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Fructose content of low calorie diets: effect on cardiometabolic risk factors in obese women with polycystic ovarian syndrome: a randomized controlled trial

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Abstract

We aimed to examine whether a whole-grain crispbread (CB) low-fructose, low-calorie diet (LCD) might be superior to a traditional LCD based on fructose-rich liquid meal replacements (LMRs) with respect to improvement of various cardiometabolic risk factors and reproductive hormones. Parallel-group randomised controlled clinical trial. Morbidly obese women with polycystic ovarian syndrome (PCOS) were randomised to either an 8-week CB-LCD or LMR-LCD (900–1100 kcal/day, fructose 17 g/day or 85 g/day). A total of 51 women completed the study. Body weight, fat mass and waist circumference reduced by mean (S.D.) 10.0 (4.8) kg, 7.4 (4.2) kg and 8.5 (4.4) cm, with no significant differences between groups. Total-cholesterol, HDL-cholesterol and Apo-A1 were significantly reduced within both groups (all P values <0.01), with no significant between-group differences. The triacylglycerol and LDL-cholesterol levels were reduced within the LMR group only, with no significant between-group differences. Blood pressure and most measures of glucose metabolism improved significantly in both diet groups, with no significant between-group difference. Uric acid levels rose by 17.7 (46.4) and 30.6 (71.5) μmol/l in the CB and LMR group, respectively, with no significant difference between groups. Gastrointestinal discomfort was significantly and equally reduced in both intervention groups. Free testosterone index was reduced in both groups, with no significant difference between groups. Morbidly obese women with PCOS who underwent either an 8-week low or high-fructose LCD-diet had similar changes in various cardiometabolic risk factors and reproductive hormones. Registration at ClinicalTrials.gov: NCT00779571.

Key Words
- low calorie diets
- fructose
- obesity
- PCOS
- weight loss
- cardiometabolic risk-factors

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Introduction

Women with polycystic ovarian syndrome (PCOS) are often overweight and have a central fat distribution (1). It is well known that abdominal obesity is associated with insulin resistance, metabolic syndrome (MS) and increased risk of type 2 diabetes and coronary heart disease (CHD) (2, 3). Insulin resistance has been shown to occur more often among both obese and normal-weight women with PCOS than in a healthy population (4, 5).

A moderate weight reduction (5–10%) in obese women with PCOS reduces hyperandrogenism, normalizes menstrual function and improves fertility (6). Furthermore, weight reduction improves several components of MS such as high blood pressure (BP), dyslipidemia and dysglycemia (7, 8).

Few studies have, however, assessed the impact of weight reduction in morbidly obese women with PCOS. One study showed that bariatric surgery resulted in a significant reduction in insulin resistance expressed as the homeostatic model assessment (HOMA), improved reproductive functions such as ovulation and more regular menstrual periods, and had beneficial effects on hirsutism-score and endocrine parameters (9). Bariatric surgery is, however, a limited treatment option which can lead to severe complications; significant and clinical meaningful weight reduction (5–10%) can also be achieved through low-calorie diets (LCDs) based on meal replacements (10, 11). Several meal replacements contain significant amounts of mono- and disaccharides, and fructose is often added as a sweetening ingredient. Human studies and animal models have demonstrated that fructose increases serum uric acid levels (12, 13). A rise in uric acid levels inhibits nitric oxide availability (13). Because insulin requires nitric oxide to stimulate glucose uptake, hyperuricemia induced by fructose might have a pathogenic role in several features (hyperinsulinemia, hypertriglyceridemia, hypertension) of MS (13). Increased serum uric acid levels have additionally been associated with increased aortic stiffness in healthy adults (14). Accordingly, a high fructose intake may increase the risk of MS and CHD (12, 13, 14). In contrast, a diet with high fiber content has several health-promoting effects, as fiber intake is associated with a lower prevalence of cardiometabolic risk factors including MS, cardiovascular inflammation and obesity (15). Additionally, fiber intake improves gastrointestinal function and may prevent development of colorectal cancer (16). Fiber intake from whole-grain cereal products (e.g. bread, CB, muesli) has also been shown to be inversely associated with risk of development of type 2 diabetes (17, 18).

In view of this, we hypothesized that a low-fructose LCD might be superior to a high-fructose LCD in terms of improvement of various cardiometabolic risk factors after weight loss. The main objective of this study therefore was to compare the effects of a traditional LCD based on fructose-rich liquid meal replacement (LMR) and an iso-caloric LCD based on whole-grain crispbread (CB) on serum levels of triacylglycerol, HDL-cholesterol, LDL-cholesterol, glucose, uric acid and BP, in morbidly obese women with PCOS. Additionally, we compared the effects of the LCD-diets on the MS, body weight, body composition, gastrointestinal symptoms and hormonal characteristics of PCOS.

Subjects and methods

Study design, population and setting

Parallel-group randomised controlled clinical trial (allocation ratio 1:1) of 18–40 years old treatment seeking morbidly obese women (either BMI $\geq$40 or 35–40 kg/m^2 combined with at least one weight-related co-morbidity) (19) with PCOS diagnosed according to the Rotterdam Consensus Workshop Group Criteria (20). Participants were recruited from three public tertiary care outpatient centres in southeast Norway. Inclusion started October 2008 and last participant completed March 2011.

This paper reports the results of the first phase (8 weeks) of 'The Female Health Dietary Intervention study – The FEMIN study' (ClinicalTrials.gov Identifier NCT00779571). The study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects were approved by the Regional Ethics Committee for Medical Research in South East Norway. All participants gave written informed consent before enrolment.

Interventions

After enrolment, participants were randomized to follow an LCD (<1100 kcal/day) for 8 weeks, either an LMR- or a CB-diet, respectively. The former was based on flavoured meal replacement shakes (n=8/day, Nutrilett, Contract Foods Ltd, Redditch, Worcestershire, UK for Axellus AS, Oslo, Norway) with main ingredients soy protein, fructose (~9 g/shake) and soy fibres. Additionally, an unlimited intake of selected vegetables low in fibre (e.g. salads, cucumber, tomatoes, onions), <150 g root vegetables (e.g. carrots, cabbage, kohlrabi, broccoli, cauliflower) and

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one fruit (5–10 g fructose) per day were allowed. Fructose content of the LMR-diet was ~85 g/day (~72 g from the LMR, ~7 g in one 150 g fruit and ~6 g in 150 g root vegetables plus 350 g tomatoes, salad and other low-fibre vegetables together). The women were encouraged to drink >2 l of water or other energy-free liquids daily in addition to the shakes.

The CB-diet was based on whole grain CB (provided by Wasa, Ideal Wasa AS) combined with low-fat, high-protein products for three of four daily meals. The CB-diet contained ~17 g fructose per day (~7 g in one 150 g fruit, ~10 g in 850 g vegetables). Dinner consisted of a specified amount of fish, poultry or lean meat combined with vegetables, potatoes, rice or pasta. Participants were instructed to drink >1.5 l of water or other energy-free liquid per day. Supplement of one daily multivitamin and mineral pill was recommended (Collett Kostpluss, Axellus Oslo, Oslo, Norway). Additionally, participants could eat an unlimited amount of vegetables and one fruit per day. Estimated macronutrient intakes from fat, protein, total carbohydrate and fructose are shown in Table 1. To strengthen motivation, answer possible questions and ensure dietary compliance, a registered dietician or a study nurse had weekly telephone contact with all participants.

Outcomes

The main outcomes were the 8-week changes in blood lipids, glucose metabolism, BP and uric acid concentrations. In addition, we assessed changes in the prevalence of MS, body weight, body composition, gastrointestinal symptoms and hormonal characteristics of PCOS.

Table 1 Estimated percentage energy content in the crispbread and the liquid meal replacement diet.

Nutrient	Crispbread	Liquid meal replacement
Energy (kJ)	4576	4502
(kcal)	1095	1072
Protein (g)	92.5	101
(E%)	33.8	37.7
Fat (g)	24.1	21.2
(E%)	19.8	17.8
Carbohydrate (g)	123.9	117.4
(E%)	45.3	43.8
Fructose, total (g)	17.0	85.0
in fruit/vegetables (g)	17.0	13.0
in LMR (g)		72.0
(E %)	6.2	32
Added sugar (g)	1.3	77
(E%)	0.5	29
Fibre (g)	34.4	45.5

Physical examinations

All measures were performed after an overnight fast. Weight and height were measured with patients wearing light clothes but no shoes and BMI was calculated. Body composition was measured by bioelectrical impedance using Tanita Body Composition Analyzer, BC 418 MA, Tanita Corporation, Tokyo, Japan. Waist, hip and neck circumference were measured to the nearest cm with a soft tape. Waist and hip circumference were measured with the patients standing, at the midpoint between the iliac crest and the lowest rib, and at the level of the major trochanter, respectively.

BP was measured three times with patients sitting in an upright position after at least 5 min of rest using an electronic ausculatory BP recorder (Dinamap ProCare Series, G.E. Medical Systems, WI, USA). The average of the second and third measurement was recorded.

The degree of hirsutism was self-reported using Ferriman–Gallway score (21). The gastro-intestinal symptom rating scale (GSRS) was used to assess gastrointestinal discomfort (22).

Biochemical measurements

Blood samples were obtained after an overnight fast by venipuncture in vacutainer gel tubes with EDTA and NA citrate (serum was separated from cells within 2 h). The samples were analysed at accredited laboratories at Oslo University Hospital and Vestfold Hospital Trust as is described in detail below.

C-peptide, insulin and insulin-like growth factor 1 (IGF1) were analysed by enzymatic chemiluminescence, immunometric method using Immulit 2000 (Siemens AG, Erlangen Germany) at Oslo University Hospital Rikshospitalet (Oslo, Norway). Prolactin, sexual hormone binding globuline (SHBG), estradiol, testosterone, progesterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyroid-stimulating hormone (TSH) and free thyroxine (free T_4) were analysed with quantitative electrochemiluminescence method (ELICIA) using Modular E 170 (Diamond Diagnostics, Holliston, MA, USA) at Oslo University Hospital Rikshospitalet. At Vestfold Hospital Trust, FSH, LH, TSH and free T_4 were measured using a chemiluminescent microparticle immunoassay (CMIA) technology assayed on Architect i2000SR (Abbot Diagnostica). Androstendione was analysed with quantitative electrochemiluminescence method (ELICIA) using Modular E 170 (Diamond Diagnostics) at Oslo University Hospital Aker. In ovulatory women, the gonadotropins

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and steroid hormones were analysed in the early follicular phase (cycle day 2–3), while in anovulatory women the analyses were performed randomly. Apo-A1, Apo-B and C-reactive protein (CRP) were analysed by an immunturbidimetric method using Modular P800 (Diamond Diagnostics) at Oslo University Hospital Rikshospitalet, whereas CRP was analysed using a dry reagent slide technology on Vitros FS 5.1 (Ortho-Clinical Diagnostics, New York, USA) at Vestfold Hospital Trust. HbA1c was analysed by an immunturbidimetric method using Modular P800 (Diamond Diagnostics) at Oslo University Hospital Rikshospitalet or by HPLC using Tosoh HLC-723 G (Tosoh Corporation, Tokyo, Japan) at Vestfold Hospital Trust. Serum glucose, uric acid and blood lipids (total, LDL- and HDL-cholesterol and triglycerides) were analysed using spectrophotometric method using Modular P800 (Diamond Diagnostics) at Oslo University Hospital Rikshospitalet or with dry reagent slide technology on Vitros FS 5.1 (Ortho-Clinical Diagnostics) at Vestfold Hospital Trust. Fibrinogen was analysed by Clauss clotting method using STA-R-Evolution (Diagnostica Stago S.A.S., Paris, France). All measurements from the same participant (before and after intervention) were analysed at the same laboratory. We did not find any significant differences in the baseline biochemical measurements analysed in different laboratories (FSH, LH, TSH, free T_4, CRP, HbA1c, glucose, uric acid, total, LDL- and HDL-cholesterol and triglycerides). Comparison of analyses between laboratories, coefficients of variation and limits of detection are given in the Supplementary Tables 1, 2 and 3, see section on supplementary data given at the end of this article.

The HOMA-insulin resistance (HOMA-IR) was calculated as (fasting serum glucose (mmol/l)×fasting serum insulin (pmol/l)) (23). The free testosterone index (FTI) (testosterone/SHBG×10) was used as a surrogate estimate of free testosterone (20). Participants were categorised as having the MS if they had ≥3 of the following risk factors (24): waist circumference ≥80 cm, fasting triacylglycerols ≥1.7 mmol/l, fasting HDL-cholesterol <1.3 mmol/l, BP ≥130/≥85 mmHg or use of BP-lowering medication, glucose-lowering medication or if fasting glucose ≥5.6 mmol/l or 2-h glucose ≥7.8 mmol/l.

Sample size

We assumed that the LMR and CB diets would be associated with a mean (S.D.) 8-week decline in triacylglycerol (primary outcome) of 0.3 (0.5) and 0.6 (0.5) mmol/l, respectively (25). At least 90 patients had to complete the study in order to attain a power of more than 80% (α=0.05) to reveal this possible difference.

Randomization, allocation and implementation

Participants were randomized in blocks of six (three participants to each group). Sealed pre-numbered containers were opened by the research secretary. Group allocation was revealed to participant and staff member (registered dietician or study nurse) after all baseline examinations and measures were completed.

Statistical analyses

Data are given as means and S.D.s, mean (95% CI) or proportion (%) unless stated otherwise. The primary analyses were based on the originally allocated groups including completers only. In addition, we performed sensitivity analyses of the primary outcomes based on actual treatment group (as treated) and an intention-to-treat analysis (first observation carried forward). Differences between groups were analysed using independent samples *t*-test for continuous data and Fisher's exact test for categorical data. Within-group changes were assessed with paired samples *t*-test or McNemar test. Between-groups differences in outcome variables were assessed using analysis of covariance (ANCOVA), with adjustment for age and baseline value of the dependent variable. Standardised effect sizes (Cohen's d) were calculated for differences in primary outcome variables. A 5% statistical significance level was used. Particular attention should, however, be directed towards smaller *P* values, i.e. those below 0.01, because a considerable number of *P* values have been calculated. All analyses were performed using SPSS 16.0 (SPSS, Inc.).

Results

Of the 106 morbidly obese European white women assessed for eligibility, 61 were included and randomised to either diet. A total of 31 and 30 patients were allocated to the LMR and CB diet, respectively. Four participants in the LMR group switched to the CB group during the first 2 weeks but were assessed according to their originally allocated group (LMR). Two out of these four patients completed the diet period while two withdrew. A total of ten participants withdrew (seven in LMR group and three in CB group), leaving 51 completers for analysis (Fig. 1).

The withdrawal rate did not differ significantly between groups (23% vs 10%, P=0.301).

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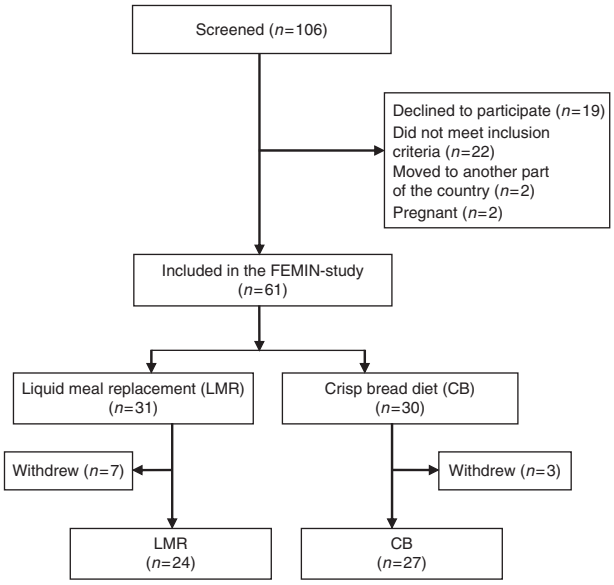

Figure 1
Participant flow. Four participants switched from the liquid meal replacement (LMR) to the crispbread (CB) diet during the first 2 weeks. These four patients were categorised to their originally allocated group (LMR). All results are based on a modified intention-to-treat analysis.

At baseline, the 51 completers had a mean (S.D.) age, BMI and waist circumference (WC) of 29.0 (5.9) years, 43.5 (5.7) kg/m^2 and 125 (11) cm, respectively, and the prevalence of MS was 73%. Baseline characteristics according to treatment group are shown in Table 2.

Changes in lipids and BP

The levels of total cholesterol, HDL-cholesterol and Apo-A1 were significantly reduced within both groups, with no significant between-group differences (Table 3). The triacylglycerol and LDL-cholesterol levels were reduced within the LMR group only, with no significant between-group differences. Further, the groups did not differ significantly with respect to changes in apolipoprotein levels or ratios (Table 3). BP improved within both groups, with no significant between-group differences. With the exception of HDL-cholesterol, the standardised effect sizes (Cohen's d) indicated either small or trivial differences in the lipid- and blood-pressure-lowering effects of the two diets (Supplementary Table 4, see section on supplementary data given at the end of this article).

Glucose metabolism, uric acid and MS

Most measures of glucose metabolism improved after weight reduction, with no significant between-group differences (Table 3). Fasting uric acid increased significantly in the LMR group only, with no significant between-group difference. The standardised effect sizes (Cohen's d) indicated either small or trivial differences in the effects of the two diets on serum glucose, HbA1c and uric acid (Supplementary Table 4).

The prevalence of MS was reduced from 63 to 44% in the CB group and from 83 to 67% in the LMR group ($P=0.125$ and $P=0.219$), with no significant between-group difference (Fig. 2).

Two supplementary sensitivity analyses of the between-group differences in total, HDL- and LDL-cholesterol, trigacylglycerol, systolic and diastolic BP, fasting glucose, HbA1c and uric acid based on either actual treatment group (as treated) or first observation carried forward (intention to treat) revealed similar results (data not shown).

Changes in anthropometric measures and body composition

The patients lost ~10 kg body weight during the study. As shown in Fig. 3, more than 80% of the completers lost ≥5% of their body weight, whereas 33% of the patients in the CB group and 50% of those in the LMR group lost ≥10% after 8 weeks, respectively ($P=0.265$). There were no differential effects of the two LCD diets on changes in body weight, waist circumference, fat-free mass or fat mass (Table 3).

Gastrointestinal responses and reproductive hormones

The GSRS-score was significantly reduced in both groups, with no significant between-group difference (Table 3). SHBG and progesterone levels increased, whereas the testosterone levels and FTI decreased significantly within the CB group but not in the LMR group (Table 3). However, no significant differences were observed between groups in the changes of reproductive hormones (Table 3).

Discussion

The results of this 8-week randomized controlled study did not confirm our hypothesis that a low-fructose (17 g) CB LCD was superior to a high-fructose (85 g) LMR LCD with respect to improvement of cardiometabolic risk factors in morbidly obese women with PCOS. There were no substantial differences between groups in terms of changes in waist circumference, blood lipids, BP, glucose

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Table 2 Baseline characteristics of the 51 women who completed the 8-week crispbread or liquid meal replacement diet.

Clinical and biochemical characteristics	Crispbread diet	Liquid meal replacement diet	*P*
Age (years)	29.0 (5.6)	29.0 (6.3)	0.980
Body weight (kg)	124.1 (17.8)	121.5 (16.5)	0.587
BMI (kg/m^2)	44.0 (5.8)	43.0 (5.6)	0.535
Waist circumference (cm)	126 (11)	124 (11)	0.526
Hip circumference (cm)	135 (12)	133 (9)	0.531
Neck circumference (cm)	41 (3)	41 (3)	0.655
Fat mass (kg)	61.8 (12.6)	60.7 (11.2)	0.747
Fat free mass (kg)	62.3 (6.5)	60.8 (6.8)	0.411
Diabetes (*n* (%))	4 (16)	6 (25)	0.496
Hypertension (*n* (%))	13 (48)	14 (58)	0.577
Metabolic syndrome (*n* (%))	17 (63)	20 (83)	0.127
Glucose metabolism			
Glucose (mmol/l)	5.3 (1.0)	5.3 (1.0)	0.991
HbA1c (%)	5.6 (0.4)	5.6 (0.6)	0.758
HOMA-IR	5.5 (4.6)	5.7 (3.2)	0.852
Insulin (pmol/l)[a]	129 (76)	142 (70)	0.537
C-peptide (nmol/l)[a]	1.3 (0.5)	1.4 (0.5)	0.478
Lipid metabolism and blood pressure			
Total-cholesterol (mmol/l)	5.1 (0.9)	5.0 (0.9)	0.511
HDL-cholesterol (mmol/l)	1.1 (0.3)	1.1 (0.2)	0.837
LDL-cholesterol (mmol/l)	3.3 (0.7)	3.1 (0.7)	0.255
Triacylglycerol (mmol/l)	1.6 (1.0)	1.7 (0.8)	0.583
Apolipoprotein-A1 (g/l)[b]	1.4 (0.2)	1.4 (0.3)	0.931
Apolipoprotein-B (g/l)[b]	0.9 (0.2)	0.9 (0.3)	0.879
Apo-B/Apo-A1-ratio[b]	0.70 (0.18)	0.70 (0.26)	0.981
LDL-cholesterol/Apo-B-ratio[b]	1.38 (0.20)	1.32 (0.19)	0.350
Systolic BP (mmHg)	127 (15)	130 (12)	0.375
Diastolic BP (mmHg)	79 (13)	79 (12)	0.961
Reproductive measures			
Prolactin (mIU/l)[c]	199 (61)	235 (78)	0.114
Sexual hormone binding globuline (SHBG) (nmol/l)	28.1 (11.2)	27.6 (14.4)	0.892
Estradiol (nmol/l)[d]	0.2 (0.1)	0.2 (0.1)	0.703
Testosterone (nmol/l)	2.1 (1.0)	1.9 (1.0)	0.362
Free testosterone index (FTI)	0.9 (0.6)	0.8 (0.4)	0.536
Follicle-stimulating hormone (FSH) (U/l)	6.3 (2.0)	4.9 (2.9)	0.024
Luteinizing hormone (LH) (U/l)	9.1 (3.3)	6.5 (5.0)	0.027
Progesterone (nmol/l)[d]	1.4 (1.0)	3.4 (7.2)	0.216
Androstendione (nmol/l)	5.5 (2.9)	5.2 (3.4)	0.782
Hirsutism (score)	17 (7)	14 (5)	0.066
Other measures			
Uric acid (μmol/l)	358 (75)	375 (74)	0.421
IGF1 (nmol/l)[e]	16.5 (6.4)	19.7 (9.3)	0.258
CRP (mg/l)	6.8 (7.4)	10.9 (10.2)	0.103
Fibrinogen (g/l)[a]	3.8 (0.7)	4.0 (0.8)	0.451
TSH (mU/l)[d]	2.3 (1.6)	2.3 (1.0)	0.961
Free T_4 (pmol/l)[d]	14.2 (1.6)	13.9 (1.1)	0.563
Gastrointestinal symptom rating scale (GSRS)	36 (13)	32 (10)	0.284

Mean values (s.d.) or *n* (%). Independent samples *t*-test or Fisher's exact test as appropriate.
[a]*n*=50.
[b]*n*=44.
[c]*n*=39.
[d]*n*=38.
[e]*n*=33.

metabolism or uric acid levels. Further, the two diet groups did not differ significantly with respect to amount of weight loss and changes in body composition, gastrointestinal symptoms and reproductive hormone concentrations.

Lipids and glucose

Our results partly confirmed the well-known association between weight loss and favourable changes in total cholesterol, LDL-cholesterol and triacylglycerol levels

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Table 3 Changes in various outcomes in the 51 women who completed the 8-week crispbread or liquid meal replacement diet.

Clinical and biochemical characteristics	Crispbread ($n=27$)	P^a	Liquid meal replacement ($n=24$)	P^a	Adjusted difference between groups (CB-LMR)	P^b
Body weight (kg)	−9.6 (4.9)	<0.001	−10.4 (4.8)	<0.001	1.0 (−1.7, 3.6)	0.480
BMI (kg/m^2)	−3.4 (1.7)	<0.001	−3.7 (1.7)	<0.001	0.3 (−0.6, 1.2)	0.529
Waist circumference (cm)	−8.7 (4.4)	<0.001	−8.2 (4.6)	<0.001	−0.4 (−3.0, 2.2)	0.766
Hip circumference (cm)	−5.9 (3.7)	<0.001	−6.5 (4.9)	<0.001	0.6 (−1.7, 3.0)	0.594
Neck circumference (cm)	−1.4 (1.4)	<0.001	−2.2 (1.2)	<0.001	0.7 (0.1, 1.3)	0.029
Fat mass (kg)	−7.0 (4.4)	<0.001	−7.8 (4.1)	<0.001	1.0 (−1.4, 3.3)	0.421
Fat free mass (kg)	−2.7 (1.8)	<0.001	−2.6 (1.8)	<0.001	0.1 (−0.9, 1.0)	0.902
Glucose metabolism						
Glucose (mmol/l)	−0.33 (0.98)	0.093	−0.35 (0.68)	0.020	0.0 (−0.2, 0.3)	0.874
HbA1c (%)	−0.24 (0.32)	0.001	−0.26 (0.37)	0.002	0.0 (−0.1. 0.1)	0.989
HOMA-IR	−2.0 (3.0)	0.003	−2.3 (2.6)	<0.001	0.3 (−0.8, 1.4)	0.545
Insulin (pmol/l)	−37 (51)	0.001	−54 (58)	<0.001	12 (−14, 38)	0.371
C-peptide (nmol/l)	−0.2 (0.3)	0.005	−0.3 (0.3)	0.001	0.1 (−0.1, 0.2)	0.560
Lipid metabolism and blood pressure						
Total-cholesterol (mmol/l)	−0.4 (0.7)	0.008	−0.6 (0.6)	<0.001	0.2 (−0.1, 0.6)	0.228
HDL-cholesterol (mmol/l)	−0.2 (0.2)	0.001	−0.1 (0.1)	<0.001	0.0 (−0.1, 0.2)	0.065
LDL-cholesterol (mmol/l)	−0.2 (0.6)	0.075	−0.4 (0.5)	0.001	0.2 (−0.1, 0.5)	0.113
Triacylglycerol (mmol/l)	−0.2 (0.4)	0.068	−0.3 (0.5)	0.028	0.1 (−0.2, 0.3)	0.524
Apolipoprotein-A1 (g/l)	−0.23 (0.18)	<0.001	−0.25 (0.25)	0.001	0.0 (−0.1, 0.1)	0.710
Apolipoprotein-B (g/l)	−0.05 (0.17)	0.156	−0.14 (0.18)	0.006	0.1 (0.0, 0.2)	0.045
Apo-B/Apo-A1-ratio	0.10 (0.16)	0.008	0.02 (0.20)	0.645	0.1 (0.0, 0.2)	0.105
LDL-cholesterol/Apo-B-ratio	−0.01 (0.18)	0.767	−0.02 (0.17)	0.676	0.5 (−0.0, 1.1)	0.270
Systolic blood pressure (mmHg)	−7.6 (15.3)	0.018	−8.2 (12.7)	0.004	−1.6 (−7.5, 4.3)	0.582
Diastolic blood pressure (mmHg)	−4.4 (9.4)	0.024	−4.1 (8.0)	0.020	−0.1 (−4.3, 4.1)	0.953
Reproductive measures						
Prolactin (mIU/l)	2.5 (71)	0.880	−4.8 (67)	0.767	−6.1 (−48.9, 36.7)	0.774
Sexual hormone binding globuline (SHBG) (nmol/l)	4.5 (8.2)	0.009	2.1 (8.6)	0.278	2.5 (−2.1, 7.2)	0.283
Estradiol (nmol/l)	0.1 (0.3)	0.077	0.1 (0.2)	0.171	0.4 (−0.1, 0.2)	0.609
Testosterone (nmol/l)	−0.3 (0.6)	0.014	−0.2 (0.8)	0.313	−0.0 (−0.4, 0.3)	0.885
Free testosterone index (FTI)	−0.2 (0.5)	0.033	−0.2 (0.3)	0.072	−0.0 (−0.2, 0.2)	0.730
Follicle-stimulating hormone (FSH) (U/l)	−0.8 (2.6)	0.130	0.2 (2.4)	0.738	0.0 (−1.2, 1.3)	0.993
Luteinizing hormone (LH) (U/l)	0.7 (8.4)	0.664	0.9 (3.5)	0.201	1.6 (−2.0, 5.1)	0.370
Progesterone (nmol/l)	4.2 (8.6)	0.047	2.0 (11.7)	0.477	0.2 (−6.1, 6.5)	0.957
Androstendion (nmol/l)	−0.2 (2.6)	0.746	0.7 (3.4)	0.319	−0.8 (−2.3, 0.6)	0.258
Hirsutism (score)	−0.7 (3.3)	0.320	−0.3 (3.0)	0.633	0.4 (−1.3, 2.1)	0.662
Other measures						
Uric acid (μmol/l)	17.7 (46.4)	0.058	30.6 (71.5)	0.047	−15.6 (−49.3, 18.2)	0.358
IGF1 (nmol/l)	4.4 (6.1)	0.014	5.7 (6.8)	0.004	−1.4 (−6.3, 3.5)	0.557
CRP (mg/l)	−0.6 (3.8)	0.411	−3.2 (5.7)	0.011	1.3 (−1.1, 3.6)	0.278
Fibrinogen (g/l)	0.11 (0.47)	0.245	−0.02 (0.33)	0.800	0.1 (−0.1, 0.3)	0.275
TSH (mU/l)	−0.7 (1.2)	0.021	−0.3 (0.9)	0.176	−0.5 (−0.9, −0.1)	0.020
Free T_4 (pmol/l)	0.5 (1.3)	0.106	0.4 (1.3)	0.163	0.1 (−0.9, 1.0)	0.919
Gastrointestinal symptom rating scale (GSRS)	−7.8 (8.2)	<0.001	−4.0 (7.8)	0.025	−2.6 (−6.6, 1.4)	0.198

Unadjusted within-group differences are given as mean (s.d.).
[a]Paired samples *t*-test.
[b]Adjusted between-groups differences and corresponding *P* values are calculated with ANCOVA and presented as mean (95% CI). Between-group differences are adjusted for age and baseline values.

(26), with comparable effects between groups. In contrast, the LDL-cholesterol/apoB ratio, which may reflect the LDL particle size, remained unchanged in both treatment groups (Table 3). Previous studies have indicated that weight reduction is associated with favourable changes in LDL particle size (27, 28). Study participants in these studies were however not similar to the women included in our study, and the results may therefore not be comparable. As has also been noted in other studies, HDL-cholesterol decreased significantly in both groups after the relatively rapid weight loss (29, 30). Surprisingly, the patients in the LMR group had a slightly, although

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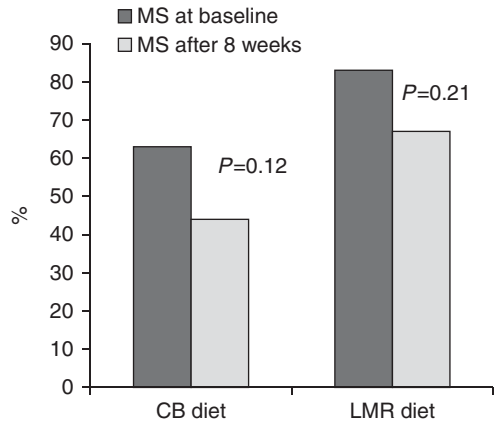

Figure 2
Prevalence of metabolic syndrome (MS) in the two diet groups at baseline and after 8 weeks. *Y*-axis indicates prevalence of MS (%). Dark grey bars indicate prevalence of MS at baseline and light grey bars indicate prevalence of MS after 8 weeks. *P* values are for comparison of prevalence of MS before and after intervention within each diet group (McNemar test).

non-significant ($P=0.065$), lower decline in HDL-cholesterol. A high fructose intake is associated with hyperuricemia, hypertension, diabetes, dyslipidemia, MS and CHD (12, 13, 14, 31). As the LMR contained significant amounts of the monosaccharide fructose, we anticipated that the LMR diet would result in a less beneficial or, even worse, metabolic risk profile compared to the CB diet. Further, obese women with PCOS often have severe insulin resistance (32). We therefore found the marked reduction in glucose, HOMA-IR and insulin in both the high- and low-fructose diets of particular interest. However, as there were significant and similar positive effects of both diets on several markers of the MS (including lipids, glucose and BP), one might speculate that the marked weight reduction itself could hide possible adverse metabolic effects of fructose. The lack of differences between diet groups might, however, also be explained by a too short observation time or lack of adherence to the diets.

Uric acid

Although weight reduction is usually associated with declining serum uric acid, the mean uric acid levels rose in both groups in the present study. This is in accordance with some previous studies, where uric acid levels rose after 12–117 days of fasting and after the first 4–6 weeks of rapid weight loss following sleeve gastrectomy (33, 34).

Gastrointestinal symptoms

Severely obese patients suffer from more gastrointestinal disorders (gastritis, vomiting and diarrhea) than normal-weight persons (35, 36), and weight loss is known to alleviate gastrointestinal symptoms (37). We hypothesized that the CB diet with a high level of dietary fiber from whole-grain products would have a more positive effect on gastrointestinal function that the LMR diet supplemented with soy fiber. However, after 8 weeks of LCD, participants in both diet groups had significantly less gastrointestinal discomforts. The improvements were mainly explained by less upper abdominal discomfort (reflux/dyspepsia). This might be explained by the significant and similar reduction in weight and waist circumference in both groups (37).

Reproductive variables

It is well documented that treatment of obesity is important for the management of PCOS (38) and that weight loss improves abnormal reproductive measures (39, 40). Our results are in accordance with previous findings that LCDs reduce levels of free testosterone (FTI) and increase SHBG. Weight reduction may reduce the adverse effect of androgens on developing follicles by lowering both leptin-induced LH secretion and insulin-driven androgen synthesis in the ovary (41, 42). However, we found no significant differences in the changes in reproductive measures between the two LCD groups. This is in accordance with a recent review that weight loss through calorie restriction improved the presentation of PCOS regardless of dietary composition (43).

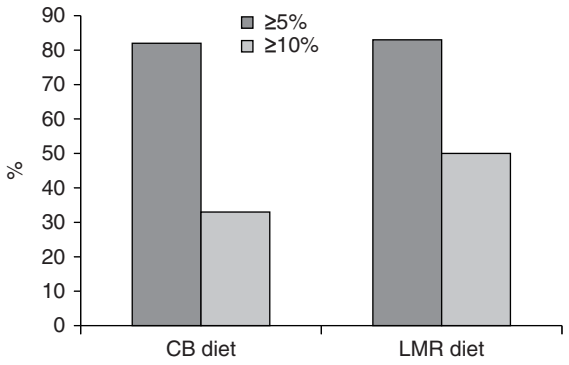

Figure 3
Participants with weight loss ≥5 and ≥10% after 8 weeks in the two diet groups. *Y*-axis indicates percentage of subjects. Dark grey bars indicate weight loss ≥5% and light grey bars indicate weight loss ≥10%.

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Clinical aspects

The sweet taste, the whiff of soy protein and the consistency of the LMR shakes caused nausea and aversion in four women who subsequently switched from LMR diet to CB diet a few days after intervention start. This is in accordance with our clinical experience, which indicates that more patients succeed in implementing the CB diet as compared to the LMR diet. Although both LCD diets have similar positive effects on weight and metabolic risk factors, better practicability and lower cost favour the CB diet.

Study limitations

The strength of our study includes the prospective randomized controlled trial design with a low risk of bias and high internal validity. The study also has limitations. Two different laboratories performed the biochemical analyses. Although no significant differences were found between laboratory results, this may limit the validity of the results.

The participants did not perform dietary records. Therefore, the actual intake of nutrients may diverge from the estimated in Table 1. One could also question whether the difference in daily fructose intake (68 g) between groups was sufficiently high to demonstrate any possible effect on cardiovascular risk factors. Further, the final sample size, and accordingly power, was lower (57 and 65% in the main analysis and the intention to treat (ITT) analysis, respectively) than was planned in the original protocol. However, supplementary sensitivity analyses revealed similar results, and the standardised effect sizes (Cohen's d) were either small or trivial regarding possible differences in beneficial cardiometabolic effects of the two diets.

Conclusion

Both LCDs (LMR and CB) were associated with significant improvements in several cardiometabolic risk factors and reproductive hormones in morbidly obese Caucasian women with PCOS. No significant differences in the effects of the two LCD diets on metabolic or reproductive variables were demonstrated.

Supplementary data

This is linked to the online version of the paper at http://dx.doi.org/10.1530/EC-15-0047.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

L K Johnson, T Tanbo, K B Holven and J Hjelmesæth designed the research, and L K Johnson conducted the research; J R Mellembakken examined the 14 patients from Oslo University Hospital, Rikshospitalet; L K Johnson performed statistical analyses; L K Johnson and J Hjelmesæth analyzed the data; L K Johnson and J Hjelmesæth wrote the paper; J Hjelmesæth had primary responsibility for final content. All authors helped to interpret the data, revise the manuscript and approve the final version.

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