat mass, LCHF: low-carbohydrate, high fat diet, LYMQOL: lymphoedema quality of life, NNR: Nordic Nutrition Recommendations, QoL: quality of life, SMM: skeletal muscle mass, SQS: Sleep Quality Scale, TBW: total body water, VAS: Visual Analogue Scale, WOMAC: Western Ontario and McMaster Universities Arthritis Index						

Appendix 2: Daily food records

Mandag Dato: _____

Måltid	Matrett nr.	Kommentar
Frokost		
Lunsj		
Middag		
Kveldsmat		
Mellommåltid		

Tirsdag Dato: _____

Måltid	Matrett nr.	Kommentar
Frokost		
Lunsj		
Middag		
Kveldsmat		
Mellommåltid		

Onsdag Dato: _____

Måltid	Matrett nr.	Kommentar
Frokost		
Lunsj		
Middag		
Kveldsmat		
Mellommåltid		

Torsdag Dato: _____

Måltid	Matrett nr.	Kommentar
Frokost		
Lunsj		
Middag		
Kveldsmat		
Mellommåltid		

Fredag Dato: _____

Måltid	Matrett nr.	Kommentar
Frokost		
Lunsj		
Middag		
Kveldsmat		
Mellommåltid		

Lørdag Dato: _____

Måltid	Matrett nr.	Kommentar
Frokost		
Lunsj		
Middag		
Kveldsmat		
Mellommåltid		

Søndag Dato: _____

Måltid	Matrett nr.	Kommentar
Frokost		
Lunsj		
Middag		
Kveldsmat		
Mellommåltid		

Øvrige kommentarer:

Appendix 3: Pre-coded food diaries

Dagbok

Fyll inn:

Kjønn ☐ Skriv 1 hvis gutt/mann, 2 hvis jente/kvinne

Alder ☐☐ år

Ukedag ☐ 1=mandag, 2=tirsdag, 3=onsdag, 4=torsdag, 5=fredag, 6=lørdag og 7=søndag

Dato ☐☐.☐☐.☐☐

Var denne dagen en vanlig dag? Skriv ja eller nei i rutene.

☐☐☐

Hvis det var en uvanlig dag, forklar hvorfor denne dagen var uvanlig:

Hvor finner jeg matvarene i dagboken?

	Side		Side
Drikke	**2-4**	**Poteter/ris/pasta**	**13**
Brød	**4**	**Grønnsaker**	**13-14**
Smør/margarin	**5**	**Saus/dressing**	**14**
Pålegg	**5-7**	**Is/dessert**	**15**
Yoghurt	**7**	**Kaker/kjeks**	**16**
Frokostgryn/grøt	**8**	**Frukt/bær**	**17**
Kjøttretter	**9-10**	**Snacks**	**17**
Fiskeretter	**11**	**Godterier**	**18-19**
Andre retter/salater	**12**	**Tran/kosttilskudd**	**19**

HUSK:

Alt du spiser/drikker skal skrives opp

Sett ikke kryss i dagboken

Sett bare bokstaver i de orange rutene

Sett bare tall i de sorte rutene

847602

31963

Drikke

For størrelsen på glasset du drikker av, se bildeserie 1.
Fyll inn bokstaven i den orange ruten.

	Antall	kl. 6-10	kl. 10-14	kl. 14-18	kl. 18-22	kl. 22-6
Vann	glass					
Helmelk, søt/sur (eks. helmelk, kefir)	glass					
Lettmelk, søt/sur (eks. lettmelk, Cultura)	glass					
Ekstra lett lettmelk	glass					
Skummet melk	glass					
Drikkeyoghurt	glass					
Sjokoladem. av helmelk (eks. O'boy, Nesquick)	glass					
Sjokoladem. av lettmelk (eks. Nesquick, Litago)	glass					
Sjokoladem. av ekstra lett lettmelk (eks. O'boy)	glass					
Sjokoladem. av skummet melk (eks. O'boy, Nesquick)	glass					
Litago sjokoladem.	1/2 liter					
Kakao av helmelk	kopp					
Kakao av lettmelk	kopp					
Kakao av ekstra lett lettmelk	kopp					
Kakao av skummet melk	kopp					
Appelsinjuice	glass					
Eplejuice/eplemost	glass					
Nektar (eks. eple, tropisk frukt, annen frukt)	glass					
Brus med sukker (eks. Cola, Solo)	glass					
Brus med sukker (eks. Cola, Solo)	1/2 liter					
Brus, kunstig søtet (eks. Cola light, Solo lett)	glass					
Brus, kunstig søtet (eks. Cola light, Solo lett)	1/2 liter					

847602

2

31963

Smør eller margarin på brød.

1 skive = 1/2 rundstykke = 1 knekkebrød
= 2 vaffelhjerter = 2 kjeks = 1/2 cabotta

	Antall	kl. 6-10	kl. 10-14	kl. 14-18	kl. 18-22	kl.22-6
Meierismør	til antall skiver					
Bremykt	til antall skiver					
Brelett	til antall skiver					
Margarin (eks. Soya, Per, Melange)	til antall skiver					
Lettmargarin (eks. Soft light)	til antall skiver					
Annet beskriv best mulig hva, hvor mye og når:						

Hvor mye smurte du på brødet?

Se bildeserie 3 og skriv bokstaven for det bildet som ligger nærmest opp til den smør-/margarinmengden du brukte på brødet. Hvis du hadde forskjellig mengde smør/margarin på de brødskivene du spiste innenfor det angitte tidsrommet, kan du anslå et gjennomsnitt for skivene.

	kl. 6-10	kl. 10-14	kl. 14-18	kl. 18-22	kl. 22-6
Bildeserie 3					

Pålegg

Du skal oppgi mengde pålegg i forhold til brødskiver. Har du spist to typer pålegg på samme brødskive, fører du opp begge (eks. 1 hvitost helfet og 1 skinke). Hvis du bare har spist pålegg og ikke brød, anslå til hvor mange skiver du kunne brukt dette pålegget.

1 skive = 1/2 rundstykke = 1 knekkebrød
= 2 vaffelhjerter = 2 kjeks = 1/2 cabotta

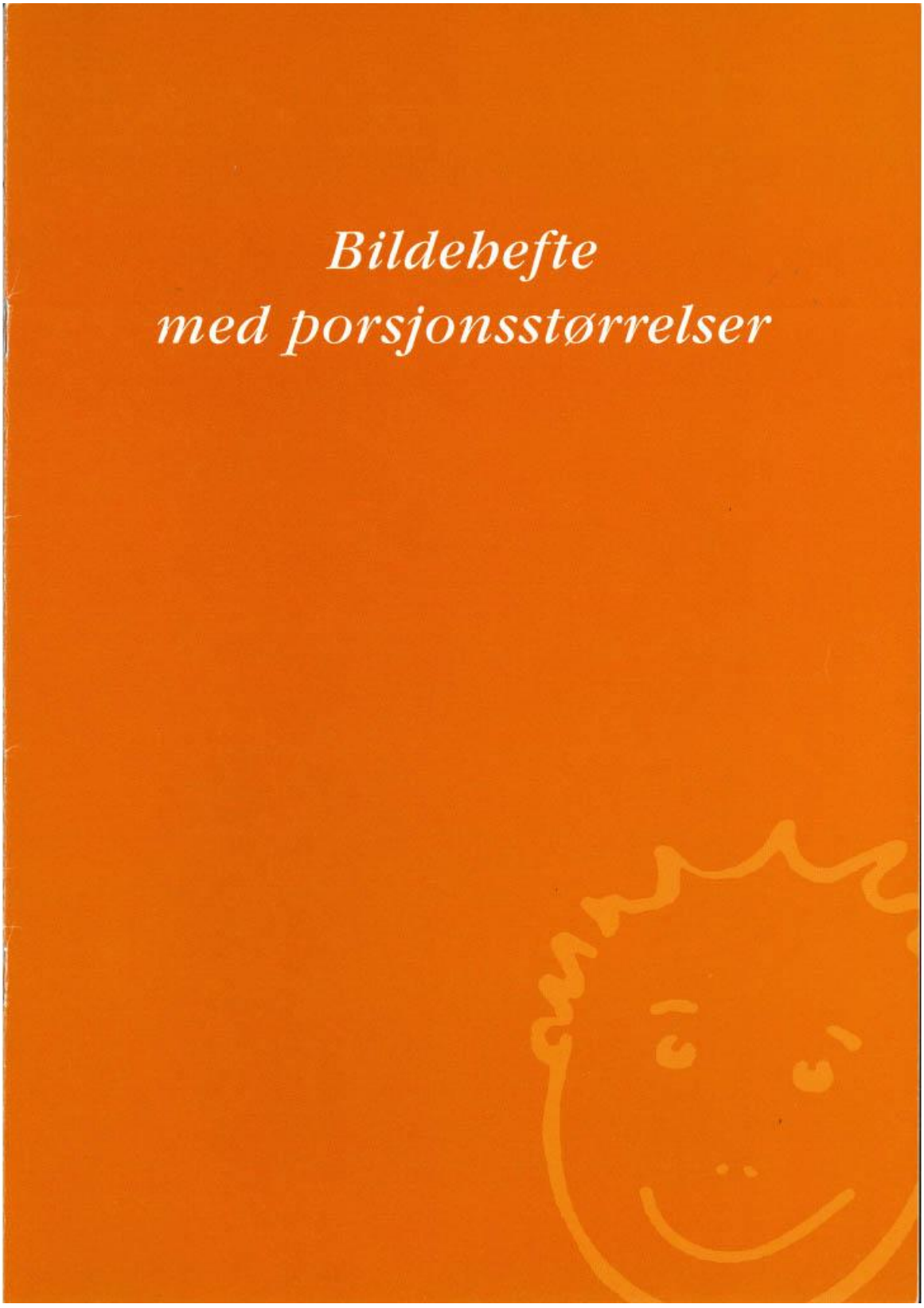
Kjøttpålegg	Antall	kl. 6-10	kl. 10-14	kl. 14-18	kl. 18-22	kl. 22-6
Servelat, vanlig	til antall skiver					
Kokt skinke, spekeskinke, lett servelat	til antall skiver					
Salami, spekepølse, fårepølse	til antall skiver					
Leverpostei, vanlig	til antall skiver					
Leverpostei, mager	til antall skiver					
Kalkun-/kyllingpålegg	til antall skiver					

Ost	Antall	kl. 6-10	kl. 10-14	kl. 14-18	kl. 18-22	kl. 22-6
Hvitost helfet 27% fett (eks. Jarlsberg, Norvegia)	til antall skiver					
Hvitost halvfret 16% fett (eks. Norvegia lettere)	til antall skiver					
Brunost helfet (eks. Gietost, G35, Fløtemysost)	til antall skiver					
Brunost halvfet, prim	til antall skiver					
Smøreost, vanlig (eks. Baconost, Snøfrisk)	til antall skiver					
Smøreost, mager (eks. mager skinkeost)	til antall skiver					
Kremost (eks. Philadelphia, Gourmetoster)	til antall skiver					
Dessertost (eks. Brie, Gräddost, Ridderost)	til antall skiver					

Fiskepålegg	Antall	kl. 6-10	kl. 10-14	kl. 14-18	kl. 18-22	kl. 22-6
Kaviar	til antall skiver					
Røkt laks/ørret	til antall skiver					
Makrell i tomat, røkt makrell	til antall skiver					
Sardiner, sursild, ansjos	til antall skiver					

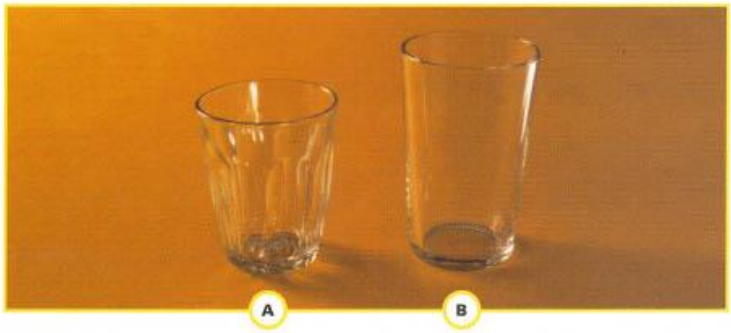
Syltetøy/søtpålegg	Antall	kl. 6-10	kl. 10-14	kl. 14-18	kl. 18-22	kl. 22-6
Syltetøy vanlig, gelé, marmelade	til antall skiver					
Syltetøy lett, frysetøy	til antall skiver					
Honning	til antall skiver					
Peanøttsmør	til antall skiver					
Sjokolade-/nøttepålegg	til antall skiver					
Hapå/Litegopålegg	til antall skiver					
Annet beskriv best mulig hva, hvor mye og når:						

Appendix 4: Illustrative booklet of portion sizes



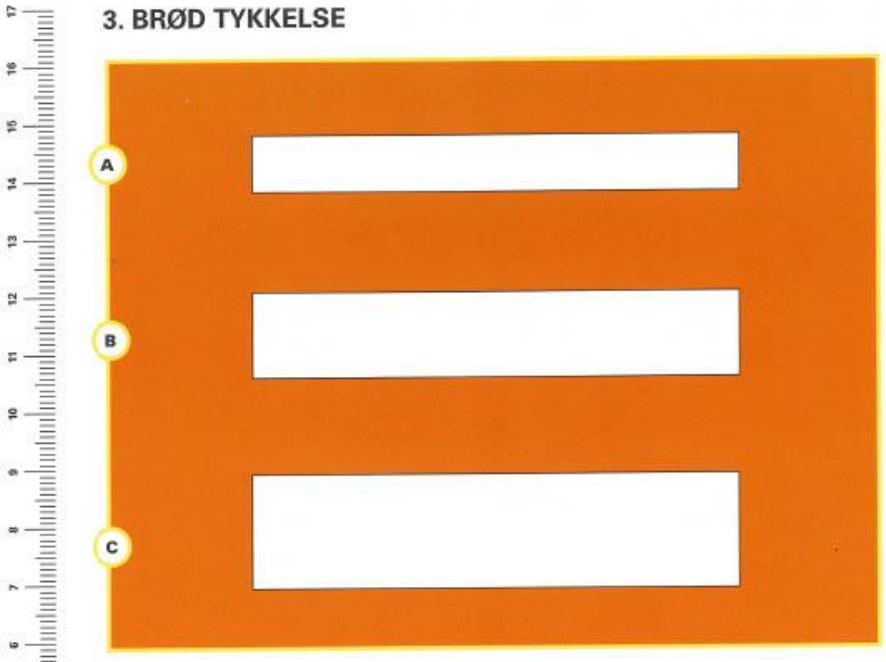
DETTE BILDET VISER STØRRELSEN PÅ TALLERKENENE SOM ER BRUKT I BILDEHEFTET

1. GLASS

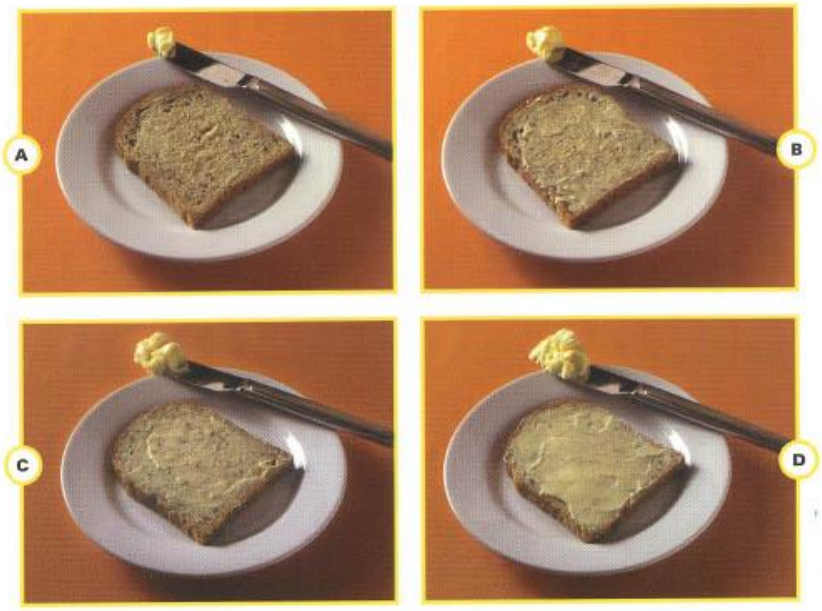


2. KOPPER

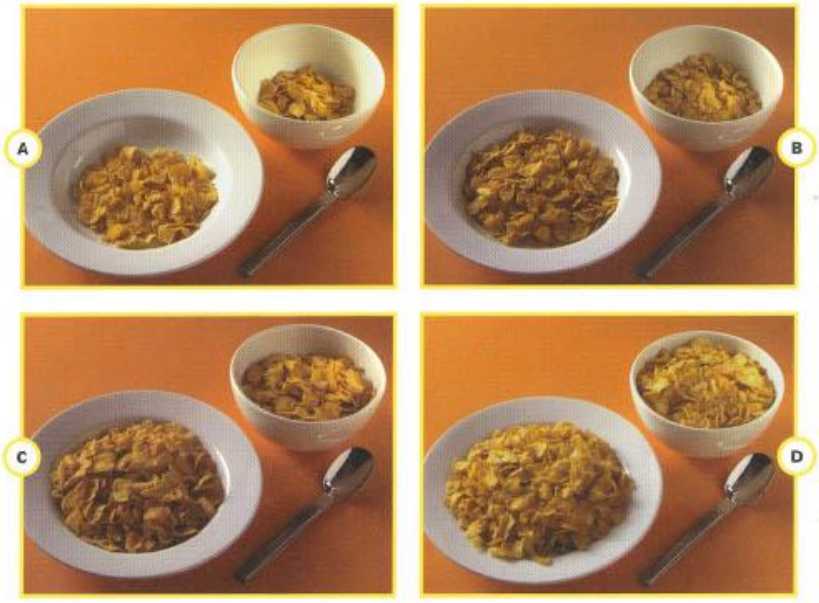
3. BRØD TYKKELSE



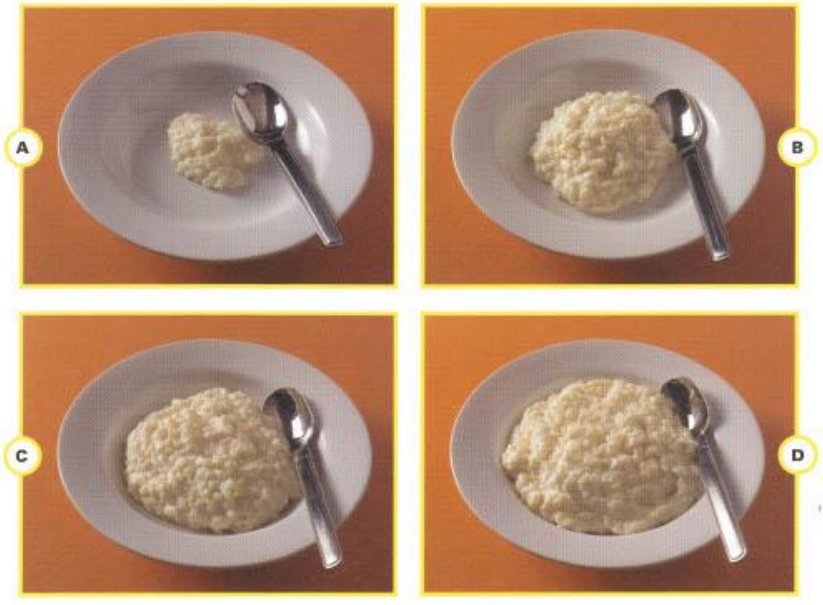
4. SMØR/MARGARIN PÅ BRØDET



5. CORNFLAKES (FROKOSTBLANDING)



6. GRØT



Appendix 5: Color chart for ketostix

mmol/l	0	0.5	1.5	4	8	16

Appendix 6: Example of the ketogenic diet plan

	KH PROTEIN FETT	KCAL
FROKOST: HAVRE-CHIAGRØT 1 stor ss lettkokte havregryn (10 g) 2 ss chiafrø (20 g) 1,5 dl usøtet mandeldrikke (fra Alpro) 0,5 dl vann ¼ ts kanel og ½ ts kardemomme Topping: 40 g bær (ca. 2 små håndfuller) **eller** 20 g banan 5 stk. hakkede valnøtter	25 g inkl. fiber 12 g u/fiber 8 g protein 16 g fett	250
LUNSJ: EGG MED KAVIAR & GULROT 1 Brisk knekkebrød med ½ ss Polar kaviar (8 g) og 1 kokt egg. 1 gulrot (80 g) ved siden 	11 g inkl. fiber 6 g u/fiber 13 g protein 18 g fett	250

GRATINERT SQUASH 1 squash (250g) 80 g karbonadedeig 2 stk. sjampinjong (35 g) 30 g rødløk/gul løk 1 fedd hvitløk 80 g hakkede tomater 25 g revet lettost (1 neve) Oregano Salt og pepper Salat: 30 g agurk, 40 g tomat, 30 g bladsalat/spinat, 1 ss olivenolje. Topp med 2 ss lettrømme. 	18 g inkl. fiber 13 g u/fiber 33 g protein 23 g fett	400
KVELDSMAT: GRESK YOGHURT MED BÆR OG NØTTER 130 g gresk yoghurt naturell fra Synnøve Topping: 10 stk. hakkede valnøtter 50 g blåbær **eller** bringebær.	10 g inkl. fiber 6 g u/fiber 12 g protein 16 g fett	250
MELLOMMÅLTID: NØTTER & FRUKT 4 mandler og 60 g eple/pære	8 g inkl. fiber 7 g u/fiber 1 g protein 2 g fett	50

Appendix 7: Example of the conventional diet plan

	KH PROTEIN FETT	KCAL
HAVREGRØT MED CHIA & BANAN 5 ss lettkokte havregryn (30 g) 0,5 ss chiafrø (4 g) 2 dl vann 1 dl ekstra lett melk 1 ts kanel 80 g moden banan	48 g inkl. fiber 41 g u/fiber 9 g protein 5 g fett	260
LUNSJ: WRAP MED MAGEROST 2 stk. speltlomper 40 g Kavli magerost Jalapeño 50 g agurk 40 g rød paprika En god neve bladspinat/ruccola 1 liten frukt, eks. eple/pære (90 g) ved siden av 	44 g inkl. fiber 38 g u/fiber 12 g protein 4 g fett	250
MIDDAG: KYLLINGWOK 80 g kyllingfilet 200 g klassisk wokblanding 40 g fullkornsris (målt i tørrvekt) 2 ss sursøt chillisaus (30 g)	59 g inkl. fiber 52 g u/fiber 26 g protein 9 g fett	400

KVELDSMAT: KNEKKEBRØD MED HVITOST 2 tynne skiver lettost (15 g) fordelt på 2 stk. Wasa Sport+ med skrapet lag lettmargarin 120 g eple/pære 1 dl appelsinjuice		47 g inkl. fiber 38 g u/fiber 9 g protein 6 g fett	250
MELLOMMÅLTID: LETTYOGHURT 1 beger dobbel 0 yoghurt		12 g inkl. fiber 10 g u/fiber 5 g protein	50

Appendix 8: Informed consent form

HELSE NORD-TRØNDELAG

FORESPØRSEL OM DELTAKELSE I FORSKNINGSPROSJEKTET

EFFEKT AV KETOSE PÅ LIPØDEM

Lipødem en er underdiagnostisert tilstand, som mangler behandlingstilbud. Et sunt kosthold og fysisk aktivitet er sett på som et ikke-fungerende behandlingsalternativer for personer med lipødem. Allikevel er det rapportert fra personer med lipødem at en ketogen diett med høyt fett- og lavt karbohydratinnhold, kan redusere smerter. Det er behov for en klinisk studie, som undersøker om effekten skyldes ketose med eller uten vektreduksjon, for å se om dette kan være et fremtidens behandlingstilbud for denne tilstanden.

Dette er et spørsmål til deg om å delta i et forskningsprosjekt for å undersøke om forskjellig innhold i karbohydrater i kostholdet og kan føre til endring i smerte, livskvalitet og kroppssammensetning. Hvis du har lipødem eller mistanke om at du har det og ønsker å delta i denne studien, ber vi deg ta kontakt med prosjektleder.

HVA INNEBÆRER PROSJEKTET?

- Uttrekning til 8 uker på (1) lav-karbohydrat og høy-fett (LCHF)-diett eller (2) lav energi-diett (LED), begge med vektreduksjon.
- Samtaler og kostveiledning med masterstudent veiledet av klinisk ernæringsfysiolog
- Måling av kroppssammensetning og hvilestoffskiftet (energiforbrenning i hvile)
- Blodprøver for å utelukke negativ effekt av dietten, som nyreproblemer eller forhøyede fettstoffer i blodet, i tillegg til sult og metthetshormoner og inflammasjonsmarkører
- MRI i Levanger for å undersøke underhudsfett
- Fettvevs prøve
- Spørreskjema
- Studien varer i ca. 8 uker

I prosjektet vil vi innhente og registrere opplysninger om deg. Vi registrer bare nye opplysninger som nevnt over, men trenger innsyn til journal for å få tilgang til lipødem-diagnosen og laboratorie-resultater.

Deltakerne blir tilfeldig uttrekt til en av de 2 diett-gruppene. Alle vil få vektreduksjon på ca. 10% noe som kan ta lengre tid for noen. Diettene vil bestå av vanlige matvarer.

Hver andre uke gjennom studien må du møte opp til noen få målinger og samtaler på St. Olavs hospital i Trondheim eller på sykehuset Levanger/Namsos. På disse oppfølgingsmøtene vil du få kostholdsveiledning, det gjøres målinger av vekt og ketoner i blodet (ketoner oppstår når karbohydratinntaket fra maten blir lavt og kroppen begynner å forbrenne mer fett). Konsultasjonen tar ca. 30 minutter. Møtene ved oppstart og slutt vil vare i ca. 4 timer, fordi målinger av hvileforbrenning, kroppssammensetning, mål (liv, hofte og legg) og spørreskjema (smerter og livskvalitet) skal gjennomføres. MRI vil bli gjennomført på en egen dag ved sykehuset Levanger før og etter gjennomføringen av studien.

MULIGE FORDELER OG ULEMPER

Du kan få mulighet til å prøve ut et kosthold som kan føre til en reduksjon i smerter og gi bedret livskvalitet på grunn av reduksjon i fettmasse, to av diettene gir vektreduksjon. Kostholdet er tilpasset dine matpreferanser og du vil under hele studien bli tett fulgt opp. Du får målt kroppssammensetning, hvilestoffskiftet, aktivitet og beregnet ditt daglige energibehov. Diettutprøvingen anses ikke som risikabel, men kan gi noen bivirkninger.

Bivirkningene vil for de fleste oppleves som mest plagsomme i begynnelsen og avta etter hvert, og variere fra person til person. Rapporterte bivirkninger av å stå på en ketogen diett er:

- Kvalme
- Tretthet
- Irritabilitet
- Svimmelhet
- Forstoppelse
- Menstruasjonsforstyrrelser
- Nyrestein
- Forhøyet fettinnhold i blodet

Klinisk ernæringsfysiolog, fysioterapeut og lege er ansvarlige medarbeidere i studien og vil bistå masterstudenten. Lege vurderer blodprøvesvar i forhold til nyresykdom og fettstoffer i blodet ditt. Masterstudenten er tilgjengelig på telefon og mail for deltakerne under hele studien.

Måling av kroppssammensetning vil skje ved hjelp av DXA (dual X-ray absorbiometry) skanning. Dette er en smertefri og lavdose røntgenundersøkelse. Mengden stråling ved DXA er mindre enn en tiendedel av dose ved et standard røntgenbilde av brystet, og mindre enn mengden av naturlig stråling du blir utsatt for til daglig.

Prosjektet er ikke invasivt (føres inn i kroppen) med unntak av innsetning av venflon for blodprøver (et lite stikk for innsetting av et lite plastrør) og fettvevsprøver (med lokalbedøvelse og gir ikke arr) som vil bli gjennomført ved St. Olavs hospital av forskningssykepleiere.

FRIVILLIG DELTAKELSE OG MULIGHET FOR Å TREKKE SITT SAMTYKKE

Det er frivillig å delta i prosjektet. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke. Dette vil ikke få konsekvenser for din videre behandling. Dersom du trekker deg fra prosjektet, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner. Dersom du senere ønsker å trekke deg eller har spørsmål til prosjektet, kan du kontakte Siren Nymo, 99514188 og siren.nymo@ntnu.no.

HVA SKJER MED OPPLYSNINGENE OM DEG?

Opplysningene som registreres om deg skal kun brukes slik som beskrevet i hensikten med prosjektet. Du har rett til innsyn i hvilke opplysninger som er registrert om deg og rett til å få korrigert eventuelle feil i de opplysningene som er registrert. Du har også rett til å få innsyn i sikkerhetstiltakene ved behandling av opplysningene.

Alle opplysningene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger gjennom en navneliste. Det er kun Siren Nymo, prosjektleder og andre autoriserte prosjektmedarbeidere som har tilgang til denne listen.

Opplysningene om deg vil bli anonymisert eller slettet fem år etter prosjektslutt.

DELING AV DATA OG OVERFØRINGER TIL UTLANDET

Ved å delta i prosjektet, samtykker du også til at opplysninger som blodprøver blir sendt til utlandet for analyser (fettstoffer og appetitthormoner) som ledd i forskningssamarbeid og publisering. Dette kan være land med lover som ikke tilfredsstiller europeisk personvernlovgivning. Prosjektleder vil sikre at dine opplysninger blir ivaretatt på en trygg måte.

Koden som knytter deg til dine personidentifiserbare opplysninger vil ikke bli utlevert.

HVA SKJER MED PRØVER SOM BLIR TATT AV DEG?

Prøvene som tas av deg skal oppbevares i en forskningsbiobank tilknyttet prosjektet. Dette gjelder blodprøver for fettstoffer, betennelse og hormoner i blod og fettprøver fra underhuden.

Biobanken opphører ved prosjektslutt.

Blod for fettstoffer vil bli sendt til Finland og noen av appetitt hormonene sendes til Danmark for analyser og destrueres etter at de er analysert.

FORSIKRING

Under studien er du dekket under pasientskadeloven.

ØKONOMI

Det vil ikke gis premiering for å delta i studien. Og det gis heller ingen økonomisk støtte til innkjøp av mat, eller kompensasjon for eventuelle reiseutgifter. Deltakeren må derfor være villig og i stand til å dekke disse utgiftene selv.

GODKJENNING

Regional komité for medisinsk og helsefaglig forskningsetikk har vurdert prosjektet, og har gitt forhåndsgodkjenning REK (2093888 /2020).

Etter ny personopplysningslov har behandlingsansvarlig Helse Nord-Trøndelag og prosjektleder Siren Nymo, prosjektleder et selvstendig ansvar for å sikre at behandlingen av dine opplysninger har et lovlig grunnlag. Dette prosjektet har rettslig grunnlag i EUs personvernforordning artikkel 6 nr. 1a og artikkel 9 nr. 2a og ditt samtykke.

Du har rett til å klage på behandlingen av dine opplysninger til Datatilsynet.

KONTAKTOPPLYSNINGER

Dersom du har spørsmål til prosjektet kan du ta kontakt med Siren Nymo, 99514188, og siren.nymo@ntnu.no

Personvernombud ved institusjonen er fredrikhoie.jordet@helse-nordtrondelag.no.

JEG SAMTYKKER TIL Å DELTA I PROSJEKTET OG TIL AT MINE PERSONOPPLYSNINGER OG MITT BIOLOGISKE MATERIALE BRUKES SLIK DET ER BESKREVET

Sted og dato

Deltakers signatur

Deltakers navn med trykte bokstaver

Jeg bekrefter å ha gitt informasjon om prosjektet

Sted og dato

Signatur

Rolle i prosjektet

Appendix 9: Table of physical activity at baseline, week 3, and week 8

	BL	Δ BL-Wk 8	P-value	Δ BL-Wk 3	P-value	Δ Wk 3 - Wk 8	P-value
MET (kcal/kg/hour)							
Keto	1.07 ± 0.12	-0.02 ± 0.07	0.448	0.00 ± 0.06	1.000[S]	-0.01 ± 0.07	0.778
Control	1.08 ± 0.08	-0.10 ± 0.30	0.863[S]	-0.05 ± 0.09	0.170	0.01 ± 0.08	0.874[S]
PA duration							
Keto	00:14:36 ± 00:15:54	00:02:27 ± 00:11:46	0.799[S]	-00:00:51 ± 00:05:55	0.672[S]	00:05:51 ± 00:14:33	0.588[S]
Control	00:24:50 ± 00:16:03	-00:00:15 ± 00:32:25	1.000[S]	00:00:52 ± 00:17:04	1.000[S]	00:11:20 ± 00:21:57	0.345[S]
Sedentary time							
Keto	20:01:03 ± 01:38:33	00:35:14 ± 01:05:55	0.237[S]	-00:08:49 ± 00:42:54	0.612[S]	00:55:36 ± 01:26:35	0.345[S]
Control	18:42:07 ± 03:07:03	02:01:04 ± 04:03:20	0.173[S]	02:00:25 ± 04:13:23	0.484[S]	00:01:50 ± 01:00:49	0.753[S]
Light PA							
Keto	03:10:21 ± 01:14:29	-00:10:05 ± 00:38:29	0.499[S]	00:02:16 ± 00:45:02	0.735[S]	-00:01:34 ± 00:32:17	0.893[S]

Control	03:37:47 ± 01:22:38	-00:07:57 ± 02:45:23	0.600[S]	-00:49:48 ± 01:34:48	0.263[S]	00:57:49 ± 01:50:19	0.249[S]
Moderate PA							
Keto	00:15:48 ± 00:16:17	00:01:54 ± 00:10:18	1.000[S]	-00:01:40 ± 00:06:56	0.499[S]	00:05:51 ± 00:15:24	0.686[S]
Control	00:27:48 ± 00:21:17	00:01:14 ± 01:21:18	0.753[S]	00:04:55 ± 00:23:53	0.889[S]	00:11:47 ± 00:19:35	0.345[S]
Vigorous PA							
Keto	00:00:00 ± 00:00:00	00:00:02 ± 00:00:05	0.317[S]	00:00:00 ± 00:00:00	1.000[S]	00:00:03 ± 00:00:06	0.317[S]
Control	00:00:01 ± 00:00:04	00:00:21 ± 00:01:00	0.655[S]	00:05:08 ± 00:14:37	0.655[S]	00:00:24 ± 00:00:58	0.317[S]
Steps per day							
Keto	5810.5 ± 2399.5	-633.6 ± 1025.7	0.091[S]	-152.1 ± 957.5	0.689	-264.2 ±1227.9	0.686[S]
Control	7198.8 ± 2281.3	-1617.9 ± 3126.3	0.237[S]	-866.0 ± 2286.8	0.320	-29.7 ± 2018.5	0.753[S]
PAL							
Keto	1.53 ± 0.15	-0.14 ± 0.07	0.026*[S]	-0.06 ± 0.05	0.046*[S]	-0.07 ± 0.07	0.080
Control	1.49 ± 0.11	-0.08 ± 0.18	0.492[S]	-0.05 ± 0.11	0.236	0.02 ± 0.13	0.749

Data is presented as mean ± SD. Δ BL-Wk 9 in each group were analyzed by the paired samples t-test for normal distributed data and the Wilcoxon test ([S]) for skewed data. Statistical significance was attributed as * $p < 0.05$. Keto: n = 12 (BL), n = 7 (Wk 3), n = 8 (Wk 8), Control: n = 12 (BL), n = 9 (Wk 3), n = 6 (Wk 8). BL: baseline, Kcal: kilocalories, MET: metabolic equivalents of task, PA: physical activity, PAL: physical activity level, Wk: week