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ORIGINAL ARTICLE

Results from a randomized controlled trial comparing two low-calorie diet formulae

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Summary
Background: Very low and low-calorie diets ((V)LCD) are commonly used in the early phase of obesity treatment programmes. Recently, a new formula, Allévo®, was introduced in Scandinavia. No study has hitherto assessed its efficacy compared to the commonly used (V)LCD Nutrilett®.
Objective: To compare Allévo® with Nutrilett® regarding short-term effects on weight and BMI loss, ketonaemia, compliance, and body composition.
Design: Thirty-six males (baseline: age 46.5 ± 10.9 year; BMI 39.2 ± 3.8 kg/m^2; %BF 38.8 ± 3.9%) participated in a randomized trial comparing two LCDs, differing mainly in protein and dietary fibre composition. Body composition was measured by DXA at baseline and end, while body weight was measured weekly during the 8-week (V) LCD-intervention. The main outcome measures were weight, BMI, waist-circumference (WC), and body fat percentage (%BF).
Results: No significant differences between groups in age, weight, blood pressure, or %BF were observed at baseline (all $p > 0.3$). The mean BMI change over the study period was −4.4 ± 0.3 and −4.2 ± 1.9 kg/m^2 for Nutrilett® and Allévo®, respectively ($p = 0.72$), while WC was reduced by 9.6 ± 1.0 and 10.1 ± 3.2 cm, respectively ($p = 0.51$). About 49% of the weight loss consisted of fat. When examining the weight development during the intervention, with the eight repeated measures, no significant difference in the slope of the weight loss curve could be detected ($p = 0.50$—0.65). Ketonaemia developed similarly in both groups, and did not correlate to weight loss.
Conclusion: Allévo® and Nutrilett® appear to have equivalent efficacy regarding weight, BMI, WC, and %BF loss in short-term interventions.

Introduction

Very low and low-calorie diets ((V)LCDs) constitute an established tool in the treatment of obesity.

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The European task force SCOOP has extensively summarized the role of (V)LCDs in obesity therapy recently, and has raised the recommended energy level to 800 kcal/day [1]. Safety and absence of any advantage at lower energy levels were the main reasons for this recommendation. Often these products are called VLED, substituting calorie for energy; in this paper, we adhere to the SCOOP terminology and refer to these products as (V)LCDs. They are safe and effective, since they provide a balanced hypocaloric diet with sufficient amounts of necessary vitamins, minerals and trace elements [2]. Most of their energy content, today typically up to 1000 kcal/day, is provided by proteins. There seems, however, to be little benefit in (V)LCDs with an energy content of less than 800 kcal/day. The reason for their effect depends on the fact that they induce a marked negative energy balance but also that the ensuing ketogenesis may facilitate adherence to the program, since it seems to induce satiety [3]. After the 1st day of adaptation to a (V)LCD, subjects manage surprisingly well with little hunger or nausea [4–7]. The role of ketones in weight loss and appetite suppression is not firmly established by proper scientific methods, although some studies suggest that administration of 3-betahydroxybutyrate prevented hunger feelings [8]. As always, (V)LCDs as the sole source of energy are only effective to induce weight loss in the short term, and need to be followed by long-term treatment strategies [7], otherwise relapse is largely inevitable.

We have used (V)LCDs for decades to break patients' vicious circles in the clinic, such as treatment of obesity-mediated sleep apnea, polycystic ovary syndrome, orthopedic complications of weight bearing joints, pre-operative improvement of metabolism, etc. [4,6,9]. Although Franklin and Summerbell [2] in their textbook chapter state the need for close medical supervision, our experience has been that with proper selection and qualified nurse supervision, the need for further medical surveillance is minimal.

Over the years, various (V)LCD-formulae have been used in Sweden, mainly resulting in similar clinical outcome. The foreseen shift from Nutrilett® to Allévo® prompted the comparison presented in this article, which includes change in body composition, compliance, the effects of ketonaemia on short-term weight loss outcome, and the application of a more advanced statistical model to detect small differences in BMI change.

Subjects and methods

Data were collected from participants in a randomized intervention study evaluating two different (V)LCD-formulae. The subjects were recruited from our waiting list for patients, for whom initial (V)LCD was considered an adequate clinical approach. Most patients were awaiting weight loss treatment as a start for their sleep apnoea therapy. The number of obese men who were screened prior to randomization was 38. During screening, five men did not complete dual X-ray absorptiometry (DXA) measurement for various reasons, and two of these dropped out, resulting in complete data from 33 men at baseline for DXA, while data on weight, height, blood pressure, ketonaemia, and waist-circumference were available for the 36 patients before and after treatment.

Patients were randomly allocated to either treatment, 7–8 sachets per day, spread over the hours to fit optimally with their working schedule and convenience. Allévo® is based on milk and soy protein, Nutrilett® on soy protein only. The fibre composition of the products is also markedly different: Nutrilett® contains 3.5 g soy fibre/sachet, Allévo® 4 g/sachet of beta-glucans plus cikoria root (inulin). However, both diets provide adequate g of fibre to meet daily requirements. Each Allévo® sachet (several tastes) contained 109–119 kcal, each Nutrilett® sachet (one taste only) 112 kcal each. The content of the two formulae are shown in Supplementary Table S1.

At the 8-week follow-up, complete data on body composition were collected on 33 men. All measurements were carried out in a fasting condition on the same day with less than 2 h between the different body composition measurement procedures.

Side effects were registered according to the standard questionnaire at the Obesity Unit. Ketone bodies to ensure compliance were measured biweekly in morning urine by means of Ketostix® (Bayer Diagnostics Europe, Dublin, Ireland). The shift to (V)LCD started without any run-in but after careful information about the anticipated early symptoms. Refeeding was done by gradually introducing one normal meal per day over a 1-week period. The patients then went into the standard behaviour modification program at the clinic, running for an additional year with group treatment, weight classes, nutrition education, physical activity enhancement and life style modifications [10,11]. All subjects were screened by a physician (Dr. S. Rossner.), but the entire treatment program was run by a nurse.

Fatness measurements

Body composition was estimated by use of DXA. DXA measurements were performed by using a total body scanner (Lunar Prodigy; Lunar Radiation Company). The subjects were measured in underwear without any metal items in their clothing or elsewhere. The same operator performed a whole body scan on each subject lying in a supine position. Fat free soft tissue (muscle, body water, and internal organs, excluding bone mass), fat soft tissue, and bone mineral densities were measured. Percentage body fat (%BF) was calculated by dividing fat soft tissue mass by entire body mass using the software supplied by the manufacturer. The software provided by the Lunar Co. PRODIGY for whole body composition analysis also provides data of different regions of interest, e.g., trunk, arms, and legs.

Height was measured to the nearest half centimetre by use of a wall-mounted stadiometer. Body weight was measured to the nearest 0.1 kg by use of the Lunar DXA equipment, and body mass index (BMI) was determined as Quetelet's index ($kg\,m^2$). Waist-circumference (WC) was measured at the minimum circumference between the iliac crest and the rib cage with subjects standing dressed in underwear. WC was rounded to the nearest 0.5 cm. Blood pressure was measured twice in the supine position by use of a manual sphygmanometer. If the two measurements differed by more than 5 mmHg, a third measurement was performed. The mean of the two, or the two closest, measurements was used.

The Medical Research Ethics Committee in Stockholm, Sweden, approved the study. All participants provided written informed consent.

Statistics

The SPSS package (Version 14.0; SPSS Inc., Chicago, IL, USA) and SAS (Version 9, SAS Institute Inc., Cary, NC, USA) were used for statistical analyses. Summary statistics used for central tendency and dispersion are means and standard deviations. Independent *t*-tests were used to compare change in body composition and blood pressure between the two intervention groups. To compare the weight development during the study, using the eight weekly repeated measurements, a mixed effects model with a random intercept was used with PROC MIXED. This method utilizes all the repeated measurements, and is able to take unevenly spaced follow-up measurements and missing data points into account. This enables within-subject changes in BMI to be estimated with great precision since each individual acts as his own control [12]. The analysis was designed to estimate how individuals' BMI changed throughout the duration, and to contrast the BMI trajectories for the two intervention groups. Time (in days) and a dummy variable for intervention group (Allévo®/Nutrilett®) were used as predictors, together with an interaction term (group × time). If the interaction term is significant, then the BMI trajectories differ between intervention groups. An additional model with a quadratic time-term (time × time) was also constructed to allow for greater weight losses in the beginning of the treatment. In all models the sandwich covariance estimator was used [12].

Akaike's information criterion (AIC) was used to compare models, where smaller values of AIC represent a better fit. A p-value of <0.05 was considered statistically significant.

Results

Subject characteristics are presented in Table 1. No significant differences between the groups were seen in any of the body composition variables at baseline, although the Nutrilett® group was slightly older, and had a slightly lower BMI (all $p > 0.3$). The whole sample was obese (BMI > 30 kg/m^2) at baseline, with a mean BMI at approximately 39 kg/m^2.

Table 1 Baseline characteristics

	Mean ± S.D. (Nutrilett®)	Mean ± S.D. (Allévo®)	p for difference
Age (year)	47.6 ± 10.8	45.8 ± 10.7	0.61
Weight (baseline; BIA)	121.0 ± 12.5	124.2 ± 18.3	0.55
Height (m)	1.78 ± 0.06	1.76 ± 0.08	0.50
BMI (baseline)	38.2 ± 3.4	39.8 ± 3.5	0.18
Waist-circumference (end)	130 ± 10	132 ± 10	0.56
Systolic blood pressure (baseline)	143 ± 18	143 ± 15	0.91
Diastolic blood pressure (baseline)	92 ± 16	88 ± 11	0.40
%BF (baseline; DXA)	38 ± 4	39 ± 3	0.41

$n_{\text{Nutrilett®}} = 17$; $n_{\text{Allévo®}} = 16$.

All subjects also exceeded the cut-off for WC for men of 102 cm, and the mean was approximately 130 cm (Table 1).

Drop-out

One patient in each group dropped out—one moved out of the country (Nutrilett® group) and one subject withdrew because of his distaste of both types of powdered (V)LCD supplements (Allévo® group). No subjects reported adverse events in the form of either hair loss or constipation. No other adverse events were reported.

Weight, waist-circumference and %BF change

At follow-up, the subjects had lost more than 13 kg of bodyweight, 4 kg/m^2 in BMI, approximately 10 cm in WC, and 6–7 kg of fat mass (Table 2). Also, significant reductions of large magnitude were observed for both systolic and diastolic blood pressure. No significant differences between the two groups could be detected for any of the changes.

Weight loss trajectory

When examining the BMI loss trajectory during the study, they appeared similar from visual inspection of the mean BMI changes (group BMI loss trajectories are shown in Fig. 1). The longitudinal regression model showed that the subjects lost approximately 0.5 kg/m^2 per week (0.08 kg/m^2/day), and that this was not significantly affected by either the choice of (V)LCD (Nutrilett® or Allévo®; $p = 0.50$ for interaction with time) or age (Table 3). A somewhat better model fit, as assessed by AIC, was produced by the model with a quadratic time trend (AIC = 881.1 versus AIC = 739.9), but none of the findings changed; the interaction term group × time was still non-significant ($p = 0.65$).

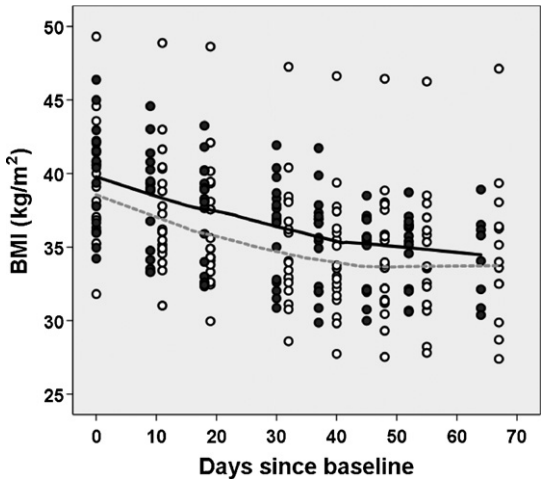

Figure 1 Individual BMI loss trajectories for the Nutrilett® (white circles; dashed grey line; $n = 17$) and Allévo® (black circles; full black line; $n = 16$) groups over 8 weeks.

Ketosis

No significant difference in ketosis was seen between the two groups, with an average of 6.3 mmol/l for Nutrilett® and 6.6 mmol/l for Allévo® ($p = 0.83$). There was no association between degree of ketosis and BMI (Fig. 2) or %BF change ($p = 0.41$ and 0.83, respectively).

Discussion

Our results comparing two (V)LCD products show that the general results are in agreement with earlier data [13] and reports on Nutrilett® in particular [14]. This comparison showed that the two (V)LCD diets produced similar clinical outcome regarding compliance, weight loss, and the associated changes in fat percentage. In both groups, about 50% of the total weight loss was fat. For reasons not understood this is lower than what has been suggested in the literature, where the SCOOP report

Table 2 Changes from baseline to follow-up

	Mean ± S.D. (Nutrilett®)	Mean ± S.D. (Allévo®)	p for difference
Weight (kg; BIA)	−14.2 ± 3.8	−13.5 ± 6.3	0.71
BMI (kg/m^2)	−4.5 ± 1.4	−4.6 ± 1.6	0.90
Waist-circumference (cm)	−10 ± 4	−10 ± 3	0.51
Systolic blood pressure (mmHg)	−9 ± 10	−17 ± 22	0.20
Diastolic blood pressure (mmHg)	−11 ± 15	−11 ± 11	0.96
%BF (DXA)	−2.3 ± 2.9	−0.4 ± 2.6	0.06
Fat mass (kg; DXA)	−7.6 ± 2.3	−5.7 ± 3.0	0.06

$n_{\text{Nutrilett®}} = 17_t$; $n_{\text{Allévo®}} = 16$.

Table 3 Longitudinal regression results using the eight repeated BMI measurements during the study as outcome variables, and time and intervention group (Nutrilett® $n = 17$; Allévo® $n = 16$), as well as an interaction term (time × group), as predictors (model 1)

	Intercept	Group[a]	Time (days)	Time × group	Age	Time × time	AIC[b]
Model 1	38.3	0.9 ($p = 0.43$)	−0.08 ($p < 0.0001$)	−0.005 ($p = 0.50$)	−0.001 ($p = 0.98$)	–	881.1
Model 2	39.2	0.8 ($p = 0.50$)	−0.17 ($p < 0.0001$)	0.003 ($p = 0.65$)	−0.002 ($p = 0.97$)	0.0014 ($p < 0.0001$)	739.9

In model 2, a quadratic time trend (time × time) was added to allow for a levelling off in the weight loss.

[a] Nutrilett® reference group.

[b] AIC; Akaike's information criterion—a statistic to compare models (smaller is better).

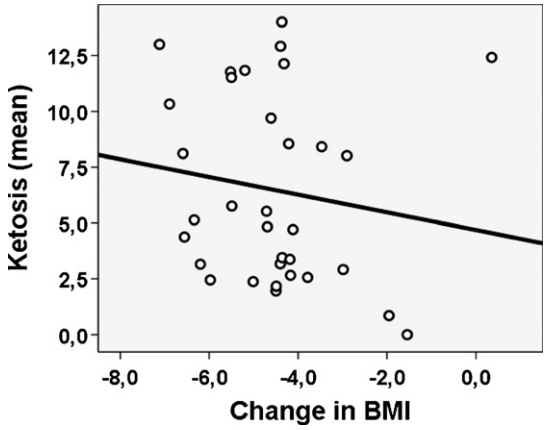

Figure 2 Relationship between mean level of urinary ketosis and BMI change ($n = 33$).

cites the Muller & Grossklaus paper, suggesting that on group levels, 75% of weight loss should be adipose tissue [15]. It is possible, that in spite of the initial BMI around 39 kg/m^2, the body fat percentage of 38% is so relatively low, that less fat is mobilized in this group during weight loss by (V)LCD.

Although the products, from their content description seem similar, it is important to demonstrate equivalence in efficacy, and investigate the risk of adverse events for a safe shift to a new product. In order to sharpen the statistical tools to detect even minor potential differences in effect, the statistical methods applied here were quite powerful using all eight weight measurements during the follow-up [12], but could still not pick up any difference.

The importance of ketosis for weight loss adherence in (V)LCD programs is not well understood. In the review by Westman et al. [3] the effects of ketogenic diets are discussed, and their long-term safety underscored. However, regarding the role of the ketonaemia for weight loss and possibly also appetite suppression, little information is available. Ketonaemia disappears over time, and after 6 months on (V)LCD ketone levels are back to baseline [1,3]. On the other hand, most of the weight loss observed with any treatment program including pharmacotherapy has taken place within that time period [3].

It would be reasonable to assume that patients with a higher degree of ketonaemia would respond better to treatment, but this was not the case. It is possible that ketosis, after all, is too blunt of an indicator of fat mobilization and signals of satiety to be useful in this setting, or that a threshold effect may be present.

The extremely low drop-out rate during the 8-week program, the marked weight loss, and the absence of major adverse events indicate that with proper supervision and training, the need for involvement of a physician in the execution of this type of program can be kept to a minimum.

Other recent studies also indicate that these programs are safe, and do not affect cardio-vascular risk factors adversely during weight loss [16]. Although the initial attempts with (V)LCDs in the 1960s had catastrophic outcomes in some cases, leading to death for some patients and to prison for at least one doctor [17], the current treatment regimens appear safe, at least as used at our clinic and at other Swedish obesity clinics [5,18,19]. This was also the conclusion of a governmental technology assessment report of obesity and related treatments [20]. Previously, transient hair loss, constipation and frozenness have been reported as side effects [4,20]. These side effects were routinely asked for in the current study. All are reversible if they occur, but none was reported in the current study groups. Development of abnormal liver tests or gallstone formation, described as side effects during rapid weight loss in general, have rarely occurred under our treatment conditions. No lab tests were, however, taken after initiation of the (V)LCD therapy to confirm the absence of changes in liver function or other parameters.

In summary, Allévo® and Nutrilett® appear to have equivalent efficacy regarding weight, BMI, WC, and %BF loss in short-term interventions in short-term meal replacement programs. In addition, they both seem to be safe when delivered under the supervision of an experienced nurse and with regular bi-weekly physical meetings where possible problems or adverse events can be detected.

Conflicts of interest

S.R. received unrestricted grant money from Cederroths.

Acknowledgements

MN organized the DXA measurements, performed the statistical analyses and drafted the manuscript with S.R. S.R. designed the study.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.orcp.2007.04.001.

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