The effect of very-low calorie diets on renal and hepatic outcomes: A systematic review.

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Key words: Obesity, systematic review, very-low-calorie diet, liver, kidney

Running title: Very-low calorie diets and renal and hepatic function

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Abstract:

Very low calorie diets (VLCDs) are an effective means by which to induce clinically significant weight loss. However, their acceptance by health care practitioners and the public is generally lower than that for other non-surgical weight loss methods. Whilst there is currently little evidence to suggest any detriment to hepatic and renal health, data assessing these factors remain limited. We carried out a systematic review of the literature for randomised controlled trials which had a VLCD component and reporting outcomes for hepatic and renal health, published between January 1980 and December 2012. Cochrane criteria were followed and eight out of 196 potential articles met the inclusion criteria. A total of 548 participants were recruited between the 8 studies. All 8 studies reported significant weight loss following the VLCD. Changes in hepatic and renal outcomes were variable but generally led to either no change or improvements in either of these. Due to the heterogeneous nature of the quality and methodology of the studies included, the effect of VLCDs on hepatic and renal outcomes remain unclear at this stage. Further standardised research is therefore required to fully assess the impact of VLCDs on these outcome measures to better guide clinical practice.

Introduction:

The prevalence of overweight and obesity is increasing globally and effective weight loss treatment is of great importance from both a health and socioeconomic perspective Wang et al.¹ Very low calorie diets (VLCDs) are an effective means by which to induce a clinically significant weight loss.² However their acceptance by health care practitioners and the public in general is much lower than that for other non-surgical weight loss methods. This is likely to be due to the adverse effects of nutritionally insufficient VLCDs in the 1970s which resulted in a number of deaths due to vitamin and mineral deficiencies and poor quality or inadequate amounts of protein.³⁴ These are however completely different from the nutritionally replete
variants of modern day VLCDs and despite the fact that the fast weight loss seen in followers of a VLCD is generally perpetuated as being unsafe, there is no convincing evidence to suggest that this is the case. Indeed, the European Food Safety Authority (EFSA) has approved a health claim with regards to the efficacy of VLCDs on weight loss in a target population of obese adults.5

A VLCD is defined as a diet of <800 kcal/day6 and there are many commercially available variants which provide energy intakes between 300-800 kcal/day. There is sufficient evidence in the literature to ensure the safe use of VLCDs in healthy overweight and obese patients in the short-term7,8 however, there remains limited evidence on the effects of VLCDs on specific disease groups over this same period of time. This is likely to in part be due to the strict protocols and monitoring which are advised with this type of dietary approach to weight loss. Although evidence for the benefits of VLCDs is mounting in certain groups of individuals at higher cardiovascular risk, for example those with type 2 diabetes mellitus (T2DM),9,10 there is little evidence of outcomes in other obesity-related secondary diseases, such as non-alcoholic fatty liver disease (NAFLD). In a recent review, Mulholland et al12 investigating long-term (>12 month) randomised control trials of VLCD identified only 2 studies which evaluated effect on liver and kidney function.11,12 One paper,11 described that at 2 years follow-up, there were no significant changes in liver transaminases. The other paper,12 reported both statistically and biologically significant improvements in both hepatic and renal health including changes in alanine aminotransferase, alkaline phosphatase, γ-Glutamyl transferase, creatinine, eGFR and urea. The observed changes in liver enzymes indicated an improvement in hepatic steatosis and an improvement in biochemical markers associated with renal and hepatic pathology.
Furthermore, a recent study by Lim et al\textsuperscript{13} reported that in patients with T2DM who followed a VLCD, the resulting acute negative energy balance reversed T2DM by normalising both insulin sensitivity and beta cell function. The authors suggested this observation was due to the reduction of fat in the liver and pancreas. These results are in keeping with our previous findings which demonstrated improvements in liver enzymes following a VLCD.\textsuperscript{12}

Whilst there is currently little evidence to suggest any detriment to liver or kidney health, data assessing these factors remain limited. Thus, we aim to carry out a systematic review of the literature for studies using a VLCD and reporting outcomes for liver and kidney health, published between January 1980 and December 2012.

**Methods:**

The protocol used for this systematic review follows the methods recommended by the Cochrane Collaboration.\textsuperscript{14} Further details of the approach are described below.

**Inclusion Criteria**

This review is intended to assess the literature in this field. Studies from January 1980 to December 2012 were evaluated. Studies prior to 1980 were not included due to health concerns associated with formulations of VLCDs in the1970s.\textsuperscript{3,4} Interventions where the participants had a mean or median BMI of $\geq 28$ kg/m$^2$ were included, and restricted to studies in adults only (18 years and over). Only randomised controlled trials with a VLCD component were evaluated. The variation of time on diet using active intervention, follow up and different follow up treatments was recorded and accounted for where possible.
Types of Intervention

The focus of this review was to examine the effect of VLCDs on hepatic and renal outcomes. The types of dietary interventions evaluated were VLCDs also known as very low energy diets defined as a dietary intake of 800kcal/day or less.

Outcome Measures

Weight loss was the main outcome assessed from the studies included in the review. With regard to hepatic or renal status, the following outcomes were also included:

- Liver enzymes (alanine aminotransferase (ALT), alkaline phosphatase (ALKP), aspartate transaminase (AST), gamma-glutamyl transpeptidase (GGT), albumin).
- Electrolytes, urea and kidney function (sodium, potassium, chloride, creatinine, and estimated glomerular filtration rate (eGFR))
- Non-alcoholic fatty liver disease (NAFLD)

Search Strategy for the Identification of Included Studies

This systematic review was restricted to studies where the full study report was available. A search strategy on MEDLINE was applied to identify as many studies evaluating dietary interventions using VLCDs as possible and which were relevant to hepatic and renal status. The search strategy incorporated the following terms “very low calorie/energy diet”. Reference lists of included studies and reviews were searched and authors contacted for further details of their trials.

Quality Assessment of Studies

The protocol used for the quality assessment follows the methods recommended by the Avenell et al. Studies were classified as having either a low risk of bias (A), an unclear risk of bias (B), or a high risk of bias (C). Subset “I” suggests that a description was provided while subset “II” suggests that no description was provided.
Full copies of studies were assessed by 2 researchers for methodological quality. The researchers were not blinded to author, journal or institution. Differences of opinion were resolved by discussion. Trial quality was assessed, including whether or not the analysis was undertaken on an intention to treat basis.

Identified Studies

A total of 8 out of 196 articles met the inclusion criteria and were included in the systematic review. Reasons for the exclusion of these studies is summarised in Figure 1.

Results:

Study Characteristics

A total of 548 participants were recruited between the 8 studies included in this systematic review. There was a large amount of heterogeneity in study design for the papers meeting the inclusion criteria. The studies included ranged from 8 weeks\textsuperscript{16} to 2 years\textsuperscript{11} in duration. Periods of VLCD ranged from 25 days\textsuperscript{11} to 9 months.\textsuperscript{12} In the follow-up phase, different studies incorporated aspects of behaviour modification,\textsuperscript{11} reduced calorie intake,\textsuperscript{17-19} or medication (acarbose) (Table 1).\textsuperscript{20}

All of the studies were designed to reduce weight or prevent weight gain and also examined hepatic and renal outcomes. Results for all the studies are summarised in Table 1.

Quality Assessment

Table 2 displays the quality assessment of reported studies. All of the studies were randomised but allocation description was generally not provided with the exception
of one paper\textsuperscript{21} where the method of concealment had a real chance of disclosure of assignment prior to formal trial entry. Four studies\textsuperscript{11,18-20} clearly stated numbers and reasons for withdrawal from the study, while two studies\textsuperscript{12,21} only provided numbers and two studies\textsuperscript{16,17} made no mention of dropouts. Three studies analysed the data with intention to treat,\textsuperscript{12,20,21} while three\textsuperscript{16,17,19} may have, but the methods of analysis was unclear and two studies\textsuperscript{11,18} presented data for completers only. Participants as well as healthcare providers were blinded to the treatment in two studies (test emulsion,\textsuperscript{18} acarbose\textsuperscript{20}). Participants were not blinded in the other six studies and it was unclear if the healthcare providers or the outcome assessors were blinded to treatment status.

Weight change

All 8 of the studies resulted in significant weight loss following the VLCD period (Table 2). Where weight change was reported after a follow up period, the implementation of either a reduced calorie diet,\textsuperscript{17} regular support through intensive or less intensive behaviour modification therapy,\textsuperscript{11} meal replacement once a day\textsuperscript{18} and ongoing use of VLCD\textsuperscript{12} resulted in the maintenance of significant weight loss compared with baseline. Although no values for weight change were provided, Hauner et al\textsuperscript{20} stated that the use of acarbose resulted in individuals remaining weight stable for the weeks following the VLCD (Table 2).

Hepatic outcomes

Table 3 displays the results for different hepatic outcomes reported in 3 of the studies. Arai et al\textsuperscript{16} observed an improvement in AST and ALT following the VLCD. Rolland et al\textsuperscript{12} also reported an improvement in ALT, as well as in ALKP, GGT and albumin following the VLCD period. Melin et al\textsuperscript{11} provided baseline values but only anecdotally reported no changes in liver transaminases.
Two other studies reported anecdotal results (i.e. no values were presented) of changes in hepatic outcomes. Olsson et al\textsuperscript{18} reported that ALT levels increased significantly during the weight reduction phase but were normalised during the 12 week weight maintenance phase, whereas Hauner et al\textsuperscript{20} reported that no changes were observed in serum transaminases in participants undergoing a VLCD followed by the use of acarbose.

Only one study investigated the effect of VLCDs on NAFLD. In the study by Lin et al\textsuperscript{21}, 41 participants with NAFLD were placed on a 450 kcal/d VLCD for 12 weeks. In this group, a 41.5\% improvement rate in NAFLD was reported where 5 of the 41 participants no longer had NAFLD and others had improvements in severity; however of the 5 participants in this group who did not have NAFLD at the beginning of the intervention, 2 had developed NAFLD by the end of the intervention. Lin et al\textsuperscript{21} also had participants on an 800 kcal/d VLCD. In this latter group, they observed a 50\% improvement rate where of the 42 participants who initially presented with NAFLD, 10 no longer had NAFLD; and of the 5 participants who did not have NAFLD at baseline, none developed it.

Renal outcomes

Table 4 displays the results for renal outcomes for the only paper\textsuperscript{12} which provided values for changes in renal function. The results demonstrated an improvement in creatinine, urea and eGFR urea levels in response to a VLCD.

Two other studies reported anecdotal outcomes for renal function. Doherty et al\textsuperscript{17} stated that there were no significant changes in potassium, sodium or chloride observed at 45 weeks in response to a VLCD followed by a balanced deficit diet. Similarly, Ryttig and Rössner\textsuperscript{20} reported that there were no significant changes in serum electrolytes (sodium, potassium) at the end of the 12 weeks of VLCD and that
there were no significant changes during the weight maintenance period between the two groups (balanced hypocaloric diet with or without a meal replacement component).

**Discussion:**

As expected from previous studies, the VLCD interventions resulted in significant weight loss. Changes in hepatic and renal outcomes resulting from the weight loss achieved using the VLCDs were variable but generally led to either no change or an improvement in hepatic and renal health. This may be due to the fact that these studies measuring kidney and liver outcomes only included adults with normal kidney and liver function with the exception of NAFLD.

The outcomes in terms of hepatic function were improved in some studies, remained the same in others, and initially increased during the VLCD phase but normalised thereafter in one study. The inconsistencies between these studies are likely to be due to a combination of things including the different lengths of treatment, different sampling times as well as different weight maintenance approaches. However, these studies certainly did not demonstrate any negative outcomes for hepatic health in response to a VLCD and subsequent follow-up. On the contrary, when looking at the outcomes for NAFLD, the effect of the weight loss achieved by the VLCD resulted in important improvements in NAFLD most likely due to the associated decrease in visceral adiposity. These results are supported by Rolland et al. who suggest that changes in liver enzymes may indicate an improvement in hepatic steatosis. Several other studies have also suggested beneficial effects of weight loss on liver size and adiposity. Colles et al. observed that during a 12 week VLCD most of the reduction in liver size occurred in the first 2 weeks of weight loss, likely due to the low carbohydrate content of the diet resulting in the depletion of liver glycogen and bound
water. Favourable changes were also observed for a range of biochemical and clinical tests (significant decrease in ALKP, bilirubin, ALT, GGT). Andersen et al. investigated the effects of weight loss induced by a VLCD on liver morphology and function in morbidly obese, but otherwise healthy individuals. They observed a marked improvement in hepatic health which correlated with the reduction of weight. However, they also observed that 24% of the patients developed a slight portal inflammation as well as a slight portal fibrosis in 12% of patients. They did not find predictors (morphological or biochemical) for these changes and hypothesised that a fast mobilisation of intracellular triacylglycerols and subsequent secretion of fatty acids had induced a portal inflammation which in turn led to fibrosis. They proposed that a rapid mobilisation of intra- and extra-hepatic fat stores may present a hepatotoxic factor common to all weight loss treatments that induce rapid weight loss. Based on their observations, they postulated that to avoid development of portal fibrosis during treatment with VLCD, a weight loss slower than 1.6kg/week should be recommended.

The issue of development of fibrosis in the Andersen study should not be confused with the development of fibrosis observed in individuals following bariatric surgery, another approach which induces rapid weight loss. Several studies have reported improvements in liver biochemical and histological outcomes but some do express concern that rapid weight loss may be a causative factor in the occurrence of fibrosis that is observed. However, as Kral et al suggest, this may be due to a decreased serum albumin and poorly managed diarrhoea which are two known potential side effects of certain types of bariatric surgery. The problems with hepatic fibrosis are well known and are probably not related to the rate of weight loss but rather to surgically induced short bowel syndrome. Certainly, the issue of fibrosis did not figure in the clinical trials highlighted in this systematic review and such situations are not generally associated with the use of low-calorie diet or VLCD interventions.
Limited information was available regarding the response of renal function to weight loss induced by VLCD. Nevertheless, the current data suggest either an improvement or no change in response to weight loss induced by a VLCD followed by a weight maintenance period. Rolland et al.\textsuperscript{12} suggest that improvements in renal function during a VLCD are possibly due to the associated increase in fluid intake and/or reduction in creatine intake.

Obesity-related glomerular disease was first identified by Weisinger et al.\textsuperscript{31} in the 1970's, and the prevalence of obesity-related glomerulopathy has been increasing as a consequence of the obesity epidemic.\textsuperscript{32} It has been suggested that reducing the glomerular hyperfiltration observed in the obese, may provide a way to prevent or delay the development of renal disease in these individuals.\textsuperscript{33} Indeed, Chagnac et al.\textsuperscript{33} demonstrated improvements in GFR following weight loss induced by a gastroplasty. This was supported by the review by Navaneethan et al.,\textsuperscript{34} where they reported that in patients with chronic kidney disease, bariatric surgery was associated with a decrease in BMI with resultant normalisation of glomerular hyperfiltration. They did, however, state that it remains to be clarified whether this normalisation resulted in long-term renal benefits. Rolland et al.\textsuperscript{12} reported an improvement in eGFR following the VLCD. The use of eGFR, however, is a poor indicator of improved renal function in this case. As a direct result of the use of VLCDs, the intake of creatine drops dramatically and hence the serum creatinine also drops. This may give a false impression of improved renal function. Also, the use of eGFR significantly underestimates measured kidney function with obesity, and measuring changes in eGFR when body surface area is also changing is problematic.\textsuperscript{35} In addition, the use of eGFR is not validated in patients with normal kidney function.

\textit{Strengths and Limitations}
The main limitation of this review is the small number of studies included as well as the lack of data presented in many of these. In addition, the heterogeneous nature in terms of study quality, treatment duration, outcomes measured and time points for these rendered it impossible to carry out a meta-analysis. It is also important to highlight that only one study\textsuperscript{16} reported hepatic outcomes and none reported renal outcomes immediately post (or during active VLCD) compared with at follow-up (long after the VLCD was completed).

Finally, in assessing kidney function outcomes, it would have been beneficial to have information about renal blood flow, arterial pressure and albuminuria.

**Conclusion**

There are currently no effective treatments for NAFLD other than weight reduction and lifestyle modification.\textsuperscript{36,37} The effect of VLCDs on hepatic and renal outcomes remain unclear at this stage. There have been a number of improvements observed in terms of hepatic and renal outcomes, however, there may be some concern about the onset of fibrosis in some individuals, although no evidence for this was observed in the current systematic review. Renal outcomes seem little affected by VLCDs, however the studies measuring kidney function included only adults with normal kidney function, and the results cannot be extrapolated to those with any degree of kidney dysfunction. At this stage, further standardised research is required to fully assess the impact of VLCDs on hepatic and renal health and to better advise clinical practice.

**Disclosure:** CR has received lecture honoraria and has attended national/international meetings as a guest of LighterLife Ltd, UK. CR, IB have been involved with other companies with an interest in obesity.
IB and KLJ are employed by LighterLife Ltd, UK.

**Acknowledgements:** This research was funded by LighterLife Ltd, UK.
References


5. European Food Safety Authority. Scientific Opinion on the substantiation of health claims related to very low calorie diets (VLCDs) and reduction in body weight (ID 1410), reduction in the sense of hunger (ID 1411), reduction in body fat mass while maintaining lean body mass (ID 1412), reduction of post-prandial glycaemic responses (ID 1414), and maintenance of normal blood lipid profile (1421) pursuant to Article 13(1) of Regulation (EC) No 1924/20061. *EFSA Journal* 2011; 9: 2271.


Figure 1: Summary of literature search

Total number of references (n=196)

Duplicates excluded (n=2)

Titles & abstracts screening (n=194)

Excluded based on titles & abstracts
- Not VLCD (n=15)
- Not RCT (n=95)
- No liver/kidney outcomes (n=57)

Potential papers eligible for inclusion (n=27)

Not in accordance with inclusion criteria (n=19)
- Not RCT (n=8)
- No liver/kidney outcomes (n=11)

Total studies included for review (n=8)
Table 1: Summary of studies included in the review.

<table>
<thead>
<tr>
<th>Author</th>
<th>N (males)</th>
<th>Study</th>
<th>Mean BMI (kg/m²)</th>
<th>Inclusion Criteria</th>
<th>Duration of VLCD</th>
<th>Duration of follow up</th>
<th>Weight (kg) at baseline</th>
<th>Weight (kg) at the end of the VLCD period</th>
<th>Weight (kg) at the end of the follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arai et al13</td>
<td>45 (12)</td>
<td>RCT where patients undertook either 1) Supplemental LCD (3515-5021kJ/d with use of 2-3 packages of Optifast 70 and 2678-3682 kJ of conventional balanced meals consisting of a mixture of 88g P, 30-80g CHO, 4-9g F) or 2) VLCD where participants used 5 packages of Optifast 70 (daily energy intake of 1757kJ, 70g protein, 30g CHO, 2g F).</td>
<td>SLCD: 31.9 (4.4)</td>
<td>Overweight adult men and women</td>
<td>8 weeks</td>
<td>-</td>
<td>SLCD: 81.5 (14.0)</td>
<td>SLCD: 76.3 (14.7) a</td>
<td>-</td>
</tr>
<tr>
<td>Doherty et al17</td>
<td>26 (0)</td>
<td>RCT where patients received either 1) Control: diet of their choosing throughout the 45 weeks (Control); 2) VLCD: one week 1200kcal/d BDD and a 420kcal/d liquid diet for weeks 2-17. Patients were realimented during weeks 18-24 increasing the daily caloric intake by ~150kcal/wk until reached ~1150kcal/d at week 24. Patients were instructed to consume a balanced diet providing 1200-1500kcal/d</td>
<td>Control: 33.4 (2)</td>
<td>Obese women</td>
<td>15 weeks</td>
<td>29 weeks</td>
<td>Control: 94.7 (5.0)</td>
<td>Control: Δ 2.7 (1.2)</td>
<td>Control: Δ 3.9(2.3)</td>
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<td></td>
<td></td>
<td></td>
<td>VLCD: 111.2 (5.0)</td>
<td></td>
<td></td>
<td></td>
<td>VLCD: Δ -21.3 (2.1) a,d</td>
<td>VLCD: Δ -22.4 (3.4)a,d</td>
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<td></td>
<td></td>
<td></td>
<td>BDD + exercise: 40.4 (2)</td>
<td></td>
<td></td>
<td></td>
<td>BDD + exercise: Δ -10.3 (2.7) a,d</td>
<td>BDD + exercise: Δ -14.5 (5.5) a,d</td>
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</table>
for the remainder of the treatment (weeks 26-45).

3) BDD + exercise: consume a BDD providing 1000-1500 kcal/d (15-20% protein; 50-55% CHO, 30% fat) for 45 weeks. Instructed (at week 8) to begin a program of aerobic activity (mostly consisting of walking). Initially 10-20 mins 2-3x/wk. By end of study, they reported exercising for 20-40 mins 3-5x/wk.

**Hauner et al**

RCT where patients underwent a pre-treatment phase of VLCD/LCD (700-1000 kcal/d) to achieve a weight loss of at least 2.3 BMI units. Afterwards, participants asked to maintain an individually tailored weight maintaining diet and were either prescribed a placebo or acarbose (treatment started with 50mg once/day and titrated up to a maximum of 100mg t.i.d. at weekly intervals.)

<table>
<thead>
<tr>
<th>Group</th>
<th>BMI (SD)</th>
<th>Weight Change (SD)</th>
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<tbody>
<tr>
<td>Placebo</td>
<td>34.8 (2.2)</td>
<td>0.6kg</td>
</tr>
<tr>
<td>Acarbose</td>
<td>34.7 (2.3)</td>
<td>weight stable (no values)</td>
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**Lin et al**

RCT where patients undertook a 2 week introduction phase where they consumed a 1200kcal/d diet. This was followed by a 450kcal/d diet.

<table>
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<td>VLCD 450</td>
<td>450kcal/d: Δ -8.37 (0.70)</td>
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<tr>
<td>VLCD 800</td>
<td>800kcal/d: Δ -8.42 (0.70)</td>
</tr>
</tbody>
</table>

for the remainder of the treatment (weeks 26-45).

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<td>800kcal/d: Δ -8.42 (0.70)</td>
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<tr>
<td>Study</td>
<td>Design</td>
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<tr>
<td>-----------------------</td>
<td>---------------------------------------------</td>
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<tr>
<td>Melin et al&lt;sup&gt;11&lt;/sup&gt;</td>
<td>RCT where patients undertook a 25 day VLCD followed by hypocaloric diet. Patients were divided into 2 groups.</td>
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<tr>
<td>Olsson et al&lt;sup&gt;18&lt;/sup&gt;</td>
<td>RCT where patients were assigned to a 6 week VLCD to achieve at least a 5% reduction in body weight after which they resumed habitual eating patterns except for lunch which was replaced by Nutrilett Intensive meal (111kcal) mixed with a control or a test emulsion.</td>
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<tr>
<td>Rolland et al&lt;sup&gt;12&lt;/sup&gt;</td>
<td>RCT where patients were assigned to a 600 calorie deficit diet for 3 months. Those who did not achieve a 5% were randomised to either: LCHP or VLCD for the following 9 months.</td>
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<tr>
<td>Ryttig and</td>
<td>RCT where patients were assigned to 12 weeks of</td>
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VLCD followed by a gradual increase of normal food during 1 week. After transition, patients were assigned to either:

- **Group 1**: normal, well-balanced hypocaloric diet containing 1600kcal/d of which 220kcal was provided by two sachets of the Cambridge diet
  - Group 1: 38.0 (4.9)

- **Group 2**: normal, well-balanced hypocaloric diet containing 1600kcal/d of solid food only
  - Group 2: 40.3 (6.0)

Meal replacement: 108.1 (15.8)  
Meal replacement: 85.7 (14.7) a

BMI ≥ 30 kg/m², between 19-65y, with stable body weight within the last 2 months (less than 3kg fluctuation)

Abbreviations: BDD – balanced deficient diet; BMI – body mass index; CHO – carbohydrate; LCD – low calorie diet; LCHP – low carbohydrate high protein; RCT – randomised controlled trial; t.i.d – three times daily; SE – standard error; SLCD- supplemental low calorie diet; VLCD – very low calorie diet.

Values are reported as means with standard deviations in brackets unless stated otherwise

Δ represents a change
- a - p<0.05 from baseline
- b - p<0.001 from baseline
- c - p<0.0001 from baseline
- d - p<0.05 between groups
- e - p<0.001 between groups

the weight maintenance period between the groups (no values provided)
Table 2: Quality assessment of included RCTs.

<table>
<thead>
<tr>
<th>Study</th>
<th>Quality of random allocation concealment</th>
<th>Description of withdrawals and dropouts</th>
<th>Intention to treat?</th>
<th>Participants blinded to treatment status?</th>
<th>Healthcare providers ‘blind’ to treatment status?</th>
<th>Outcome assessors blinded to treatment status?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arai et al16</td>
<td>B (I)</td>
<td>C</td>
<td>B</td>
<td>C</td>
<td>B (I)</td>
<td>B (I)</td>
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<tr>
<td>Doherty et al17</td>
<td>B (I)</td>
<td>C</td>
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<td>Hauner et al20</td>
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<tr>
<td>Lin et al21</td>
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</tr>
<tr>
<td>Melin et al18</td>
<td>B (I)</td>
<td>A</td>
<td>C</td>
<td>C</td>
<td>B (I)</td>
<td>B (I)</td>
</tr>
<tr>
<td>Olsson et al18</td>
<td>B (I)</td>
<td>A</td>
<td>C</td>
<td>A(II)</td>
<td>A(II)</td>
<td>B (I)</td>
</tr>
<tr>
<td>Rolland et al12</td>
<td>B (I)</td>
<td>B (I)</td>
<td>A</td>
<td>C</td>
<td>B (I)</td>
<td>B (I)</td>
</tr>
<tr>
<td>Rytting and Rössner19</td>
<td>B (I)</td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>B (I)</td>
<td>B (I)</td>
</tr>
</tbody>
</table>

A - low risk of bias (A); B - unclear risk of bias; C - high risk of bias.

Subset “I” suggests that a description was provided while subset “II” suggests that no description was provided.
Table 3: Summary of liver results.

<table>
<thead>
<tr>
<th>Author</th>
<th>Patient Groups</th>
<th>AST (IU/L)</th>
<th>ALT (IU/L)</th>
<th>ALKP (IU/L)</th>
<th>GGT (IU/L)</th>
<th>Total bilirubin (mol/L)</th>
<th>Albumin (g/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Pre</td>
<td>Post VLCD</td>
<td>Study end</td>
<td>Pre</td>
<td>Post VLCD</td>
<td>Study end</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arai et al16</td>
<td>SLCD</td>
<td>26.3 (24.5)</td>
<td>16.0 (6.4)c</td>
<td>-</td>
<td>35.2 (39.5)</td>
<td>13.0 (8.3)c</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>VLCD</td>
<td>22.9 (18.3)</td>
<td>12.6 (4.7)c</td>
<td>-</td>
<td>27.6 (20.7)</td>
<td>14.1 (9.8)c</td>
<td>-</td>
</tr>
<tr>
<td>Melin et al11</td>
<td>Group 1:</td>
<td>29.4 (5.9)</td>
<td>-</td>
<td>No Δ</td>
<td>29.4 (11.8)</td>
<td>-</td>
<td>No Δ</td>
</tr>
<tr>
<td></td>
<td>less intensive</td>
<td>29.4 (5.9)</td>
<td>-</td>
<td>No Δ</td>
<td>29.4 (11.8)</td>
<td>-</td>
<td>No Δ</td>
</tr>
<tr>
<td>Rolland et al12</td>
<td>VLCD</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>30.0 (17.8)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>LCHP</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>35.4 (23.0)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>35.4 (23.0)</td>
<td>-</td>
<td>39.6 (51.2)</td>
</tr>
</tbody>
</table>

Abbreviations: ALT – alanine aminotransferase; ALKP – alkaline phosphatase; AST – aspartate transaminase, GGT – gamma-glutamyl transpeptidase; LCD – low calorie diet; LCHP – low carbohydrate, high protein diet; SLCD – supplemental; VLCD – very low calorie diet;

Values are reported as means
Δ represents a change
a - p<0.05 from baseline
b - p<0.05 between groups
c- likely to be significantly different from baseline, but no p value provided
Table 4: Results of kidney (renal) results

<table>
<thead>
<tr>
<th>Author</th>
<th>Patient Groups</th>
<th>Creatinine (µmol/L) Pre</th>
<th>Post VLCD</th>
<th>Study end</th>
<th>eGFR (mL/min) Pre</th>
<th>Post VLCD</th>
<th>Study end</th>
<th>Urea (mmol/L) Pre</th>
<th>Post VLCD</th>
<th>Study end</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rolland et al</td>
<td>LL</td>
<td>82.6 (9.2)</td>
<td>-</td>
<td>79.8 (6.6)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>77.1 (11.6)</td>
<td>-</td>
<td>79.7 (11.4)&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>4.5 (1.0)</td>
<td>-</td>
<td>4.3 (1.1)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>LCHP</td>
<td>82.1 (9.6)</td>
<td>-</td>
<td>83.1 (11.6)</td>
<td>74.0 (11.0)</td>
<td>-</td>
<td>73.1 (12.3)</td>
<td>4.7 (1.4)</td>
<td>-</td>
<td>5.2 (1.4)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Abbreviations: eGFR – estimated glomerular filtration rate; LCHP – low carbohydrate, high protein diet; LL – LighterLife; VLCD – very low calorie diet;

Values are reported as means

a - p<0.05 from baseline
b - p<0.05 between groups