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

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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.[3,4] 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/day[6] 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-term[7,8] 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 al[2] 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[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.[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.[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.[3,4] Interventions where the participants had a mean or median BMI of ≥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.[15] 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 betweem 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[16] to 2 years[11] in duration. Periods of VLCD ranged from 25 days[11] to 9 months.[12] In the follow-up phase, different studies incorporated aspects of behaviour modification,[11] reduced calorie intake,[17-19] or medication (acarbose) (Table 1).[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[21] where the method of concealment had a real chance of disclosure of assignment prior to formal trial entry. Four studies[11,18-20] clearly stated numbers and reasons for withdrawal from the study, while two studies[12,21] only provided numbers and two studies[16,17] made no mention of dropouts. Three studies analysed the data with intention to treat, [12,20,21] while three[16,17,19] may have, but the methods of analysis was unclear and two studies[11,18] presented data for completers only. Participants as well as healthcare providers were blinded to the treatment in two studies (test emulsion,[18] acarbose[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,[17] regular support through intensive or less intensive behaviour modification therapy,[11] meal replacement once a day[18] and ongoing use of VLCD[12] resulted in the maintenance of significant weight loss compared with baseline. Although no values for weight change were provided, Hauner et al[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[16] observed an improvement in AST and ALT following the VLCD. Rolland et al[12] also reported an improvement in ALT, as well as in ALKP, GGT and albumin following the VLCD period. Melin et al[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[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[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[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[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[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,[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[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 theses 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. [22] These results are supported by Rolland et al[12] 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,[23] 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.[24] Favourable changes were also observed for a range of biochemical and clinical tests (significant decrease in ALKP, bilirubin, ALT, GGT). Andersen et al[25] 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[25] 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[26-28] but some do express concern that rapid weight loss may be a causative factor in the occurrence of fibrosis that is observed.[27-29] However, as Kral et al[28] 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[30] 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[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[31] in the 1970's, and the prevalence of obesity-related glomerulopathy has been increasing as a consequence of the obesity epidemic.[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.[33] Indeed, Chagnac et al[33] demonstrated improvements in GFR following weight loss induced by a gastroplasty. This was supported by the review by Navaneethan et al,[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[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.[35] In addition, the use of eGFR is not validated in patients with normal kidney function.

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[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.[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 disfunction. 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.

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CR, IB have been involved with other companies with an interest in obesity.

IB and KLJ are employed by LighterLife Ltd, UK.

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References

1. Wang YC, McPherson K, Marsh T, Gotmaker SL, Brown M. Health and economic burden of the projected obesity trends in the USA and the UK. *Lancet* 2011; 378: 815-825.

2. Mulholland Y, Nicokavoura E, Broom J, Rolland C. Very-low calorie diets and morbidity: A systematic review of longer term evidence. *Br J Nutr* 2012; 108: 832-51.

3. van Itallie TB. Liquid protein mayhem. *JAMA.* 1978; 240**:** 144.

4. Center For Disease Control. Liquid protein diets. Public health service report. Atlanta, GA: *CDC;* 1979*.*

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.

6. National Task Force. Very low-calorie diets. National task force on the prevention and treatment of obesity, national institutes of health. *JAMA* 1993; 270**:** 967-974.

7. Capstick F, Brooks BA, Burns CM, Zilkens RR, Steinbeck KS, Yue DK. Very low calorie diet (VLCD): A useful alternative in the treatment of the obese NIDDM patient. *Diabetes Res Clin Pract* 1997; 36**:** 105-111.

8. Williams KV, Mullen ML, Kelley DE, Wing RR. The effect of short periods of caloric restriction on weight loss and glycemic control in type 2 diabetes. *Diabetes Care* 1998; 21: 2-8. 9. Dhindsa P, Scott AR, Donnelly R. Metabolic and cardiovascular effects of very-low-calorie diet therapy in obese patients with Type 2 diabetes in secondary failure: outcomes after 1 year. *Diabetic Med* 2003; 20: 319–24.

10. Jazet IM, de Craen AJ, van Schie EM, Meinders AE. Sustained beneficial metabolic effects 18 months after a 30-day very low calorie diet in severely obese, insulin-treated patients with type 2 diabetes. *Diabet Res Clin Pr* 2007; 77: 70–6.

11. Melin I, Karlstrom B, Lappalainen R, Berglund L, Mohsen R, Vessby B. A programme of behaviour modification and nutrition counselling in the treatment of obesity: A randomised 2-y clinical trial. *Int J Obes Relat Metab Disord* 2003; 27**:** 1127-1135.

12. Rolland C, Hession M, Murray S, Wise A, Broom I. Randomized clinical trial of standard dietary treatment versus a low-carbohydrate/high-protein diet or the LighterLife programme in the management of obesity. *J Diabetes* 2009; 1: 207-217

13. Lim EL, Hollingsworth KG, Aribisala BS, Chen MJ, Mathers JC, Taylor R. Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. *Diabetologia* 2011: 54: 2506-2514

14. Clarke M, Oxman AD (eds). *Cochrane Reviewer's Handbook 4.15*. In *The Cochrane Library*. Oxford: Update Software; 2002.

15. Avenell A, Broom J, Brown TJ, Poobalan A, Aucott L, Stearns SC, et al. Systematic review of the long term effects and economic consequences of treatments for obesity and implications for health improvement. *HTA* 2004; 8: 1–458.

16. Arai K, Miura J, Ohno M, Yokoyama J, Ikeda Y. Comparison of clinical usefulness of very-low-calorie diet and supplemental low-calorie diet. *Am J Clin Nutr* 1992; 56: 245S-276S.

17. Doherty JU, Wadden TA, Zuk L, Letizia KA, Foster GD, Day SC. Long-term evaluation of cardiac function in obese patients treated with a very-low-calorie diet: a controlled clinical study of patients without underlying cardiac disease. *Am J Clin Nutr* 1991; 53: 854-858.

18. Olsson J, Sundberg B, Viberg A, Haenni A. Effect of a vegetable-oil emulsion on body composition; a 12-week study in overweight women on a meal replacement therapy after an initial weight loss; a randomised controlled trial. *Eur J Nutr* 2011; 50: 235-242.

19. Ryttig KR, Rössner S. Weight maintenance after a very low calorie diet (VLCD) weight reduction period and the effects of VLCD supplementation. A prospective, randomised, comparative, controlled long-term trial. *J Intern Med* 1995; 238: 299-306.

20. Hauner H, Petzinna D, Sommerauer B, Toplak H. Effect of acarbose on weight maintenance after dietary weight loss in obese subjects. *Diabetes Obes Metab* 2001; 3: 423-427.

21. Lin WY, Wu CH, Chu NF, Chang CJ. Efficacy and safety of very-low-calorie diet in Taiwanese: A multicenter randomized controlled trial*. Nutrition* 2009; 25: 1129-1136.

22. Vilar L, Oliveira CP, Faintuch J, Mello ES, Nogueira MA, Santos TE et al. High fat diet: a trigger of non alcoholic steatohepatitis? Preliminary findings in obese subjects. *Nutrition* 2008; 24: 1097-102.

23. Colles SL, Dixon JB, Marks P, Strauss BJ, O'Brien PE. Preoperative weight loss with a vvery-lo-energy diet: quantitation of changes in liver and abdominal fat by serial imaging. *Am J Clin Nutr* 2006; 84: 304-311.

24. Olsson KE and Saltin B. Variation in total body water with muscle glycogen changes in man. *Acta Physiol Scand* 1970; 80: 11-8.

25. Andersen T, Gluud C, Franzmann MB, Christoffersen P. Hepatic effects of dietary weight loss in morbidly obese subjects. *J Hepatol* 1991; 12: 224-229.

26. JB, Bhathal PS, Hughes NR, O'Brien PE. Nonalcoholic fatty liver disease: improvement in liver histological analysis with weight loss. *Hepatology* 2004; 39: 1647-1654

27. Mattar S, Velcu LM, Rabinovitz M, Demetris AJ, Krasinkas AM, Barinas-Mitchell E, et al. Surgically-induced weight loss significantly improves non-alcoholic fatty liver disease and the metabolic syndrome. *Ann Surg* 2005; 242: 610-620.

28. Kral JG, Thung SW, Biron S, Hould FS, Lebel S, Marceau S et al. Effects of surgical treatment of the metabolic syndrome on liver fibrosis and cirrhosis. *Surgery* 2004; 135: 48-58.

29. Luyckx FH, Desaive C, Thiry A, Dewe W, Scheen AJ, Gielen JE et al. Liver abnormalities in severely obese subjects: effect of drastic weight loss after gastroplasty. *Int J Obes Relat Metab Disord* 1998; 22: 222-226.

30.Friedman SL. The cellular basis of hepatic fibrosis. Mechanisms and treatment strategies. *N Engl J Med* 1993; 328: 1828-1835.

31. Weisinger JR, Kempson RL, Eldridge FL, Swensen RS. The nephrotic syndrome: A complication of massive obesity. *Am Intern Med* 1974; 81: 440-447.

32. Mokdad AH, Serdula MK, Dietz WH, Bowman BA, Marks JS, Koplan JP. The spread of the obesity epidemic in the United States, 1991-1998. *JAMA* 1999; 282: 1519-1522.

33. Chagnac A, Weinstein T, Herman M, Hirsh J, Gafter U, Ori Y. The effects of weight loss on renal function in patients with severe obesity. *J Am Soc Nephrol* 2003; 14: 1480-1486.

34. Navaneethan SD, Yehnert H, Moustarah F, Schreiber MJ, Schauer PD, Beddhu S. Weight loss interventions in chronic kidney disease: a systematic review and meta-analysis. *Clin J Am Soc Nephrol* 2009; 4: 1565-1574.x

35. Delanaye P, Radermecker RP, Rorive M, Depas G, Krzesinski JM. Indexing glomerular filtration for body surface area in obese patients is misleading: concept and example. Neph Dial Trans 2005; 20: 2024-8.

36. Suzuki A, Lindor K, St Saver J, Lymp J, Mendes F, Muto A et al. Effect of changes on body weight and lifestyle in non-alcoholic fatty liver disease. *J Hepatol* 2005; 43: 1060-1066.

37. Clark JM. Weight loss as a treatment for non-alcoholic fatty liver disease. *J Clin Gastroenterol* 2006; 40(3 Supp 1): S39-43.

Figure 1: Summary of literature search

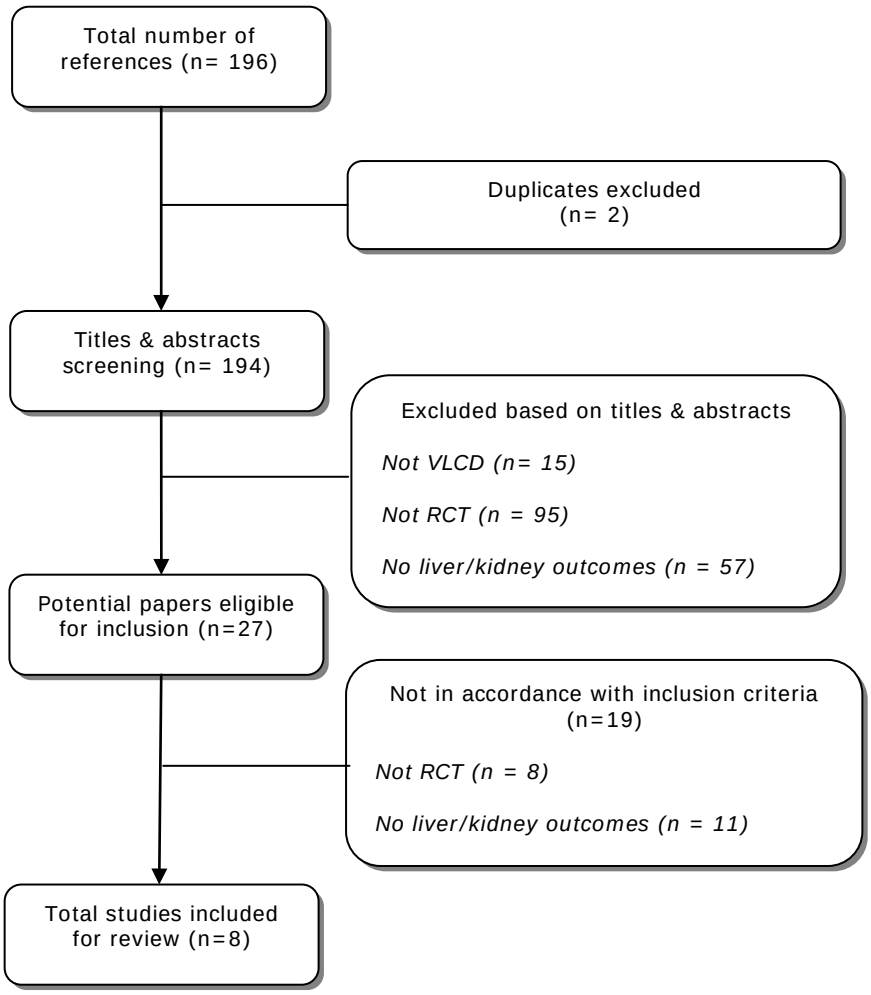

Table 1: Summary of studies included in the review.

Author	N (males)	Study	Mean BMI (kg/m^2)	Inclusion Criteria	Duration of VLCD	Duration of follow up	Weight (kg) at baseline	Weight (kg)at the end of the VLCD period	Weight (kg) at the end of the follow up
Arai et al[16]	45 (12)	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).	SLCD: 31.9 (4.4) VLCD: 32.9 (6.1)	Overweight adult men and women	8 weeks	-	SLCD: 81.5 (14.0) VLCD: 82.0(20.0)	SLCD: 76.3 (14.7) [a] VLCD: 73.0 (16.3) [a]	-
Doherty et al[17]	26 (0)	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	Control: 33.4 (2) VLCD: 40.4 (2)	Obese women	15 weeks	29 weeks	Control: 94.7 (5.0) VLCD: 111.2 (5.0) BDD + exercise: 102.8 (6)	Control: Δ 2.7 (1.2) VLCD: Δ -21.3 (2.1) [a,d] BDD + exercise: Δ -10.3 (2.7) [a,d]	Control: Δ 3.9(2.3) VLCD: Δ -22.4 (3.4)[a,d] BDD + exercise: Δ -14.5 (5.5) [a,d]

		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). Initially10-20mins 2-3x/wk. By end of study, they reported exercising for 20-40mins 3-5x/wk.	BDD: 36.5 (2)						
Hauner et al[20]	110 (22)	RCT where patients underwent a pre-treatment phase of VLCD/LCD (700-1000kcal/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.)	Placebo: 34.8 (2.2) Acarbose: 34.7 (2.3)	Weight stable obese subject with BMI 32-38 kg/m^2	10-16 weeks	26 weeks	Placebo: 97.8 (13.0) Acarbose: 97.7 (13.5)	No values	Placebo: Δ 0.6kg Acarbose: weight stable (no values)
Lin et al[21]	132 (43)	RCT where patients undertook a 2 week introduction phase where they consumed a 1200kcal/d diet. This was followed by a 450kcal/d	VLCD 450: 34.4 (3.5) VLCD 800: 34.1 (3.9)	Obese (BMI ≥30kg/m^2) Taiwanese between the ages of 18-65y	10 weeks	-	450kcal/d: 92.5 (14.1) 800kcal/d: 92.1(15.6)	450kcal/d: Δ -8.37 (0.70) [b] 800kcal/d: Δ -8.42 (0.70) [b]	-

		VLCD or an 800kcal/d VLCD for 10 weeks.							
Melin et al[11]	43 (4)	RCT where patients undertook a 25 day VLCD followed by hypocaloric diet. Patients were divided into 2 groups. Group 1:intensive behaviour modification therapy every fortnight during the first year and six meetings in the second year Group 2: planned meetings every third month.	Group 1: 35.6 (4.5) Group 2: 35.2 (4.6)	Men and women; 24-60 years old; BMI 35 kg/m^2 (29-48).	25 days	2 years	Group 1: 99.8 (SE 5.5) Group 2: 93.4 (SE 4.1)	Group 1: Δ - 8.3 (SE 0.64) [b] Group 2: Δ -10.0 (SE 0.71) [b]	Group 1: Δ - 6.8 (SE 1.4)[a] Group 2: Δ -8.6 (SE 1.6)[a]
Olsson et al[18]	43 (0)	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.	Control: 28.3 (1.6) Emulsion: 28.2 (1.4)	Female, 18- 60 years with BMI 26-31 kg/m^2	6 weeks	12 weeks	Control: 79.0 (8.3) Test emulsion: 79.7 (6.1)	Control: 71.5 (7.1)[a] Test emulsion: 73.0 (5.3)[a]	Control:70.2 (6.9)[a] Test emulsion: 72.0 (5.6)[a]
Rolland et al[12]	120 (11)	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.	LCHP: 41.6 (4.8) VLCD: 46.0 (7.0)	Men and women; >18 years old; BMI ≥35kg/m^2	6.9 months (4-9 months)	-	LCHP: 110.4 (12.2) VLCD: 129.6 (23.0)	-	LCHP: 109.1 (14.6) VLCD: 98.0 (20.3) [c,e]
Ryttig and	60 (11)	RCT where patients were assigned to 12 weeks of		Obese men and women	12 weeks	52 weeks	Solid food: 120.1 (22.5)[e]	Solid food: 97.6 (19.1)[a,d]	No significant change during

Rössner[19]	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 2: normal, well-balanced hypocaloric diet containing 1600kcal/d of solid food only.	 Group 1: 38.0 (4.9) Group 2: 40.3 (6.0)	(BMI≥30 kg/m^2), between 19-65y, with stable body weight within the last 2 months (less than 3kg fluctuation)	Meal replacement: 108.1 (15.8)	Meal replacement: 85.7 (14.7) [a]	the weight maintenance period between the groups (no values provided)

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

Table 2: Quality assessment of included RCTs.

	Quality of random allocation concealment	Description of withdrawals and dropouts	Intention to treat?	Participants blinded to treatment status?	Healthcare providers 'blind' to treatment status?	Outcome assessors blinded to treatment status?
Arai et al16	B (I)	C	B	C	B (I)	B (I)
Doherty et al[17]	B (I)	C	B	C	B (I)	B (I)
Hauner et al[20]	B (I)	A	A	A(II)	A (II)	B (I)
Lin et al[21]	B (II)	B (I)	A	C	B (I)	B (I)
Melin et al[11]	B (I)	A	C	C	B (I)	B (I)
Olsson et al[18]	B (I)	A	C	A(II)	A(II)	B (I)
Rolland et al[12]	B (I)	B (I)	A	C	B (I)	B (I)
Ryttig and Rössner[19]	B (I)	A	B	C	B (I)	B (I)

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.

		AST (IU/L)			ALT (IU/L)			ALKP (IU/L)			GGT (IU/L)			Total bilirubin (mol/L)			Albumin (g/L)		
Author	**Patient Groups**	**Pre**	**Post VLCD**	**Study end**	**Pre**	**Post VLCD**	**Study end**	**Pre**	**Post VLCD**	**Study end**	**Pre**	**Post VLCD**	**Study end**	**Pre**	**Post VLCD**	**Study end**	**Pre**	**Post VLCD**	**Study end**
Arai et al[16]	SLCD	26.3 (24.5)	16.0 (6.4)[c]	-	35.2 (39.5)	13.0 (8.3)[c]	-	-	-	-	-	-	-						
	VLCD	22.9 (18.3)	12.6 (4.7)[c]		27.6 (20.7)	14.1 (9.8)[c]													
Melin et al[11]	Group 1: intensive	29.4 (5.9)	-	No Δ	29.4 (11.8)	-	No Δ	-	-	-	30.0 (24.0)	-	No Δ						
	Group2: less intensive	29.4 (5.9)			29.4 (11.8)						24.0 (12.0)								
Rolland et al[12]	VLCD	-	-	-	30. 0 (17.8)	-	23.2 (8.9)[a,b]	81.6 (19.6)	-	77.3 (23.0)[a]	33.8 (33.7)	-	24.1 (17.7)[a,b]	9.1 (5.8)	-	9.8 (7.3)	43.0 (2.5)	-	42.8 (2.2)[a]
	LCHP	-	-	-	35.4 (23.0)	-	34.5 (27.7)	89.1 (32.9)	-	84.6 (26.7)	48.2 (77.4)	-	39.6 (51.2)	10.0 (3.6)	-	9.4 (5.1)[a]	45.0 (2.4)	-	45.6 (5.8)

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

Author	Patient Groups	Creatinine (µmol/L)			eGFR (mL/min)			Urea (mmol/L)		
		Pre	Post VLCD	Study end	Pre	Post VLCD	Study end	Pre	Post VLCD	Study end
Rolland et al[12]	LL	82.6 (9.2)	-	79.8 (6.6)[a]	77.1 (11.6)	-	79.7 (11.4)[a,b]	4.5 (1.0)	-	4.3 (1.1)[a]
	LCHP	82.1 (9.6)	-	83.1 (11.6)	74.0 (11.0)	-	73.1 (12.3)	4.7 (1.4)	-	5.2 (1.4)[a]

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