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Weight losses with low energy formula diets in obese patients with and without type 2 diabetes: systematic review and meta-analysis

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Weight loss in obese patients with and without T2DM

Aim: To provide a systematic review, of published data, to compare weight losses following Very Low Calorie (<800kcal/day VLCD) or Low Energy Liquid-formula (>800kcal/day LELD) diets, in people with and without T2DM (T2DM).

Methods: Medline Systematic electronic searches of Medline (1946-2015) and Embase (1947-2015) to identify published studies using formula Total Diet Replacement diets (VLCD/LELD). Random effects meta-analysis using Weighted Mean Difference (WMD) in body weight between groups (with and without diabetes) as the summary estimate.

Results: Final weight loss, in the 5 included studies, weighted for study sizes, (n=569, mean BMI=35.5-42.6kg/m²), was not significantly different between participants with and without T2DM : -1.2kg; 95%CI -4.1 to 1.6kg). Rates of weight loss were also similar in the 2 groups -0.6kg/week (T2DM) and 0.5kg/week (no diabetes), and for VLCD (<800kcal/day) and LELD (>800kcal/day).

Conclusions: Weight losses with liquid-formula diets are very similar for VLCD and LELD and for obese subjects with or without T2DM. They can potentially achieve new weight-loss/ maintenance targets of >15-20% for people with severe and medically complicated obesity.

Key Words: weight management, type 2 diabetes, obesity

Introduction

As populations become more obese, there is increasing concern about the rapidly rising categories of severe obesity, which demand greater weight loss to control secondary medical consequences. T2DM is closely linked to obesity, and is the main contributor to rising healthcare costs of obesity^{1,2}. Most individuals with T2DM have a BMI >25 kg/m² and about half have a BMI >30 kg/m^{2,3,4}. With a BMI over 35 kg/m², 20% of all men and 11% of women have known diabetes⁵.

There is overwhelming evidence that modest sustained weight loss, e.g. current target of 5-10%, prevents the onset of most new T2DM in people with pre-diabetes⁶, and that it improves all aspects of diabetes control (glycaemia, blood pressure, lipids and microvascular damage⁷ with reductions in drug doses for medications used to treat hypertension, diabetes and dyslipidaemia⁸. While previous guidelines have retained a 5-10% weight-loss target, the 2010 Scottish Intercollegiate (SIGN) Obesity guideline, recognising changes in obesity prevalence, and also recent evidence for more aggressive interventions, has set a new national weight loss/maintenance target of >15-20% for those with BMI >35 kg/m, or >30 kg/m² with serious medical complications such as T2DM⁹. In routine UK National Health Service diabetes care, few people achieve a weight loss of >15kg (or >15%). Bariatric surgery is recommended for obese people with T2DM by both the UK National Institute for Care Excellence (NICE)¹⁰ and SIGN⁹, and has been shown to reverse the metabolic abnormalities of T2DM rapidly following surgery, at least in people up to 6 years after diagnosis of T2DM¹¹. Surgery carries immediate and long-term risks, and is not acceptable to all people. The metabolic benefits of bariatric surgery have been reproduced by negative energy balance alone, using a low energy liquid-formula diets, but these are seldom offered as part of diabetes care¹².

Weight loss in obese patients with and without T2DM

With conventional dietary advice, obese people with T2DM usually lose less weight than people without diabetes, partly because they have already lost what they can manage, and partly because many anti-diabetic drugs are obesogenic¹³. Here we provide a data synthesis, using systematic methods, assessing published studies to compare weight losses in people with T2DM and people without diabetes prescribed 'Total Diet Replacement' using modern commercial nutrient-replete Very Low Calorie diets (VLCD, < 800kcal/d) or Low Energy Liquid formula diets (LELD, >800kcal/d).

Methods

This review was conducted following the PRISMA guidelines on systematic reviews¹⁴.

Data sources and Searches

Systematic electronic searches of Medline (1946-2015), Embase (1947-2015), and CINAHL (1946-2015) were performed to identify published studies using formula Total Diet Replacement diets. Key search terms used were: (weight adj2 (loss or lost or losing or reduc* or change*)),*Obesity/; (type 2 diabetes or non-insulin-dependent diabetic or non-insulin-dependent diabetes or type 2 diabetes mellitus); (low energy liquid diet or low energy diet or very-low calorie diet or liquid formula diet or calorie restriction or very low calorie diet). Hand searching of reference lists of retrieved studies was also conducted. The search was limited to English language, human and adults.

Study Selection

Articles were selected on the basis of title and abstract. Inclusion was dependent on the following eligibility criteria: non-randomised or randomised controlled trial with a

Weight loss in obese patients with and without T2DM

primary purpose of weight management, adult participants (>18 years), weight change reported quantitatively, and a comparison of weight change in patients with and without T2DM made. Identification of potentially relevant studies,

Studies identified by the

Database searches and review of potentially relevant studies against inclusion/exclusion criteria were carried out independently by two reviewers (WL & LH).

Quality Assessment

The quality and possible sources of bias of included studies was independently assessed by two reviewers (WL & LH) using the Cochrane Risk of Bias Assessment tool for Non-Randomised Studies of Interventions (ACROBAT-NRSI) ¹⁵.

Data analysis

A random effects meta-analysis was conducted using Comprehensive Meta-analysis (CMA; Version 3.0 for Windows). The Weighted Mean Difference (WMD) in body weight between participants with T2DM and non-diabetic subjects was used as the summary estimate. Cochrane's Q statistic was used to assess heterogeneity, with the I^2 statistic used to measure the degree of heterogeneity.

Because studies varied in duration, which necessarily affects total weight loss, a comparison was made between the rates of weight loss. Mean weekly rate of weight loss was calculated for each study by dividing mean weight loss by number of study weeks. Mean rate of weight loss for all studies was calculated by multiplying mean weekly weight loss for each study by number of study participants, and then the sum

Weight loss in obese patients with and without T2DM

of these figures was divided by the total number of participants in the group. Where weight change was reported with SEM, this was converted to SD ($SEM \times \sqrt{n}$) to provide consistency in the reported variability.

Results

The systematic search identified 151 potential studies. After duplicates were removed 121 titles and abstracts were screened. Obviously irrelevant studies were excluded for the reasons illustrated in Figure 1. Full texts of 17 studies were retrieved and reviewed for eligibility against the inclusion/exclusion. Five studies fulfilled our criteria and were included in the review.

Study Characteristics

Setting

The studies reported results from USA^{16,17} Australia¹⁸, UK¹⁹, and Sweden²⁰. The settings for studies varied. In one study the intervention was delivered on an inpatient basis¹⁶, one was set in primary care¹⁹ an endocrine clinic¹⁸, obesity clinic¹⁷, and surgical unit²⁰.

Participant demographics

All studies recruited both males and females classified as obese (BMI >30kg/m²). One study (16) included some people with BMI >25kg/m². Mean age ranged from 43-55 years.

Exclusion Criteria

Exclusion criteria were not described in 2 studies^{19,20}. Use of anti-obesity medications was an exclusion criterion in one study¹⁸, and insulin use in another¹⁶.

Weight loss in obese patients with and without T2DM

Medications

Medications used in the management of T2DM were detailed in 3 studies^{18,19,20} and included metformin, sulphonylurea and insulin. The prescribed oral hypoglycaemic agents (OHA), was not specified in 1 study¹⁶. Medications in addition to those for diabetes management were detailed in two studies^{18,19}. One study did not detail medications at all¹⁷.

Energy content and duration of formula diets and total diet replacement

Daily energy provision from the formula diets varied among the included studies and ranged from 300 to 1000kcal/day (Table 1). The durations of VLCD/LELD reported in studies ranged from 4 to 52 weeks. In one study¹⁷ participants transitioned to include a meal of ~300 kcal at different time points.

Quality of Included Studies

All 5 included studies were non-randomised (as it is impossible to randomise into T2DM or non-diabetes categories); 2 case control studies^{16,17}, 1 in which participants were allocated to the treatment of their preference¹⁹, and 2 cohort studies; one retrospective¹⁷ and one prospective²⁰. As the studies were dietary interventions, none included blinding of participants.

Confounding was considered the main possible source of potential moderate or serious bias in all included studies (Table 2). Age, gender, baseline weight, and co-morbid conditions are potential confounders in the achievement of weight loss. Only one study included adjustments for these factors¹⁷. However in this study the transition from total meal replacement to partial meal replacement varied among

Weight loss in obese patients with and without T2DM

participants, with a potential influence on weight loss, and was not adjusted for in analysis. Participant selection was considered unlikely to have introduced significant bias, as in all studies those with T2DM were compared to those without diabetes from the same or similar population. Bias in the measurement of interventions was low, as in all studies the intervention was well defined. Outcomes were ascertained using objective measurements in all studies and therefore the risk of bias was considered low.

Attrition was reported in 2 of the 5 studies^{18 17}, and weight change data were reported for completers only (excluding dropouts). One study was carried out on an inpatient basis¹⁶ and all subjects were included in weight change analyses. In one study¹⁹ the study population was small, no dropouts were reported, and we have assumed all subjects were followed up and included in the analysis. In the remaining study²⁰ all subjects completed the study and were included in the weight change analyses. Risk of bias from missing data was therefore considered low.

Weight Losses

Baseline weights ranged from 99.0-126kg (BMI 30.0-42.6kg/m²). Total weight loss ranged from 8.9 -15kg in those with T2DM and 7.9 -21kg in those without diabetes, over treatment durations of 4-52 weeks.

The greatest rates of weight loss were mostly in studies with more restrictive VLCDs^{16, 19}. Study duration did not appear to influence overall weight loss. Mean weight loss in the study of longest duration¹⁷ was similar, or greater, than that observed in studies of shorter duration (Table 1).

Meta-analysis

Data allowing meta-analysis (mean weight change (SD or SEM)) were available for 4 studies (Fig 2). Analysis showed almost identical weight changes (post intervention) in those with and without diabetes (Weighted Mean Difference: -1.2kg; 95%CI -4.1 to 1.6kg). Substantial heterogeneity was observed ($I^2= 79\%$).

Safety

Transient events including constipation, dizziness, postural hypotension, dry skin and bad breath were reported in 2 studies ^{16, 18}. Serious adverse events were reported in one study. Severe hypoglycaemia was experienced by one diabetic patient using VLCD, and one patient in each group suffered a non-fatal myocardial infarction ¹⁹. The remaining 2 studies reported that the intervention/study was completed without any adverse events ^{17, 20}.

Discussion

Substantial mean weight losses were achieved in all studies following VLCD/LELD, varying from 8-21kg in total over 4-52 weeks. That total depended on a variety of factors, including duration of diet, and clinical characteristics of groups, such as age, gender and status of health. In all the studies, the mean rate of weight loss fell below that that predicted for 100% compliance with the estimated energy deficit.

Weight losses were similar for participants with T2DM and participants without diabetes, with the exception of one study ¹⁶, where baseline weight was significantly

Weight loss in obese patients with and without T2DM

greater in participants without diabetes (126.1 ± 8.5 versus 99.7 ± 3.7 kg, $P < 0.05$), which is likely to have contributed to greater weight loss in the non-diabetic group.

The data generated on weight loss per week, as studies varied widely in duration, also showed similar rates of weight loss in those with T2DM and those without. As with overall weight loss this was with the exception of the study by Henry ¹⁶, in which a greater rate of weight loss was observed in those without diabetes, again reflecting the higher baseline weight.

The mean weight loss in people with T2DM reported here, in studies which compared people with T2DM and those without T2DM, is similar to a previous meta-analysis of VLED in T2DM which reported substantial weight loss of 9.6% by people with T2DM over a 6 week period, at a rate of around 1.6 kg/week ¹³. Studies using similar diets among only non-diabetic participants report similar mean weight losses ^{21, 22, 23}.

Similar weight losses with VLCD &LELD have been reported previously in the study by Christensen ²¹, which compared VLCLD & LELD, with weight losses of around 11kg was observed in both study groups over 8 weeks. Greater energy restriction also conferred no additional benefit in the study by Lin ²² with a mean weight loss of 8 kg observed in both groups (450 vs.800 kcal/d) after 12 weeks. Wikstrand and colleagues ²³ reported mean weight losses of 20kg and 16kg in free living non-diabetic, male and female participants respectively.

Amongst the studies included in the present review, rates of weight loss were consistent, at 1.2-3.2 kg/week except for much lower rates in studies by Li ¹⁷ 0.3 kg/week, and Baker ¹⁸, 0.7 kg/week. The study by Li was over a much longer period

Weight loss in obese patients with and without T2DM

of 52 weeks, and the duration of the exclusive formula diet phase was variable amongst participants over the 1 year period, as they could opt to include a meal of ~300 kcal at different time points. which may have contributed to the lower rate of weight loss. Lower weight loss in comparison to other studies was acknowledged by Baker and colleagues. Factors suggested by the authors to explain this were a “calendar effect” and also that the study population were well established patients at a tertiary referral centre and may have represented a more “difficult to treat group” than that of other studies.

The metabolic benefits of bariatric surgery appear to be reproducible by VLCD/LELD. The Newcastle Counterpoint study ¹² achieved reversal of T2DM with mean weight loss of 15.3kg in 11 people with T2DM within 4 years of diagnosis, using a 600 kcal/d low energy liquid diet. The normalisation of fasting plasma glucose persisted for up to 3 months after return to normal diet. Normalisation of HbA1c, or fasting blood glucose, following VLCD was reported in one study included in the present review ¹⁹, with mean absolute weight loss similar to that achieved by Lim and colleagues ¹². However normalisation of metabolic status relates both to ongoing energy restriction and on overall weight loss. Acute energy restriction has been shown to improve plasma glucose values and insulin sensitivity even before significant weight loss occurs ^{12,13}.

Formula diets, with a period of total diet replacement, are widely used and popular outside healthcare settings. There is some published evidence that they are successful, with little or no evidence for serious safety problems ²⁴, although large-scale safety testing has not been undertaken. The serious adverse events reported

Weight loss in obese patients with and without T2DM

in one study included in the present review were not considered directly related to the diet. Despite clear evidence for efficacy and lack of safety concerns, there is a continuing reluctance by medical staff and in clinical guidelines to support the use of formula diets. Guidelines published in the USA and Australia^{25,26} advocate the use of very low calorie/energy diets for weight management, but recommend these should be delivered in medical settings, with close medical monitoring.

At present formula diets are not funded directly within routine UK NHS care, whereas bariatric surgery is. In the 1970s there was concern about safety of ill-designed modified fasting diets²⁷. Beliefs that more intensive interventions and rapid weight loss lead to greater weight regain, are not supported by evidence from controlled trials. Comparison of weight regains, following either a 12 week rapid weight loss programme or a 36 week gradual programme, found no difference in the proportion of weight regained at 144 week follow up²⁸. Effective strategies for long-term weight-loss maintenance have been described^{29,30}. A study conducted within routine NHS primary care²⁹ found that an 810 kcal/d Low Energy Liquid-formula Diet (LELD) was well accepted by 91 severely obese participants (mean BMI 48 kg/m²), and by GP's and nurses. Those who attended had a mean weight loss of around 17kg in 12 weeks. Critically around 33% of all 91 entrants maintained >15kg weight loss at 12 months. The study was in people without diabetes, but the present review would suggest that results in those with T2DM would not differ greatly. One year follow up of patients with knee osteoarthritis also found that a structured weight maintenance programme resulted in good maintenance of weight loss.³⁰

It is estimated that by 2025, without new interventions for prevention of weight gain and obesity, five million people in the UK will have diabetes, mostly T2DM

Weight loss in obese patients with and without T2DM

(DiabetesUK.org). Despite the recommendations in current clinical guidelines, there is no realistic prospect of bariatric surgery being offered to most obese people because of surgical and follow-up resource limitations. In addition, many people will not agree to surgery. New weight management approaches are required for obese people with T2DM that can be implemented in routine care, where most of these people are managed. The present results suggest that the weight loss phase of weight management can be achieved by a period of 'Total Diet Replacement' TDR, using micronutrient-complete formula diets. This approach towards the SIGN weight loss target of >15kg (enough to reverse most recent onset T2DM), in many cases is more cost-effectiveness than bariatric surgery²⁹.

Most published studies do not adequately describe whether adverse events were sought systematically, or simply reported on an ad-hoc basis. Future research should include systematic data collection. At present there is no evidence for serious adverse events, and no specific medical monitoring is necessary except for withdrawal or dose reduction of hypoglycaemic, diuretic or anti-hypertensive drugs.

Limitations

This systematic review was limited by the very small number of published studies, using a range of TDR methods, which directly compared weight losses in people with and without T2DM. There was substantial heterogeneity in the studies included, although due to the limited number of studies subgroup analysis could not be conducted to explore heterogeneity. Differences in diets (ie. different calorie provisions across VLCD and LELD) and in particular the very different study durations probably explain much of the statistical heterogeneity. We therefore expressed the results as kg lost per week, in order to reduce the effect of study

Weight loss in obese patients with and without T2DM

duration. There was no clear pattern to suggest different rates of weight loss between VLED and LELD, despite different prescribed energy deficits, indicating differences in compliance. This supports the conclusion of Christensen et al that weight losses are similar on VLED or LELD ²¹. Heterogeneity may also have arisen from differences in prescribed medications and other aspects of diabetes care between the studies included. Despite the heterogeneity, the results from the different studies remain rather similar both within and between the patient groups, which provides some confidence that there is no important difference in the weight loss responses of T2DM and non-diabetic people when treated with a formula 'Total Diet Replacement'. Future studies should include more complete data on clinical details (e.g. medications) and complete data on the outcomes for all entered subjects. The extent of data among people with T2DM does not permit assessment of any diabetes-specific safety issues.

Conclusion

These data demonstrate that weight losses with VLCD or LELD are very similar, and that weight losses, following interventions of 4-52 weeks duration, are no different for obese people with or without T2DM. This result is novel, since most published studies of diet and lifestyle interventions have shown less weight loss among subjects with diabetes. It provides a firm baseline upon which the use of LELD may be further developed to achieve new weight-loss targets of >15-20% for those with severe and medically complicated obesity. Further research is warranted to evaluate the delivery of more intensive, and better sustained, non-surgical weight-management approaches for routine NHS application, which could offer great benefit to people with T2DM.

Weight loss in obese patients with and without T2DM

Contribution statement: ML & RT conceived of the idea. WL & LH collected and analysed the data. WL drafted the paper. All authors reviewed and revised the paper, and approved the final version.

Competing interests: WL, ML & RT are currently engaged on the Diabetes Remission Clinical Trial (DiRECT) funded by Diabetes UK with additional support in kind from Cambridge Weight Plan. ML and RT have received support related to the use of formula diet products from Cambridge Weight Plan and from Nestle.

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Weight loss in obese patients with and without T2DM

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Weight loss in obese patients with and without T2DM

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Weight loss in obese patients with and without T2DM

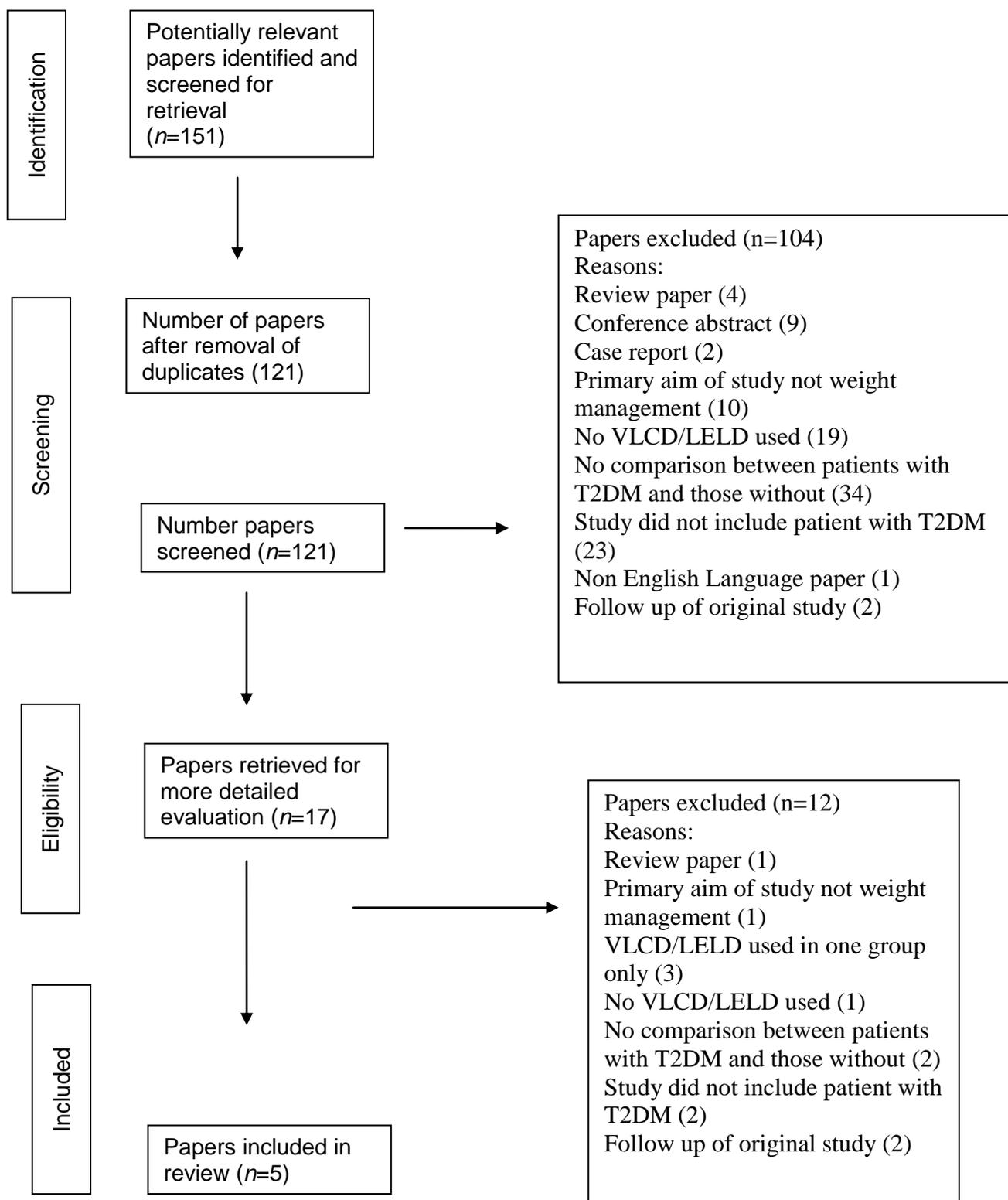
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Weight loss in obese patients with and without T2DM

Figure 1: Flowchart of progress of papers through the review.



Weight loss in obese patients with and without T2DM

Table 1: Studies that directly compared weight loss using VLCD or LELD in patients with and without T2DM

Reference	n #	Mean age (SD)		Sex (m/f %)		Mean BMI at Baseline (kg/m ²)		VLCD/LELD Duration (wk)	Energy provision (kcal/d)	Mean Weight Loss kg (SD)		Mean weekly weight loss (kg)	
		Diabetic	Non-diabetic	Diabetic	Non-diabetic	Diabetic	Non-diabetic			Diabetic	Non-diabetic	Diabetic	Non-diabetic
Noren ²⁰ (2014)	25**	48.8(8.3)		N/A		39.8		4	680	(n=7) 8.9(1.9)	(n=18) 7.9(2.8)	2.2	2.0
<i>Sweden</i>													
Li ¹⁷ (2014)	444*	48.4 (10.0)	44.3 (11.6)	30/70	23/77	36.0	34.7	52	500-1000	(n=109) 14.5(11.4)	(n=337) 14.5(11.8)	0.3	0.3
<i>USA</i>													
Baker ¹⁸ (2012)	51*	54.4 (7.3)	48.5 (11.4)	50/50	33/67	38.1	36.6	12	800	(n=24) 8.5(6.3)	(n=27) 9.3(6.2)	0.8	0.7
<i>Australia</i>													
Paisey ¹⁹ (1998)	34**	50.3 (8.8)	53.0 (5.5)	47/53	32/68	30		12-16	Men 540-570	(n=15) 15 ≠	(n=19) 21 ≠	1.2	1.7
<i>UK</i>													
Henry ¹⁶ (1986)	15**	49.9 (11.7)	43.2 (3.5)	20/80	40/60	35.5	42.6	5	300	(n=10) 11.1 (2.2)	(n=5) 16.2 (2.4)	2.2	3.2
<i>USA</i>													
Participant Total	569	Mean weekly rate of weight loss on VLCD/LELD (all studies combined weighted for numbers of subjects)										0.6kg	0.5kg

number used for analysis of weight change following VLCD/LELD; either * per protocol, or ** ITT ;≠ SD or SEM not reported

Weight loss in obese patients with and without T2DM

Table 2: Risk of bias assessment

Reference	Risk of Bias
Noren (2014) ²⁰	<i>Confounding: Serious risk</i> <i>Selection of participants: Low risk</i> <i>Measurement of interventions: Low risk</i> <i>Missing data: Low risk</i> <i>Measurement of Outcomes : Moderate risk</i>
Li (2014) ¹⁷	<i>Confounding: Moderate risk</i> <i>Selection of participants: Low risk</i> <i>Measurement of interventions: Low risk</i> <i>Missing data: Low risk</i> <i>Measurement of Outcomes : Low risk</i>
Baker (2012) ¹⁸	<i>Confounding: Moderate risk</i> <i>Selection of participants: Low risk</i> <i>Measurement of interventions: Low risk</i> <i>Missing data: Low risk</i> <i>Measurement of Outcomes : Low risk</i>
Paisey (1998) ¹⁹	<i>Confounding: Serious risk</i> <i>Selection of participants: Moderate risk</i> <i>Measurement of interventions: Low risk</i> <i>Missing data: Low risk</i> <i>Measurement of Outcomes : Low risk</i>
Henry (1986) ¹⁶	<i>Confounding: Serious risk</i> <i>Selection of participants: No information</i> <i>Measurement of interventions: Low risk</i> <i>Missing data: Low risk</i> <i>Measurement of Outcomes : Low risk</i>

Weight loss in obese patients with and without T2DM

Figure 2: Meta-analysis (WMD) of studies comparing weight losses in those with type 2 diabetes and non-diabetic subjects

