Impact of weight loss achieved through a very-low calorie diet on compensatory mechanisms activated during weight reduction in obese individuals

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Abstract

Background: Diet-induced weight loss is accompanied by compensatory mechanisms, with increased drive to eat, and reduced energy expenditure, which try to restore energy balance. Ketosis has been shown to modulate some of these compensatory mechanisms, particularly at the level of appetite, but few studies have been done in this field.

Purpose: Evaluate the impact of losing weight with a ketogenic very low calorie diet (VLCD) on subjective feelings of appetite, resting metabolic rate (RMR), fat oxidation and exercise efficiency in obese subjects. A secondary aim was to assess if age, baseline BMI, and magnitude of WL correlated with the strength of the compensatory mechanisms activated during WL.

Methods: Fifty-one obese subjects (30<BMI) were recruited to follow a VLCD for 8 weeks. Body composition, RMR, respiratory quotient (RQ), exercise efficiency at 10, 25 and 50 watt, and subjective ratings of appetite (in fasting and for 2,5 h after breakfast) were assessed at baseline, and at the end of VLCD.

Results: 8 weeks of VLCD led to a significant reduction in body weight (15,6±2%, $p< 0.0001$), RMR (-178±137 kcal/day, $p<0.0001$), RQ (-0,09±0,06, $p<0.0001$) and an increase in exercise efficiency at all resistance levels ($p<0.05$). Fasting hunger increased significantly, while prospective food consumption decreased. Area under the curve (AUC) hunger, desire to eat and prospective food consumption decreased, while fullness increased. Baseline BMI correlated positively with changes in exercise efficiency (25 watt), while magnitude of WL was positively correlated with change in RMR, exercise efficiency, AUC hunger and desire to eat. Age showed no significant correlation with any of the compensatory mechanisms measured.

Conclusion: A 15% WL achieved with a ketogenic VLCD led to a significant reduction in RMR, an increase in fat oxidation and exercise efficiency, and changes in appetite ratings towards increased hunger in fasting despite increased postprandial fullness. Baseline BMI and magnitude of weight loss, but not age, seem to modulate the strength of several compensatory mechanisms activated with WL.

Relevance

Knowledge and understanding about the activation of compensatory mechanisms after weight loss is crucial in understanding why so many are unsuccessful in long-term weight-loss maintenance. This knowledge is important for developing successful weight-maintenance strategies for managing the obesity epidemic worldwide.

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Table of content

Abbreviations

Abbreviation	Meaning
AUC	Area under the curve
BMI	Body mass index
CCK	Cholecystokinin
DIT	Diet-induced thermogenesis
EE	Energy expenditure
EI	Energy intake
FM	Fat mass
FFM	Fat-free mass
GLP-1	Glucagon-like peptide-1
GME	Gross mechanical efficiency
METs	Metabolic equivalents
NEAT	Non-exercise activity thermogenesis
PA	Physical activity
PO	Power input
PI	Power output
PYY	Polypeptide YY
RMR	Resting metabolic rate
RQ	Respiratory quotient
SD	Standard deviation
TEE	Total energy expenditure
VAS	Visual analogue scale
VLCD	Very low calorie diet
WL	Weight loss

Introduction

The prevalence of overweight and obesity is increasing worldwide, providing major challenges for public health and the economy (1). Norway is no exception, with a prevalence of obesity of 22,1% for men, and 23,1% for women (HUNT3)(2). Obesity is a well-known risk factor for several comorbidities including; cardiovascular disease, hypertension, type 2 diabetes, osteoarthritis, metabolic disorders, respiratory diseases, cancer and psychological problems (3). By sustaining a weight loss (WL) of 5-10% of initial body weight large health benefits can be achieved (4, 5). The first line treatment of obesity should be by a conservative approach, through changes in lifestyle involving diet, exercise, and behavioural change (6). However, even though significant WL can be obtained in the short-term, the majority of individuals are not able to sustain this loss in the long-term. Studies have shown that only approximately 20% of obese individuals are able to maintain a WL of 10% over 1 year (7, 8). Weight regain is, therefore, likely to be the main challenge in obesity management (9).

Compensatory mechanisms activated during weight reduction

Despite the beneficial health effects that WL has on reducing the risk of comorbidities, long-term weight loss maintenance is difficult and the majority will experience weight regain (8, 10-12). Although psychological factors such as compliance, motivation and willpower can explain some of the weight regain, biological adaptions to the weight reduced state also play a role (13, 14). These adaptions involve metabolic, behavioural, neuroendocrine and autonomic responses, favouring increased energy intake (EI) and decreased energy expenditure (EE)(9). The association between these compensatory mechanisms and weight regain remains somewhat unclear, but it is well known that they increase the risk of weight regain and therefore represents a major obstacle when managing obesity (15).

Appetite and energy intake

Previous studies have shown that a weight-reduced state is characterized by alterations in appetite, both through homeostatic and non-homeostatic mechanisms, favouring increased EI (12, 16, 17). The majority of studies show that a diet-induced weight loss is followed by increased subjective feelings of hunger, desire to eat and prospective food consumption and reduced feelings of fullness (15, 18). Moreover, loss of fat mass (FM) causes a decline in adiposity signals, such as leptin and insulin (19, 20), known to inhibit food intake (17, 21). Weight loss is also followed by an increase in the plasma levels of ghrelin, a hormone associated with increased feelings of hunger and EI (22, 23). Decreased levels of satiety hormones including; polypeptide YY (PYY), glucagon-like peptide-1 (GLP-1) and

cholecystokinin (CCK), have also been reported in the weight-reduced state (23, 24). Interestingly, the previously described alterations, both in appetite-related hormone and subjective feelings of appetite seem to persist in the long term (1 year follow up), despite partial weigh regain (23).

Ketogenic diets are characterized by reducing the intake of carbohydrates below what is needed (less than 100grams/day), and a relative increase in the proportions of protein and fat (25). Any diet causing ketosis can therefore be called a ketogenic diet, including VLCD, since carbohydrate- and total energy content of this diet is below the threshold for daily need(25-28). Previous studies have suggested an appetite-suppressive effect of ketone bodies (29-31) and WL induced by ketogenic diets does not seem to be associated, at least in the short-term, with increased hunger or reduced fullness (32).

Total energy expenditure

Total energy expenditure (TEE), consisting of resting metabolic rate (RMR), which is the energy spent at rest, diet-induced thermogenesis (DIT), which is the thermic effect of feeding, non-exercise activity thermogenesis (NEAT), and physical activity (PA) is also decreased after WL (12, 13, 33, 34). This decrease in TEE has been shown to be higher than predicted after accounting for the changes in body weight and composition (13, 14, 35-38). This is known as adaptive thermogenesis (38). The reduction in energy expenditure, both predicted and adaptive, seems to persist in the long-term (13, 36), which predisposes for weight regain (15).

RMR

RMR is closely related to fat-free mass (FFM), and the reduction seen in RMR after weight loss is mostly due to the loss of FFM (39). RMR contributes with approximately 60-70% of daily energy expenditure, making it the largest component of TEE (35, 40). A lower RMR has been shown among former obese compared with weight-matched controls (36, 41), and is seen as a risk factor for weight regain (34, 42). Moreover, RMR has also been shown, in some studies, to decrease with WL beyond what can be explained by the loss of FM and FFM (13, 35, 41). However, the issue of whether a greater than predicted decrease in RMR occurs during WL remains controversial (43).

Non-resting energy expenditure

A larger than expected decrease in non-resting energy expenditure (NEAT, exercise and DIT) after WL has also been shown, and seems to account for the majority of the larger than expected decrease in TEE observed with WL (44). This decrease is largely due to increased skeletal muscle efficiency, which is known to occur with WL, particularly at low intensity levels of exercise (13, 44, 45). This means that exercise-induced energy expenditure for a given volume of exercise is reduced (13, 44). Moreover, even though DIT, as a percentage of calories ingested, has been shown unaffected by WL, an absolute reduction occurs due to lower energy consumed (35, 46).

Substrate oxidation

Previous studies have also demonstrated a lower fat oxidation in weight- stable formerly obese compared with weight-matched controls (who never lost weight), both at rest and during exercise (47, 48). A lower postprandial and 24-h fat oxidation rates, and blunted ability to increase fat-oxidation in response to a high-fat meal have been seen in former obese compared with lean control subjects (34, 49-51). A high RQ indicating low fat oxidation has been associated with gain of fat mass (52), and may therefore predict future weight gain.

To my knowledge, no study has looked at the impact of a large weight loss achieved with VLCD (ketogenic diet) on compensatory mechanisms activated both at the level of EI and EE (appetite, RMR, fat oxidation and exercise efficiency). Moreover, no study has looked at the potential modulating effect of baseline BMI, magnitude of WL, and age on the previously mentioned compensatory mechanisms after WL. Even though Sumithran and colleagues (2013) have already demonstrated that losing weight with a ketogenic diet (VLCD) is not associated with the expected increase in hunger, reduction in fullness feelings, and increase in ghrelin levels, the study is limited since it did not include pre-menopausal women and had a high mean age (54,4±10,9 years). Therefore, more research is urgently needed in this area.

Aims and hypothesis

The main aim of this study was to assess the impact of WL (achieved by a VLCD) on compensatory mechanisms at both the level of EI (subjective appetite feelings) and EE (resting metabolic rate (RMR), exercise efficiency, and substrate oxidation).

Secondary aims were to assess if baseline BMI, magnitude of WL, and age are correlated with the strength of the compensatory mechanisms activated during WL.

The main hypothesis of this study were that WL achieved with a VLCD will not lead to increased levels of hunger and reduced levels of fullness, but will lead to a reduction in RMR, decreased fat oxidation and increased exercise efficiency. Other hypotheses were that a higher age, a higher baseline BMI, and a higher magnitude of WL, are associated with stronger compensatory mechanisms (decrease in RMR, fat oxidation, and increased exercise efficiency).

Method

Study design

Longitudinal study with pre-and post-intervention measurements. The intervention had a duration of 8 weeks, and participants served as their own controls.

Subjects

Adult obese (BMI: >30kg/m^2 - <47 kg/m^2) individuals were recruited for this study by posting and advertisement through NTNU and St.Olavs webpage, and the local newspaper. Participants were all in good health and not using medication (except contraception). Participants were also weight stable (<2kg variation in the last 3 months) and not currently dieting to lose weight.

Exclusion criteria included: pregnancy, breastfeeding, drugs or alcohol abuse within the last two years, current medication known to affect appetite, or induce weight loss and enrolment in another obesity treatment program. Moreover, subjects with a history of psychological disorders, eating disorders, diabetes type 1 or 2, gastrointestinal (particular colelithiasis), kidney, liver, lung, cardiovascular disease and malignancies were also not accepted in this study. Given that RMR and subjective feelings of appetite have been shown to vary across the menstrual cycle in normally ovulating women (53, 54), only women taking hormonal contraceptives, with a regular menstrual cycle (28+/-2 days), or post-menopausal were included in the study.

This project was based on voluntary participation, and the subjects provided their fully informed and written consent before participation (see attachment). The collection of data was anonymous and was treated confidentially. The protocol was approved by the regional ethical committee (Ref. 2012/1901).

Detailed description of the study

Participants underwent 8 weeks of VLCD (provided by Allevo (Cederroth, Sweden)) and were asked not to change their PA levels. The products included milkshakes, smoothies and soups, which provided 110 kcal/pack. Products for 1 week were given at the start of the intervention, and all participants were given new supplies every week at follow up. All subjects were given instructions on how to follow the VLCD, which provided 550 (women) - 660 (men) kcal/day. The participants were allowed to drink calorie-free drinks and low starch vegetables (maximum 100 grams/day), and advised to drink at least 2,5 litres of water.

The goal of the VLCD was to induce a weight loss of approximately 14% of initial body weight over an 8-week period. This was estimated by the use of body weight simulator (55). The male/female example used in the simulation had an average age of 35 years, BMI 35 kg/m^2, a light activity level (1,5) and consumed 660/550kcal/day. This gave an estimated WL of 14% for men, and 13% for women.

During week 9 and 10 participants were gradually introduced to ordinary foods. In week 9 women were advised to have two meal replacements a day, while men were advised to have three. In week 10, both men and women were advised to have one meal replacement a day. Meal replacements were stopped after week 10. After the end of VLCD all participants had a consultation with a dietician, and received individual counselling and a written program aiming for weight stabilization. This diet consisted of a low fat diet (<30% from fat) that was consistent with their estimated energy expenditure. They were also advised to increase their intake of fruits, vegetables, poultry, fish, and lean meat, and limit dairy fats, fatty meat, sweets, pastries, and desserts. The subjects were also advised to increase their overall level of daily physical activity, and endurance exercise (such as walking, skiing, jogging, or swimming).

Compliance and follow up

All participants came to the Research unit every week for follow up. This included checking of compliance with the diet by measurement of urinary ketone bodies (using Ketostix (Bayer Corp, Elkhart, IN)), and measurement of body weight. If ketone bodies were negative more than once, participants were excluded from the study. Body weight was measured without shoes and with light clothing. All subjects were asked to keep diet logs every week, and those were reviewed and discussed under each visit. Furthermore registration of any side effects was also conducted at these visits.

Armbands (SenseWear, BodyMedia, Pittsburgh) were used to make sure participants did not change their PA levels and were, therefore, compliant with the intervention. Participants were asked to worn the armbands over the triceps on the upper left arm (right-handed), and contrary for left-handed for seven days at baseline, and weeks 4 and 8. Data was considered valid if the participants had worn the armband for approximately 23 hours/day (95% of the day) (56), including at least three weekdays and one weekend day (57-59). SenseWear Armband data was provided directly via the computer software 7.0. Classification of activity types was set using metabolic equivalents (METs). Sedentary behaviour was defined as energy expenditure <1,5 METs, light-intensity activities such as walking, household activities etc. was defined as 1,5>MET <3. Moderate activities such as cycling, swimming and jogging were set at 3> MET<6, and vigorous activities >6 METs (56-60). To reduce intra- and inter-individual differences in wear time, all subjects were compared and analysed by the average activity levels during 4 days (3 weekdays, and 1 weekend day) at each time point.

Assessments

The following assessments were performed at baseline (week 0) and after the 8-week VLCD (week 9). The pre and post-intervention assessments were scheduled so that both were performed on the same phase of the menstrual cycle (for pre-menopausal women, not using hormonal contraceptives).

Body weight

Patients were weighed, using a Seca 877 digital weight (SECA, Hamburg, Germany), before the start of the test, wearing underwear and without shoes. Participants were also asked to go to the toilet before weighing. Height was measured using a Seca 217 stadiometer (SECA, Hamburg, Germany).

Body composition

Measurement of body composition was performed using air displacement plethysmography (BodPod, Cosmed, Concord, CA, USA). Before every measurement a 2-step calibration was done. Two repeated measurements were done, averaged and corrected for body surface area and thoracic gas volume using the BODPOD software. Measurements were done in fasting, wearing underwear, swimming cap, and barefoot. All jewellery was removed before entering the BodPod.

RMR

Resting metabolic rate was measured in the morning, in the post-absorptive state between 08.00 and 09.00, after an overnight fast, using indirect (hood) calorimetry (Sensormedics VO2max 29 Encore, VIASYS, Germany). Participants were instructed to travel by car or public transportation, and avoid exercise, tobacco and caffeine before the test was done (61). Before the test, participants rested on the bed for 10 minutes while calibration of the equipment was performed. Oxygen consumption and CO_2 production were measured continuously during at least 15-20 minutes (or more if measurements were not stable). The participants were asked to relax and breathe normally, but not to move, talk or fall asleep during the test. The first 5 minutes were excluded and then a 10minute period with stable data (coefficient of variation for VO_2 and VCO_2<10%) was used (40, 61).

Exercise efficiency

Whole body skeletal muscle work efficiency (exercise efficiency) was measured on a graded cycle ergometer using indirect calorimetry (Sensormedics VO2max 29 Encore,VIASYS, Germany). A mouthpiece was placed in the participant's mouth. Participants had an accommodation period of 5-10 minutes where they cycled at 10W at 60rpm. After the accommodation period a nose clip was placed on their noses, and they then cycled for 4min at 60 rpm against graded resistance of 10, 25 and 50 watt of power. Oxygen uptake ($\dot{V}O_2$), carbon dioxide production ($\dot{V}_{CO2}$), and the respiratory exchange ratio (respiratory quotient RQ) were measured continuously using a Sensormedics Vmax 29 encore metabolic cart. Exercise efficiency was expressed as gross mechanical efficiency (GME), which is defined as power output (PO)/ power input (PI) ((kcal/min, 1W=0,01433kcal/min)/(VO2-average VO2 during steady state period (lasts 2 minutes of each stage) times the oxygen equivalent)) (44).

Subjective feelings of appetite

Participants came in the fasting state and were asked to consume a standardized breakfast consisting of bread, orange juice, cheese, butter, jam and the choice of milk or yoghurt within 10 minutes. The meal contained approximately 600kcal with 48% energy from carbohydrate, 35% fat and 17% protein. Participants were asked to rate their hunger, fullness, desire to eat and prospective food consumption feelings, using validated 100-mm visual-analogue scale (VAS)(62, 63), in fasting, immediately after breakfast and at 30, 60, 90, 120 and 150 minutes postprandially.

Power calculation

The sample size estimation was based on expected changes in RMR with the intervention based on the study from Camps and colleagues (2013)(64), who used a similar methodology to the one planned in this study (8 weeks of VLCD). Thirty-three participants would be necessary to find a reduction of 160kcal/day in RMR, given an SD for the change overtime of 317kcal/day, at a power of 80% and a significance level of 5%.

Statistical analysis

Statistical analysis was carried out using SPSS statistical software (version 21) (SPSS, IBM Inc., Chicago, USA). Normality of data distributions was assessed by the Shapiro-Wilk test and visual inspection using Q/Q plots.

Changes in BMI, changes in weight, subjective feelings of appetite in fasting, and appetite AUC, RMR, RQ, exercise efficiency and body composition (normal distributed) overtime were assessed by paired t-tests. If data was not normally distributed differences between pre-intervention and post-intervention measures were analysed by Wilcoxon´s matched pairs signed rank sum test. In addition to measurements of RMR (RMRm), a prediction of RMR (RMRp) was performed using the following equation: RMRp (kcal/d) =263+4,8* FM (kg) + 15,9 * FFM (kg), obtained by linear regression using baseline data. In addition a 95% prediction interval was calculated, using R. Values outside this prediction interval was considered as lower, or higher than predicted RMR, at individual level. The ratio RMRm/RMRp was used to determine if measured RMR was above, or below the predicted RMR (values >1 indicate RMRm above RMRp, values <1 indicate RMRm below RMRp) and, therefore the absence or presence of adaptive thermogenesis.

For changes in PA levels (derived from arm bands) overtime (baseline, week 4 and week 8), a repeated measure ANOVA (with posthoc analysis using bonferroni correction) was used. Friedmans test was used if data was not normally distributed. Correlation between variables was determined using Pearson´s, or Spearmans r correlation analysis, depending of the distribution of the data. Statistical significance was set at $P<0.05$, unless otherwise stated.

At baseline, one person was missing data for VAS at 150 min (how much you think you can eat). This was handled by linear interpolation.

Results

Study participants

Of the 51 participants included in the study, 5 withdrew during the first two weeks of VLCD resulting in 46 subjects (40 women, 6 men) who completed the intervention. Two women dropped out because of inability to comply with the diet, or to personal reasons, and one woman dropped out due to diagnostic of cancer. Two men had to drop out because of vomiting after the start of VLCD. Those who completed the intervention reported minor side effects like dizziness, low energy, headache and mild constipation. Two participants experienced serious constipation, which led to consultation of a doctor. Baseline characteristics of those who commenced and completed the intervention is shown in table 1. There were no significant differences in baseline measurements between those who completed and did not complete the study.

Table 1. Baseline characteristics of the participants

Characteristics	Total (N=51)	Completed the study (N=46)
Age (yr)	45.6±8.9	45.2±8.9
Female sex (%)	43	40
Weight (kg)	103.1±15.0	103.2±14.6
BMI (kg/m^2)	36.3±4.3	36.5±4.2
Fat (%)	46.1±5.7	46.5±5

Data is presented as means ±SD. BMI: body-mass index.

Compliance

16 participants had negative ketone bodies once during the intervention, but none of them had negative ketones more than once.

Physical activity levels (steps/day, time spent on sedentary, light, moderate or vigorous activity and total PA) did not change significantly during the intervention in the 25 participants who had complete data at all time points.

Body measurements

Changes in anthropometric measurements with 8 weeks of VLCD are presented in table 2.

Table 2. Changes in anthropometric measurements after 8 weeks of VLCD

	Baseline	Week 8	P-value
BMI (kg/m^2)	36.5±4.2	30.8±3.6	<0.0001
Weight (kg)	103.2±14.6	87.1±12.2	<0.0001
Fat mass %	46.5±5	40.6±5.9	<0.0001
Fat free mass %	53.5±5	59.4±5.9	<0.0001
Fat mass (kg)	48.4±9.5	35.6±8.3	<0.0001
Fat free mass (kg)	55±8.5	51.5±7	<0.0001

Data is presented as means±SD.

After the 8-wk VLCD diet, subjects lost an average of 16.1±3.3 kg (15.6 ±2 %)(p< 0.0001for both). FM (%, kg) decreased significantly during the intervention (P<0.0001). FFM % increased significantly (p<0.0001), while FFM kg decreased significantly during the intervention (p<0.0001).

RMR and exercise efficiency

Changes in RMR, RQ and exercise efficiency are presented in Table 3.

Table 3. Changes in RMR, RQ and exercise efficiency with 8 weeks of VLCD.

	Baseline	Week 8	P-value
RMRm kcal/day	1373±196	1196±161	<0.0001
RMRp kcal/day		1252±131	
RQ (RMR)	0.86±0.05	0.77±0.007	<0.0001
Ex. eff 10 watt	0.05±0.1	0.06±0.01	<0.001
Ex. eff 25 watt	0.106±0.2	0.114±0.1	<0.0001
Ex. eff 50 watt	0.151±0.01	0.156±0.02	<0.05
RQ ex. eff 10 watt	0.9±0.05	0.8±0.05	<0.0001
RQ ex. eff 25 watt	0.9±0.04	0.8±0.05	<0.0001
RQ ex. eff 50 watt	0.920±0.05	0.852±0.06	<0.0001

Data are presented as means (SD). Ex. eff, Exercise efficiency.

Mean RMRm decreased significantly on average – 178 kcal/day after the VLCD (p<0.0001). After VLCD mean RMRm end was significantly lower than mean RMRp (-57±125kcal/day, p<0.001). 31 of the 46 participants had lower than predicted (RMRm/RMRp <1) RMR, and 14 participants (30,4 %) had values of RMR below the lower limit from the 95% prediction interval, which was considered significantly lower than predicted.

Mean fasting respiratory quotient also decreased significantly from baseline to end (p<0.0001). Exercise efficiency at all intensity levels (10, 25,50 watt) increased from baseline

values ($p<0.0001$, $p<0.0001$, $p<0.05$), while respiratory quotient from all exercise efficiency tests decreased significantly ($P<0.0001$).

Subjective feelings of appetite

Fasting

Changes in subjective appetite in fasting are presented in Table 4.

Table 4. Subjective feelings of appetite in fasting

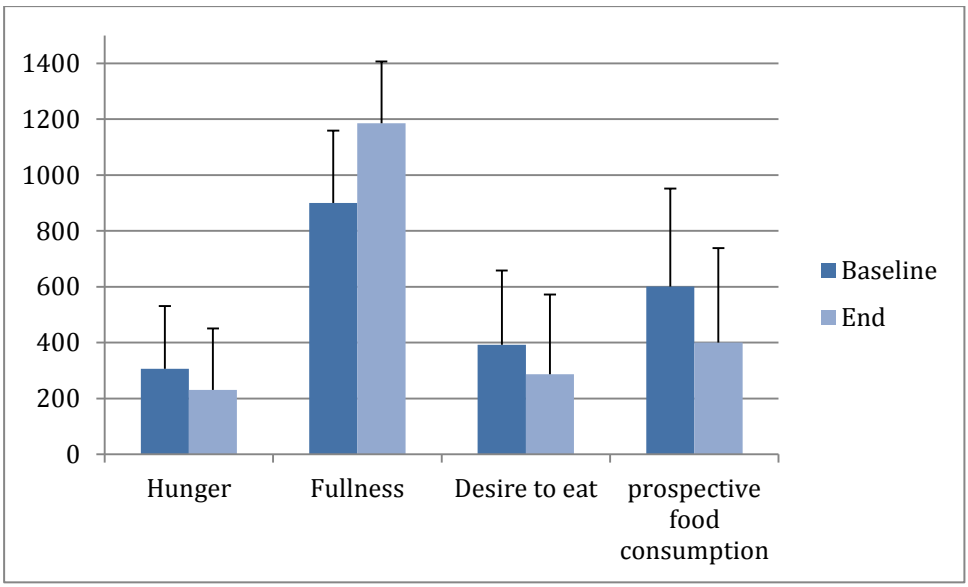
	Baseline	Week 8	P-value
Hunger (cm)	3.8±2.1	5.1±2.6	<0.01
Fullness (cm)	2.1±1.7	2.4±2.2	NS
Desire to eat (cm)	4.7±2.1	5.1±2.5	NS
Prospective food consumption (cm)	5.6±2.1	4.5±2.4	<0.01

Ratings of subjective feelings of hunger in fasting increased significantly overtime ($p<0.01$). No significant change was observed in subjective feelings of fullness and desire to eat in fasting overtime. Feelings of prospective food consumption decreased significantly at the end of VLCD, compared to baseline ($p<0.01$).

Postprandial appetite

Changes in subjective postprandial feelings of appetite are shown in Figure 1.

Figure 1. AUC for subjective feelings of appetite at baseline and after 8-week VLCD.



Data are presented as means±SD.

There was a significant decrease in AUC for feelings of hunger ($p<0.01$), desire to eat ($p<0.01$), and prospective food consumption over time ($p<0.0001$). AUC for Feelings of fullness increased significantly at the end of VLCD compared with baseline ($p<0.0001$).

Correlation analysis

Results of correlation analysis are presented in Table 5.

Table 5. Correlation between BMI at baseline, change in weight and age on compensatory mechanisms.

	BMI Baseline	Change weight	Age
BMI Baseline	1	0,586 p<0.0001	NS
Change RMR	NS	-0,467 p<0.001	NS
ChangeEE10watt	NS	0,389 p<0.01	NS
ChangeEE25watt	0,373 p<0.012	0,450 p<0.002	NS
ChangeEE50watt	NS	0,392 p<0.01	NS
ChangeAUC hunger	NS	0,420 p<0.01	NS
Change AUC fullness	NS	NS	NS
ChangeAUC desire	NS	0,336 p<0.05	NS
Change AUC prospective food consumption	NS	NS	NS
Change fasting hunger	NS	NS	NS
Change fasting fullness	NS	NS	NS
Change fasting desire	NS	NS	NS
Change fasting prospective food consumption	NS	NS	NS

NS; Not significant.

No correlation was found between age and any of the compensatory mechanisms. There was also no association between BMI baseline and change in weight on fasting hunger, fullness, desire to eat, or prospective food consumption.

BMI baseline was positively correlated with change in weight, and change in exercise efficiency 25 watt.

Change in weight was positively correlated with change in RMR, change in exercise efficiency at all intensity levels 10 watt, change in exercise efficiency at all intensity levels, change in AUC desire to eat, and AUC hunger.

Discussion

This study aimed to study the compensatory mechanisms, both at the level of energy intake and energy expenditure, achieved through a VLCD in obese individuals. 8 weeks of VLCD led to a mean WL of 16,1±3,3 kg, and activation of several compensatory mechanisms including; a significant reduction of RMR, a significant increase in fat oxidation, a significant increase in fasting feelings of hunger, exercise efficiency and RQ at all intensity levels (10,25,50 watt). However, at the end of VLCD participants also reported lower postprandial feelings of hunger, desire to eat and prospective food consumption and higher feelings of fullness. Moreover, a higher baseline BMI and a larger magnitude of WL were found to be associated with stronger compensatory mechanism (RMR, exercise efficiency, and subjective appetite).

As expected, RMRm decreased after VLCD compared to baseline, with an average decline of – 178 kcal/day. The fact that RMR declines after a diet-induced WL is well described (13, 35, 44, 65, 66) and is primarily due to the loss of FFM (39, 67). However, the issue of whether the decrease in RMR is larger than expected (adaptive thermogenesis) remains controversial(43). In this study mean RMRm was also seen to be significantly lower than mean RMRp (-57±125 kcal/day, $p<0.001$), indicating a greater than expected decrease in RMRm based on the changes in body composition, and therefore the presence of adaptive thermogenesis. This is in agreement with the findings from other authors (13, 35, 68). Moreover, the significant lower than predicted RMRm seen in 14 participants (30,4%) could possibly account for the entire lower than predicted mean RMRm. Moreover, the fact that only 30,4% showed presence of adaptive thermogenesis suggests an individual variability in adaptive thermogenesis in the reduced obese participants. Similar results have been reported by Astrup and colleagues (1999) who found 15,3% of former obese to have lower than predicted decline in RMR after adjusting for body composition, compared with 3,3% in the control group (who had never been obese)(65).
The conflicting results regarding RMR may be due to the heterogeneity between reduced obese subjects(69), lack of statistical power to detect small differences in RMR(65), and the timing of RMR measurement and body composition after the weight loss period (70, 71). In this study, assessments of RMR were done immediately after the end of the VLCD. Since the participants were not weight stable, the results could be affected by the metabolic adaptions to

the negative energy balance following the severe calorie restriction, or/and a carryover effect of WL, and not to the reduced body weight itself (69).

Fasting RQ decreased on average -0,9±0,6 after VLCD, indicating increased fat oxidation. This is in agreement with the findings from other authors (72, 73).
Rabøl and colleagues (2009) found RQ to decrease from 0,87 to 0,79 after 11,5% WL in young obese women(72). However, the majority of the studies have reported decreased fat oxidation following diet-induced WL(35, 74-76). The conflicting results may be due to the timing of the RQ measurements. In this study, and also the studies reporting increased fat oxidation after WL (ref 72,73), measurements of RQ were performed right after completing the VLCD, when subjects were not weight stable. In the studies reporting decreased fat oxidation (ref 34, 74-76) measurements were done after a period of weight stabilization (7-14 days). It can, therefore, be hypothesized that a reduction in fat oxidation would also be observed in the present study if measurements had been taken after a period of weight stabilization.

The increase in exercise efficiency, and reduction in RQ during exercise at all intensity levels (10,25,50 watt, by cycle ergometry) in this study is in agreement with findings from Rosenbaum and colleagues (2000, 2003) (44, 77). However, these authors did not find an increase in exercise efficiency at intensities higher than 25 watt, while in this study an increase was found at all intensities, including 50W.
A possible explanation for this may be that the measurements of exercise efficiency in Rosenbaum and colleagues were taken when patients were weight stable (±14days), while in this study measurements were done right after completing VLCD (ketotic state). Although researches have not been able to explain why this increase in exercise efficiency occurs, changes in skeletal muscle biochemistry that accompanies WL, is proposed to account for a proportion in the increased skeletal muscle work efficiency(78). Altogether, these findings suggest that the increase in muscle work efficiency is only present at low intensity levels of physical activity (<50watt) when patients are weight stable(12, 13, 44, 45). However, findings from this study suggest that when patients are in negative energy balance, the increase in exercise efficiency may also be present at higher levels of physical activity. Further studies should include testing of exercise efficiency at higher intensity levels, to determine this relationship.

This study found subjective ratings of hunger in fasting to be significantly higher at the end of VLCD compared to baseline. This is surprising, since the participants were ketotic, and the expected increase in hunger and ghrelin levels is normally suppressed during this state (32, 79). Also, the fact that prospective food consumption in fasting declined after VLCD was unexpected, since the participants felt hungrier, but they still did not feel that they could eat that much as before. Moreover, postprandial AUC for feelings of hunger, desire to eat and prospective food consumption decreased significantly, while postprandial feelings of fullness increased significantly at the end of VLCD. These findings (AUC for hunger, desire to eat, prospective food consumption, and fullness) are similar to those reported by Sumithran and colleagues (2013), who found that subjective appetite was significantly lower after 8 weeks of VLCD when participants were ketotic, but rose at week 10 when participants were no longer ketotic (32). Suppressed feelings of hunger after 10% WL during a ketotic state have also been reported by other authors(79). Furthermore, the findings that circulating ghrelin and postprandial levels of CCK seems to be sustained at pre-weight loss levels after WL during the ketotic state, supports the proposed appetite suppressed effects of ketosis (32, 80). This suggests that in a ketogenic state, appetite is not increased, as to what is normally seen after diet-induced weight loss (23). However, the fact that this study found an increase in fasting hunger is not in agreement with previous findings. One possible reason for this may be that mean % WL in the present study was 15,6%, larger than the reported in other studies (Sumithran (13%), and Johnstone (5,8%, ketogenic diet)(32, 79). Therefore it is possible that the potential appetite suppressant effect of a ketogenic diet only works up to a certain magnitude of WL, and if the body weight is reduced beyond that point, ketosis is no longer able to supress hunger.

The significant correlation between magnitude of WL and reduction in RMR shows that subjects with a higher WL also had a greater reduction in RMR. Similar results have also been reported in previous studies (34, 81). Magnitude of WL was also positively correlated with the increase in exercise efficiency at all intensity levels, indicating that greater WL induced a greater increase in exercise efficiency (although the strength of the correlations was modest). However, no effect of WL, and no increase in exercise efficiency after diet-induced WL, was reported by Amati and colleagues (2008) (82). A possible explanation for this may be due to the great differences in magnitude of WL between the groups, and also the relatively high age group (67±0,5yr) and use of a different protocol for measuring exercise efficiency.

Appetite was also seen to be associated with magnitude of WL, and there was a positive correlation between magnitude of WL and change in AUC hunger and desire to eat. This suggests that those who experience a greater WL also experience a greater increase in hunger and drive to eat. This is in agreement with previous findings(14, 18). Gilbert and colleagues (2013) reported an increase in desire to eat and reduction in fullness per kg fat loss in women(18). Other authors found an increase in hunger and drive to eat after WL, and these changes were associated with the decrease in RMR(14). Meaning that the greater reduction in RMR, the greater increase in hunger and drive to eat.
Altogether, these findings suggest that the larger the WL, the stronger were the compensatory mechanisms activated, which promotes the risk of relapse.

For baseline BMI, a significant correlation was only found for exercise efficiency at 25 watt, therefore more studies are need to assess if baseline BMI has an impact on exercise efficiency. Baseline BMI was not significantly correlated with any of the other compensatory mechanisms measured in this study. From these findings it seems that initial weight does not have a clear impact on the strength of the compensatory mechanisms activated following 8 weeks of VLCD. Moreover, opposite to our expectation, age was not correlated with any of the compensatory mechanisms measured.

Practical implication

The findings of the present study suggests that WL achieved by VLCD activate compensatory mechanisms at the level of energy intake and expenditure, and that the larger the magnitude of WL the stronger the compensatory mechanisms activated, making long-term weigh maintenance challenging. Supplementary guidance and aids, in addition to effective long-term WL strategies may be necessary for obese individuals wanting to lose weight aiming at success in the long term.

Strengths and limitations

This study presents several strengths. First, the relatively large number of participants that completed the intervention, and the large spread of age across participants. Second the fact that all assessments were done using gold standard methods. The Bod Pod air displacement system was used to measure body composition, and is an accurate and valid method for this purpose in obese subjects (83, 84). Indirect calorimetry is a gold standard in measuring energy expenditure in clinical settings (85), both for measuring resting metabolic rate and exercise efficiency. Finally, the fact that no participants showed ketone bodies more than once, and

also did not change physical activity levels during the study, shows good compliance with the intervention.

This study was not without limitations. First, we did not perform assessments after participants were weight stable (and not in ketosis). However, the aims of the study were to address the impact of compensatory mechanisms achieved through a VLCD (ketogenic diet) on several compensatory mechanisms activated during weight reduction. Second, even though physical activity levels did not change during the intervention, our findings are limited by the and the fact that only 25 of the 46 participants had sufficient data on the armband at all 3 time points (baseline, 4 weeks, 8 weeks). Finally, it would have been interesting to see if there are differences in compensatory mechanisms between genders. However, since there were only 6 males (and 40 females) in the study, it was not possible to look at the potential impact of gender.

Future research

Further research is urgently needed in this area to determine the exact relationship between WL and compensatory mechanisms (RMR, exercise efficiency and subjective appetite), especially under ketosis. New studies should include a larger number of participants of all age categories, equally divided between genders to look at the potential effect of age and gender on compensatory mechanisms. Future studies should also include post-intervention measurements when participants are weight stable (and not in ketosis). This would give us much needed information regarding how to better achieve a successful weight-maintenance after WL, and how to address these challenges.

Conclusion

Losing a large amount of weight (16%) with a VLCD leads to the activation of compensatory mechanisms at the level of EE (reduction in RMR and increase in exercise efficiency). Even though a reduction in postprandial hunger and increase in fullness was observed, likely due to ketosis, a significant increase in fasting hunger was also found, suggesting that the appetite suppressive effect of ketosis may not be operative when the magnitude of WL is very large. Moreover, baseline BMI and magnitude of WL, but not age, seem to modulate the strength of several compensatory mechanisms.

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Attachment

Forespørsel om deltakelse i forskningsprosjektet

Hvordan holde vekten etter diettindusert vekttap?

Bakgrunn og hensikt

Dette er et spørsmål til deg om å delta i en forskningsstudie med utgangspunkt i en 8-ukers streng diett etterfulgt av ett års oppfølging med sikte på å stabilisere vekten. Forskerne har to hovedfokus i denne studien:

- Er de ulike oppfølgingsprogrammene like gode?
- Hvordan påvirkes hormonene som regulerer appetitt i diettens aktive fase?

Henvendelsen går til nyhenviste pasienter ved Obesitaspoliklinikken ved St. Olavs Hospital, og det er St. Olavs Hospital som er ansvarlig for studien.

Hva innebærer studien?

Studien er delt i to faser. Den første fasen er en 8-ukers diettperioden som vil være den samme for alle som deltar. En slik lavkalorikur kan gi noen bivirkninger (beskrevet senere). Når dietten er overstått vil du gå over i studiens andre fase som dreier seg om oppfølging med sikte på å opprettholde vekttapet.

Halvparten av pasientene vil få oppfølging i poliklinikken, mens den andre halvparten får oppfølging ved Røros Rehabilitering. Hvilken oppfølging du får er avhengig av hvor det er kapasitet for oppfølging på tidspunktet du inkluderes i studien. Oppfølgingen varer i ett år og du kan lese mer om den på neste side.

Undersøkelsene er stort sett de samme uansett hvilket oppfølgingsprogram du følger og innebærer for de aller fleste blodprøver, blodtrykk, målinger av energibehov, kroppsmasse og oksygenopptak, samt ulike former for spørreskjema.

Mulige fordeler, ulemper og bivirkninger
Fordelen med studiedeltakelse kan være at man går ned i vekt og oppnår bedre helse uten kirurgisk behandling. Deltakelse kan også gjøre at du blir bedre kjent med mekanismene i din egen kropp som påvirker appetitten. Dessuten vil du spare kostnader til mat i studiens diettfase (diettproduktene får du gratis ved sykehuset). Behandlingen anses ikke som risikabel. Undersøkelsene innebærer noen blodprøver.

Lavkalorikurer kan ha flere bivirkninger. Omfanget av disse varierer fra person til person og kan være enten helt fraværende eller temmelig plagsomme. Bivirkninger er forbigående. Rapporterte bivirkninger er:

- slapphet
- svimmelhet
- forstoppelse
- hårtap
- tørr hud
- neglene kan bli sprøere
- kvalme
- diaré
- forstyrret menstruasjonssyklus
- økt kuldefornemmelse

Hva skjer med prøvene og informasjonen om deg?
Prøvene tatt av deg og informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Alle opplysningene og prøvene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger og prøver gjennom en navneliste. Noen helseopplysninger vil også lagres i din pasientjournal, og disse vil være knyttet til ditt personnummer.

Det er kun autorisert personell knyttet til prosjektet som har adgang til navnelisten og som kan finne tilbake til deg. Det vil ikke være mulig å identifisere deg i resultatene av studien når disse publiseres.

Frivillig deltakelse
Det er frivillig å delta i studien. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke til å delta i studien. Dette vil ikke få konsekvenser for din videre behandling. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Om du nå sier ja til å delta, kan du senere trekke tilbake ditt samtykke uten at det påvirker din øvrige behandling. Dersom du senere ønsker å trekke deg eller har spørsmål til studien, kan du kontakte studiekoordinator Hege Bjøru, telefon 40 87 34 24.

Studien er godkjent av Regional komité for medisinsk og helsefaglig forskningsetikk REK Midt-Norge.

Ytterligere informasjon om studien finnes i kapittel *A* – *utdypende forklaring av hva studien innebærer.*
Ytterligere informasjon om personvern og forsikring finnes i kapittel B – *Personvern, biobank, økonomi og forsikring.*

Samtykkeerklæring følger etter kapittel B.

Kapittel A – Utdypende forklaring av hva studien innebærer

Kriterier for deltakelse
De som kan delta i denne studien må

1. ha BMI mellom 35 og 45 kg/m^2,
2. være mellom 18 og 65 år,
3. ha et ønske om å gå ned i vekt ved hjelp av diett,
4. være relativt vektstabile de siste tre måneder

Kvinner må dessuten enten være over menstruerende alder eller benytte p-piller.

Mange kan ha forsøkt dietter tidligere og du bør derfor tenke deg godt om hvorvidt dette er en behandling som er verdt å forsøke igjen. Hvis dette føles galt, så bør du ikke ta del i studien.

Bakgrunn for studien
Lavkaloridietter (< 800 kcal/dag) er en relativt sikker metode for å gå ned i vekt og gir også et raskt vekttap. Slike dietter kan gi vekttap i størrelse 10-15 % og med det også bedring i overvektsrelaterte sykdommer og risikofaktorer. Langtidseffektene er imidlertid usikre og særlige utfordringer er knyttet til opprettholdelse av vekttap på sikt. Det er behov for mer kunnskap om diettens vedlikeholdsfase, spesielt knyttet til tidspunktet man går over fra diettprodukter til mer normal, energiredusert kost.

Hovedhensikt med denne studien er å sammenligne opprettholdelse av vekttap etter 8-ukers lavkaloridiett hos pasienter som deltar i to ulike oppfølgingsprogram. Oppfølgingen varer i ett år.

Vi vil også se nærmere på hvordan den hormonelle appetittreguleringen endres i diettens aktive fase. Appetitten er et komplisert samspill av blant annet hormoner som både stimulerer og reduserer matlysten og vi vil følge utviklingen i disse i løpet av de ukene dietten varer. Det er hittil gjort lite forskning på dette.

Undersøkelser
Som del av studien vil du gjennomgå ulike undersøkelser.

- Veiing og kroppsmassemåling
- Blodtrykksmåling
- Blodprøver
    - Måling av appetitthormoner
    - Testing for kjente gener som disponerer for fedme
- Indirekte kalorimetri (måling av energibehov)
- Måling av oksygenopptak
- Spørreskjema

Undersøkelsene finner sted ved studiens start, ved avslutning av dietten, og ved avslutning av oppfølgingen (etter ett år).

Tidsskjema for diettperioden (8 uker) - felles for alle
Du vil få utdelt et variert utvalg av diettprodukter (milkshakes, smoothies, supper) tilsvarende et daglig energiinntak på 550 kcal (kvinner) og 660 kcal (menn). Du skal kun spise dette i diettens aktive fase (standardisert for alle), men du oppfordres til å drikke rikelig (minst 2,5 liter) vann og evt kalorifri drikke i tillegg. Du vil så få time hos en sykepleier i Obesitaspoliklinikken i studieuke 1, 2, 4, 6, og 8. Kostdagbok, veiing og urinprøver er del av denne fasen og bivirkninger rapporteres systematisk. I studieuke 8 får du time hos klinisk ernæringsfysiolog som vil foreskrive en ny diett av normalkost som du skal følge i året som kommer.

Tidsskjema for deltakere ved Røros Rehabilitering (1 år) - halvparten av deltakerne
For de som trekkes ut til å delta på Røros Rehabilitering, innebærer deltakelse tre opphold ved Røros. Hvert opphold varer i tre uker og gjøres unna i løpet av ett år. Oppholdene innebærer mye fysisk aktivitet, oppfølging av helsepersonell både individuelt og i grupper, samt matlaging i fellesskap. Mer informasjon og tidsplan for oppholdene vil bli distribuert senere.

Tidsskjema for deltakere ved Obesitaspoliklinikken (1 år) - halvparten av deltakerne
For de som trekkes ut til å delta i Obesitaspoliklinikkens program, innebærer det en individuell konsultasjon hos klinisk ernæringsfysiolog og senere gruppemøter med ulike helsepersonell. Gruppemøtene finner sted 3, 6, 9 og 12 mnd etter dietten og fokuserer mye på ernæring og fysisk aktivitet.

Studiedeltakerens ansvar
Det er studiedeltakerens ansvar å møte til avtalt tid. For de som deltar ved Røros Rehabilitering, må de påregne å være der gjennom hele treukersperiodene.

Kompensasjon og egenandel
Det gies ingen premiering for å delta i studien, men du vil få diettproduktene i diettens aktive fase gratis. Det er viktig å standardisere dietten slik at alle spiser det samme.

For deltakere ved Røros Rehabilitering vil fastlegen gi sykmelding for perioden oppholdene varer. NAV innvilger i de aller fleste kommunenes tilfelle også fritak for arbeidsgiverperioden, men det er også noen kommuner som ikke gjør dette pr i dag.

For deltakere ved Røros Rehabilitering vil det også tilkomme egenandel. Denne dekker behandling, kost og losji og betales inntil man når beløpsgrensen for Frikort 2. (Beløpsgrense fastsettes av myndighetene fra år til år.)

Kapittel B – Personvern, biobank, økonomi og forsikring

Personvern
Ulike opplysninger vil registreres om deg som del av dette prosjektet. Prøvesvar og innledende screeningnotat vil legges i din pasientjournal og er derfor personidentifiserbart. Opplysninger på bakgrunn av testene du gjennomgår og intervjuet vil lagres på sykehusets server og vil være avidentifiserte så lenge studien pågår (det vil si at et unikt ID-nummer erstatter navnet ditt). Kodenøkkelen som knytter navn til nummer makuleres når studien er slutt, slik at data da anonymiseres. Alle som jobber med data fra studien har taushetsplikt.

Vi vil benytte et internettbasert system for å samle spørreskjemadata. Dette betinger at du har tilgang til en datamaskin eller smartphone. Rapporteringssystemet krypterer dine svar slik at det ivaretar kravene til personvern.

St. Olavs Hospital ved administrerende direktør er databehandlingsansvarlig.

Biobank
Blodprøvene for analyser av appetitthormoner og mulige fedmegener som blir tatt vil bli lagret i en forskningsbiobank ved St. Olavs Hospital. Hvis du sier ja til å delta i studien, gir du også samtykke til at det biologiske materialet og analyseresultater inngår i biobanken. Overlege Bård Kulseng er ansvarshavende for forskningsbiobanken. Det biologiske materialet kan bare brukes etter godkjenning fra Regional komité for medisinsk og helsefaglig forskningsetikk (REK).

Rett til innsyn og sletting av opplysninger om deg og sletting av prøver
Hvis du sier ja til å delta i studien, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg. Du har videre rett til å få korrigert eventuelle feil i de opplysningene vi har registrert. Dersom du trekker deg fra studien, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner.

Økonomi
Studien finansieres over driften ved St. Olavs Hospital og Røros Rehabilitering. Diettproduktene for deltakerne er gitt av produsenten.

Forsikring
Studiedeltakerne omfattes av Norsk pasientskadeforsikring, jf. pasientskadelovens §1.

Informasjon om utfallet av studien

Publikasjoner på bakgrunn av studien vil bli lagt ut på vår hjemmeside, www.stolav.no/overvekt .

Samtykke til deltakelse i studien

Jeg er villig til å delta i studien

(Signert av prosjektdeltaker, dato)

Jeg bekrefter å ha gitt informasjon om studien

(Signert, rolle i studien, dato)