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Efficacy and safety of very low calorie ketogenic diet (VLCKD) in patients with overweight and obesity: A systematic review and meta-analysis

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Abstract

Very low calorie ketogenic diet (VLCKD) has been proposed as a promising option to achieve a significant weight loss in a short time period. We conducted a systematic review and meta-analysis to evaluate its efficacy and safety in patients with overweight and obesity. Four databases were searched on May 2019. Studies reporting data on body weight, body mass index (BMI), waist circumference, body composition, blood pressure, HbA1c, lipids, and markers of liver and kidney function were selected. Discontinuation was also assessed. Twelve studies were included. VLCKD was associated with weight losses of −10.0 kg ($I^2 = 6\%$) and − 15.6 kg ($I^2 = 37\%$) in studies with a ketogenic phase up to and of at least four weeks, respectively. The weight lost during the ketogenic phase was stable in the subsequent follow-up up to two years ($p = 0.12$). Also, VLCKD was associated with reductions of BMI (−5.3 kg/m^2), waist circumference (−12.6 cm), HbA1c (−0.7%), total cholesterol (−28 mg/dl), triglycerides (−30 mg/dl), AST (−7 U/l), ALT (−8 U/l), GGT (−8 U/l), systolic and diastolic blood pressure (−8 and − 7 mmHg, respectively). No changes in LDL cholesterol, HDL cholesterol, serum creatinine, serum uric acid and serum potassium were found. Serum sodium increased during VLCKD (+1.6 mEq/l). The overall prevalence of patients discontinuing VLCKD was 7.5% and this was similar to patients undergoing a low calorie diet ($p = 0.83$). The present review supports the use of VLCKD as an effective strategy for the management of overweight and obesity. Future guidelines should include a specific recommendation for this intervention.

Keywords Very low calorie ketogenic diet · VLCKD · Obesity · Overweight · Systematic review · Meta-analysis

1 Introduction

Obesity represents one of the major public health issues worldwide since associated with several diseases, including type 2 diabetes mellitus (T2DM), coronary heart disease, cerebral vasculopathy, arterial hypertension, and dyslipidemia, which contribute to a reduction of both life quality and expectancy [1]. Over the past 40 years, there has been a rapid increase in the global rates of obesity in both men and women, which has further increased the burden of this disease [2, 3]. Nevertheless, the achievement of a weight loss of at least 5–10% is associated with significant clinical benefits on most of the obesity-related comorbidities [4–9]. In order to achieve this target, several strategies are available. These include peer-reviewed and approved lifestyle modification programs, protocolled diets, medications, and surgery. Particularly, bariatric surgery is characterized by the highest efficacy, but costs, requirement of skilled operators and limited indications make this procedure sustainable for a very small percentage of

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patients [10]. Also, a treatment gap exists for those patients who do not respond adequately to lifestyle interventions with or without drugs and who are not viable candidates for or refuse bariatric surgery [11].

In the context of protocolled diets, the very-low-calorie ketogenic diet (VLCKD) has been found to be promising. This diet is generally characterized by a multiphase protocol, including an active, a metabolic stabilization and a maintenance stage. First, patients are started on a short period of calories and carbohydrates restriction (<700-800 kcal/day, <30-50 g/day, 13-25% of total calories), with an amount of protein equivalent to 0.8-1.2 g/day per kg of ideal body weight. This first step usually lasts up to 12 weeks and is associated with increased ketone bodies production by the liver, delivering lipid-derived energy to extrahepatic organs (e.g., heart, kidney, skeletal muscle, central nervous system), where they act as an alternative fuel source [12, 13]. Moreover, ketogenesis appears to be the main mechanism responsible for the anorexigenic effect correlated with a high compliance and motivational spur to this treatment [14]. Then, a gradual reintroduction of protein foods is performed, still keeping the overall calories below 700-800 kcal/day. In the second and third phases, calories and carbohydrates are gradually raised to a low-calorie and, then, to a balanced diet with a daily intake of 800-1500 and 1500-2250 kcal, respectively, depending on the characteristics of patients [15, 16]. All in all, the temporary significant restriction of both calories and carbohydrates associated with an adequate protein intake allows for a fast and consistent weight loss, fat loss (particularly visceral fat), sparing of free fat mass, inhibition of hunger and craving. The subsequent steps are needed to allow a stabilization of these changes [17–19].

Even if a number of studies investigated the efficacy of VLCKD in patients with overweight and obesity, a high-quality evidence is currently lacking. Also, the use of different acronyms standing for VLCKD and the overlapping use of the term "VLCKD" to indicate protocols other than the one described above has generated some confusion in the scientific community. Very-low-calorie ketogenic diet was reported as VLCK by some authors [20, 21]. A number of studies have been published on the very-low-carbohydrates ketogenic diet and the same abbreviation was used, although the former is characterized by a higher calorie intake [22]. Very-low-calorie ketogenic diet was described as very-low-carbohydrate ketogenic diet by other authors [23]. Also, in the context of ketogenic diets, other protocols have been proposed, including isocaloric ketogenic diet (ICKD) and high-fat ketogenic diet (HFKD). The aim of ICKD is the ketosis without any impact on body weight; thus, they have been evaluated in patients with epilepsy or cancer [24, 25]. On the other hand, HFKD should be considered synonym of very-low-carbohydrate ketogenic diet: to reach ketosis, the carbohydrate intake should be limited and calories given through other macronutrients, either fat or protein; increasing protein intake leads to gluconeogenesis and thus the inhibition of ketosis, therefore only very-low-carbohydrate high-fat but not high-protein diets can be ketogenic [26]. Simply putting together all the different protocols above under the definition "ketogenic diet" would be associated with a relevant bias and, possibly, to mistakes in the interpretation of the available evidence [27] (Table 1). Therefore, we believe that a sound and clear information on this topic may significantly help to define the role of VLCKD in clinical practice. Accordingly, we performed a systematic review and meta-analysis focusing on the efficacy of this intervention on body weight loss as well as on the main comorbidities, including hypertension, dyslipidemia, T2DM, and non-alcoholic fatty liver disease (NAFLD). The safety of this diet was also assessed.

2 Materials and methods

The systematic review was registered in PROSPERO (registration number CRD42019131738) and performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [28].

2.1 Search strategy

A six-step search strategy was planned. Firstly, we searched sentinel studies in PubMed. Secondly, we identified keywords and MeSH terms in PubMed. Thirdly, the terms "ketogenic", "calorie" and "VLCKD" were searched in PubMed in order to test the strategy. Fourthly, CENTRAL, Scopus and Web of Science were searched with the same strategy. Fifthly, studies evaluating VLCKD in adult patients with overweight and obesity were selected. Studies reporting less than 15 patients were excluded. Lastly, references of included studies were searched for additional papers. The last search was performed on May 14th, 2019. No language restriction was adopted. Two investigators (MC, PT) independently searched papers, screened titles and abstracts of the retrieved articles, reviewed the full-texts, and selected articles for their inclusion.

2.2 Data extraction

The following information was extracted independently by the same investigators in a piloted form: 1) general information on the study (author, year of publication, study name, study type, follow-up period, number of patients, age, sex, inclusion criteria, protocol for VLCKD and comparator); 2) end-points, including body weight, body mass index (BMI), waist circumference, body composition, blood pressure, HbA1c, lipids, markers of hepatic and kidney function; 3) number of discontinued patients. The main papers and supplementary data were searched; if data was missing,

Table 1 Characteristics of diets based on restriction of calorie and carbohydrates intake, ketosis and body weight loss

	Very-low-calorie ketogenic diet	Very-low-carbohydrate ketogenic diet / High-fat ketogenic diet	Very-low-calorie diet	Low-calorie diet	Isocaloric ketogenic diet
Calorie restriction (<800 kcal/day)	Yes	No	Yes	No	No
Carbohydrates restriction (<50 g/day)	Yes	Yes	No	No	Yes
Ketosis	Yes	Yes	No	No	Yes
Body weight loss	Yes	Yes	Yes	Yes	No

corresponding authors were contacted via email. Data were cross-checked, and any discrepancy was discussed.

2.3 Study quality assessment

The risk of bias of included studies was assessed independently by two reviewers (MC, EC). For observational studies, the National Heart, Lung, and Blood Institute Quality Assessment Tool was used, and the following aspects evaluated: study question; eligibility criteria; description and delivering of intervention; definition of outcome measures; sample size calculation; blinding; duration of follow-up; loss to follow-up; statistical methods; funding. Each domain was assigned absence, unclear or possible risk of bias [29]. For randomized controlled trials (RCT), the Cochrane Collaboration's tool for assessing risk of bias was used and the following aspects evaluated: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selecting reporting. For other bias, funding was assessed. Each domain was assigned low, unclear or high risk of bias [30].

2.4 Data analysis

The primary outcome was the change in body weight from baseline to the last available follow-up on VLCKD. Secondary outcomes included changes in BMI, waist circumference, body composition, blood pressure, heart rate, HbA1c, lipids, markers of hepatic and kidney function from baseline to the last available follow-up. Also, the change in body weight from the end of the ketogenic phase to the last available follow-up on VLCKD was assessed. The number of discontinued patients was analyzed. All endpoints were analyzed as continuous variables and summarized as weighted mean difference. The last one as dichotomous, and the proportion was estimated. A comparison with diets other than VLCKD was attempted; endpoints were summarized as weighted mean difference and relative risk (RR), respectively. If standard deviation was missing in a study for a specific outcome, it was calculated from standard error, 95% confidence interval or from interquartile range; if none of these were available, the largest among the other studies was reported. A subgroup analysis based on the duration of the ketogenic phase was performed, with an arbitrary cut-off of four weeks. Heterogeneity between studies was assessed by using I^2, with 50% or higher regarded as high. Publication bias was assessed with Egger's test; the trim-and-fill method was used for estimating its effect. All analyses were two-sided and were carried out using RevMan5.3 (The Cochrane Collaboration) and Prometa3.0 (Internovi) with a random-effect model; $p < 0.05$ was regarded as significant.

3 Results

3.1 Study characteristics

A total of 816 papers were found, of which 161 on PubMed, 58 on CENTRAL, 281 on Scopus and 316 on Web of Science. After removal of 383 duplicates, 433 articles were analyzed for title and abstract; 349 records were excluded (intervention other than VLCKD; performed in patients other than adults with overweight or obesity [i.e. with epilepsy, multiple sclerosis, migraine, cancer, inflammatory bowel disease, or pediatric], case reports, case series, not in humans). The remaining 84 papers were retrieved in full-text and 12 articles corresponding to 11 studies were finally included in the systematic review (Fig. 1) [16, 17, 20, 21, 23, 31–37]. One additional study was retrieved from a personal database [38].

3.2 Study quality assessment

The risk of bias of the included studies is shown in the Electronic Supplementary Material. Concerning the observational studies, statement of the study question, eligibility criteria, description and delivering of intervention, definition of outcome measures, duration of follow-up, loss to follow-up, and statistical methods were adequate in all. No data on sample size calculation was reported. In one study outcome measures were not taken multiple times [23]. Except for one study, outcome assessors were not blinded to the intervention [37]. Finally, three studies were funded by industry [17, 23, 33]. Concerning the four RCTs, no information on random sequence generation and allocation concealment was reported.

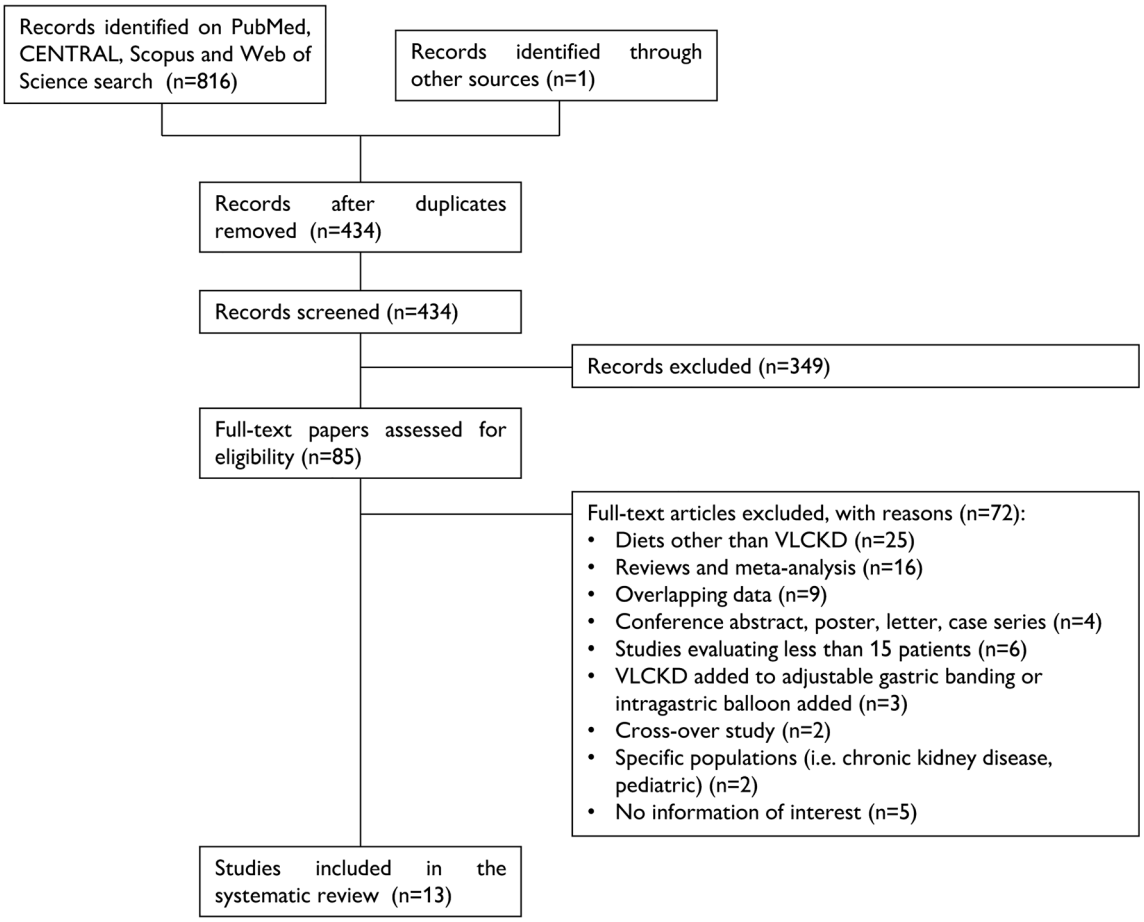

Fig. 1 Flow-chart of the systematic review

Three studies used an open-label design; since a double-blind protocol could have been adopted, the blinding of participants and personnel bias was rated as high [16, 20, 21, 36]. On the other hand, blinding of outcome assessment was rated as low since outcome measurement was not likely to be influenced by lack of blinding (i.e. change in body weight). Finally, three studies were funded by industry [16, 20, 21, 36].

3.3 Qualitative analysis (systematic review)

The characteristics of the included articles are summarized in Table 2. The studies were published between 2001 and 2019, had sample sizes ranging from 20 to 178 patients, and a follow-up from three weeks to two years. Four studies were randomized controlled trials, five prospective cohort, and one retrospective cohort; the design was not clearly state in two papers [23, 37]. The characteristics of VLCKD is reported in the Electronic Supplementary Material. The duration of the ketogenic phase was up to four weeks in six studies [23, 31–35]. VLCKD was compared with very-low-calorie diet (VLCD) and low-calorie diet (LCD) in one and three studies, respectively [16, 20, 21, 31, 33]. Participants were adult outpatients diagnosed with overweight and obesity; the only exception was the study by Albanese et al., 2019, in which patients aged from 14 to 70 years were included [31]. Three studies specifically evaluated patients with already planned bariatric surgery [31, 33, 35]. Eight hundred and one patients were included, 69% were females. The weighted-mean age was 46.1 ± 10.9 years, the weighted-mean body weight 110.9 ± 28.6 kg, and the weighted-mean BMI 40.7 ± 8.9 kg/m^2. Five hundred and ninety-five were treated with VLCKD, while 106 with VLCD and 100 with LCD.

3.4 Quantitative analysis (meta-analysis)

The primary outcome was the change in body weight from baseline to the last available follow-up. VLCKD was associated with weight losses of −10.0 kg (95%CI -13.2 to −6.8; $I^2 = 6\%$) and − 15.6 kg (95%CI -19.2 to −12.1; $I^2 = 37\%$) in studies with a ketogenic phase up to and of at least four weeks, respectively (Fig. 2). This was similar to VLCD ($p = 0.80$), but higher than LCD ($p = 0.002$) (Fig. 3). In the overall analysis, 8.5 kg out of 12.5 kg of body weight loss was represented by fat mass (66%) (Table 3). Also, the body weight lost during ketogenic phase was stable in the subsequent follow-up up to two years ($p = 0.12$) (Fig. 4).

Table 2 Characteristic of included studies

First Author, year	Country	Study design	Intervention	Comparator	Follow-up (weeks)	Duration of ketogenic phase (weeks)	Patients (n)	Inclusion criteria
Studies with duration of ketogenic phase up to four weeks								
Albanese et al., 2019 [31]	Italy	RCS	VLCKD	VLCD	3	3	178	14-70 years, planned bariatric surgery
Castaldo et al., 2016 [32]	Italy	PCS	VLCKD	–	9	3	73	18-70 years, BMI ≥ 30 kg/m^2
Leonetti et al., 2015 [33]	Italy	PCS	VLCKD	LCD	4	1.5	80	18-67 years, BMI > 40 kg/m^2, planned bariatric surgery
Merra et al., 2016 [34]	Italy	RCT	VLCKD	–	3	3	18	18-65 years, BMI ≥25 kg/m^2, percentage of body fat ≥25 for males, and ≥ 30 for females
Ministrini et al., 2019 [23]	Italy	–	VLCKD	–	3.6	3.6	52	18-65 years, BMI > 40 kg/m^2 or BMI > 35 kg/m^2 and obesity related comorbidities
Pilone et al., 2018 [35]	Italy	PCS	VLCKD	–	4	1.5	119	18-62 years, BMI > 40 kg/m^2, planned bariatric surgery
Studies with duration of ketogenic phase of at least four weeks								
Basciani et al., 2015 [38]	Italy	PCS	VLCKD	–	24	4	24	18-50 years, BMI 30-40 kg/m^2
de Luis et al., 2016 [36]	Spain	RCT	VLCKD*	–	24	8	29	18-65 years, BMI 30-35 kg/m^2, stable body weight in the previous 3 months, desire to lose weight
Goday et al., 2016 [21]	Spain	RCT	VLCKD	LCD	16	4-6	89	30-65 years, BMI 30-35 kg/m^2, type 2 diabetes mellitus
Gomez-Arbelaez et al., 2017 [17]	Spain	PCS	VLCKD	–	16	8-12	20	18-65 years, BMI ≥ 30 kg/m^2, stable body weight in the previous 3 months, desire to lose weight, history of failed dietary efforts
Krotkiewski et al., 2001 [37]	Sweden	–	VLCKD	–	4	4	66	BMI > 30 kg/m^2
Moreno et al., 2014 + 2016 [16, 20]	Spain	RCT	VLCKD	LCD	104	4-8	53	18-65 years, BMI ≥ 30 kg/m^2, stable body weight in the previous 3 months, desire to lose weight, history of failed dietary efforts

* in de Luis et al., 2016 docosahexaenoic acid was prescribed to a subgroup of patients on VLCKD. BMI, body mass index; LCD, low-calorie diet; PCS, prospective cohort study; RCS, retrospective cohort study; RCT, randomized controlled study; VLCD, very-low-calorie diet; VLCKD, very-low-calorie ketogenic diet; −, not retrieved

VLCKD was associated with reductions in BMI of −4.2 kg/m^2 (95%CI -6.4 to −2.0; I^2 = 77%) and − 6.2 kg/m^2 (95%CI -7.4 to −4.9; I^2 = 73%) in studies with a ketogenic phase up to and of at least four weeks, respectively (Fig. 5). Furthermore, it was associated with a reduction in waist circumference of −9.7 cm (95%CI -13.1 to −6.3; I^2 = 67%) and − 15.6 cm (95%CI -20.3 to −10.9; I^2 = 76%) in studies with a ketogenic phase up to and of at least four weeks, respectively (Fig. 6). Finally, it was associated with reductions in HbA1c, total cholesterol, triglycerides, AST, ALT, GGT, systolic blood pressure (SBP), and diastolic blood pressure (DBP). No change in LDL cholesterol, HDL cholesterol, serum creatinine, serum uric acid, and serum potassium were found. Serum sodium increased during VLCKD (Table 3, Electronic Supplementary Material).

The overall prevalence of patients discontinuing VLCKD was 7.5%. Compared to LCD, VLCKD was associated with a RR of discontinuation of 0.9 (95%CI 0.6 to 1.5; I^2 = 0%) (Fig. 7). In the VLCKD arm, four patients dropped out due to intervention-related adverse events (nausea, vomiting), one because of pregnancy, one underwent surgery, one showed poor compliance, while in all the remaining patients the decision was based on personal choice or reasons unrelated to the study.

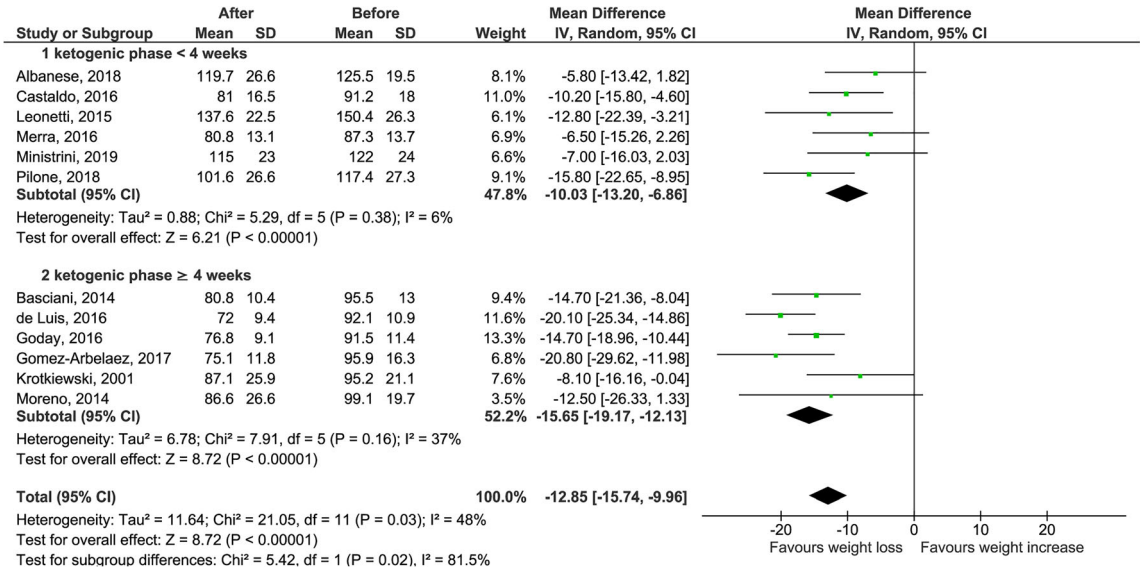

Fig. 2 Forest plot of meta-analysis for change in body weight from baseline to the last available follow-up on VLCKD

There was no evidence of publication bias, except for change in body weight on VLCKD versus other diets and change in total cholesterol on VLCKD; the trim-and-fill method did not change the statistical significance of these results (Electronic Supplementary Material).

4 Discussion

The aim of this systematic review and meta-analysis was to identify the best available evidence on the efficacy and safety of VLCKD in overweight and obesity management. Twelve studies were found, including 801 adult patients. The overall results of our meta-analysis showed a high efficacy of VLCKD on body weight, BMI, and waist circumference. Results obtained early during the ketogenic phase were stable during a follow-up up to two years. Also, VLCKD was associated with improvements in HbA1c, total cholesterol, triglycerides, AST, ALT, GGT, SBP, and DBP. No changes in LDL cholesterol, HDL cholesterol, serum creatinine, serum uric acid and serum potassium were observed, while an increase in serum sodium was recorded. Finally, the risk of discontinuation was similar between VLCKD and LCD. To our knowledge, this is the first systematic review and meta-analysis on this intervention. An extensive database search was performed, papers were searched without time or language restrictions, and inclusion criteria were defined prior to the database search.

The approach to the management of overweight and obesity is mainly based on BMI, comorbidities and age of the patient. Particularly, bariatric surgery should be generally considered in adult patients aged less than 60 with: 1) BMI $\geq$ 40 kg/m^2 without or with subclinical obesity-related risk-factors; 2) BMI between 35 and 39.9 kg/m^2 with established obesity-related chronic diseases; 3) BMI between 30 and 34.9 kg/m^2 with established end-organ damage [39]. Also, according to some guidelines, it should be considered in patients with BMI between 30 and 34.9 kg/m^2 and type 2 diabetes on an individual

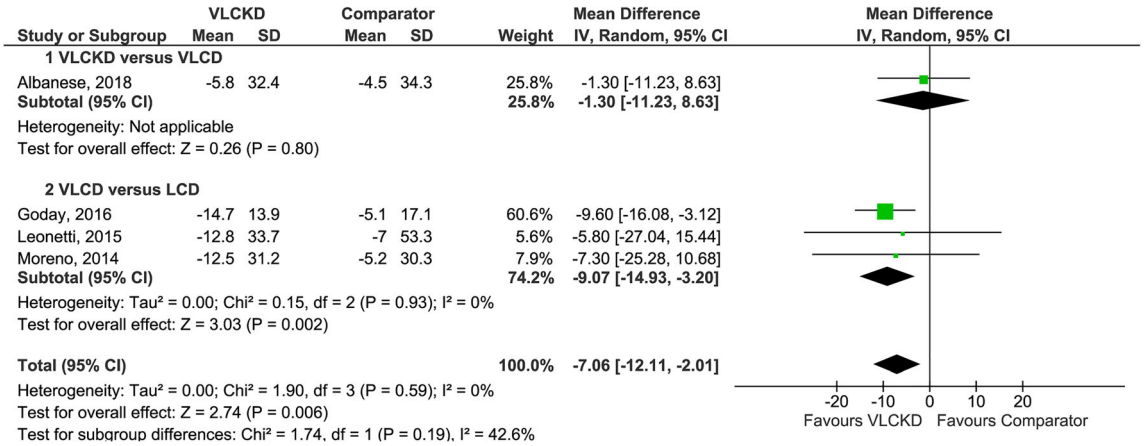

Fig. 3 Forest plot of meta-analysis for differences in body weight changes from baseline to the last available follow-up on VLCKD versus other diets

Table 3 Meta-analysis for change in other secondary outcomes on VLCKD

Parameter	Number of patients (number of studies)	Estimate	I^2	p
Fat mass (kg)	189 (7)	−8.5 (−11.1 to −6.0)	80%	<0.001
Lean mass (kg)	108 (6)	−4.4 (−5.3 to −3.6)	0%	<0.001
HbA1c (%)	185 (4)	−0.7 (−1.3 to −0.1)	87%	0.03
Total cholesterol (mg/dl)	485 (9)	−27.9 (−46.9 to −9.1)	96%	0.004
LDL cholesterol (mg/dl)	419 (8)	−6.4 (−14.8 to 1.9)	79%	0.13
HDL cholesterol (mg/dl)	419 (8)	−1.8 (−4.9 to −1.3)	66%	0.25
Triglycerides (mg/dl)	485 (9)	−29.8 (−40.1 to −19.6)	57%	<0.001
AST (U/l)	345 (6)	−7.2 (−12.1 to −2.3)	91%	0.004
ALT (U/l)	345 (6)	−7.7 (−13.2 to −2.2)	73%	0.006
GGT (U/l)	202 (4)	−8.0 (−11.3 to −4.7)	0%	<0.001
SBP (mmHg)	199 (4)	−8.5 (−11.4 to −5.6)	30%	<0.001
DBP (mmHg)	199 (4)	−7.2 (−8.9 to −5.5)	0%	<0.001
Serum creatinine (mg/dl)	293 (5)	0.0 (0.0 to 0.0)	0%	0.60
Serum uric acid (mg/dl)	293 (5)	−0.3 (−1.1 to 0.5)	92%	0.50
Serum sodium (mEq/l)	269 (4)	1.6 (0.6 to 2.5)	73%	<0.001
Serum potassium (mEq/l)	269 (4)	0.0 (−0.2 to 0.2)	89%	0.70

basis or in patients aged between 60 and 65 years [40, 41]. In patients not meeting these criteria, other interventions should be considered. Pharmacological therapy is approved for patients with BMI ≥ 30 kg/m^2 or BMI ≥ 27 kg/m^2 with any obesity-related diseases, while lifestyle intervention should be warranted in all. The recommendations above are based on results expected for each strategy. A meta-analysis of RCTs found bariatric surgery to be associated with an additional weight loss compared to lifestyle intervention of 25.9 kg in patients with a mean baseline body weight of 114.8 ± 33.7 kg and BMI of 39.5 ± 6.8 kg/m^2 at two-years follow-up [42]. Another meta-analysis of RCTs found pharmacological therapy to be associated with an additional weight loss compared to lifestyle intervention between 2.6 and 8.8 kg in patients with a baseline median body weight of 100.5 kg (range 95.3–115.8) and BMI of 36.1 kg/m^2 (range 32.6–42.0) at one-year follow-up [43]. No specific recommendations are reported for VLCKD so far [39–41]. In patients with similar characteristics at baseline, the present meta-analysis found VLCKD to be associated with a weight loss lower than bariatric surgery but greater than pharmacological therapy. Future guidelines should reflect these findings and specific criteria to identify patients to be candidate for VLCKD should be reported.

Based on fat distribution in gluteal and femoral versus abdominal regions, obesity can be classified as with gynoid and android, or peripheral and central, or "pear" and "apple" fat pattern, respectively. Besides topography, the characteristics of adipose tissue differ, with the visceral one carrying an increased risk for metabolic, cardiovascular, and cancer outcomes. As a consequence, waist circumference cut-offs have been proposed by different societies [44, 45]. VLCKD was associated with significant reductions of both fat mass and waist circumference. Also, despite the lower lean mass at the end of this intervention, no change in resting metabolic rate was found [18]. All in all, body weight loss together with favorable changes in body composition were reported.

As already stated, VLCKD consists of a multiphase protocol: patients are started on a ketogenic phase, then they are gradually shifted to LCD first, and then to an isocaloric diet. Accordingly, the ketogenic phase may differ from the duration of the diet regimen and the study follow-up too. Since the ketogenic phase is responsible for approximately 80% reduction of the excess body weight, we classified studies according to the duration of this phase, using a four-week period as cut-off [16]. Interestingly, despite the differences in body weight at baseline, no heterogeneity was found for body weight

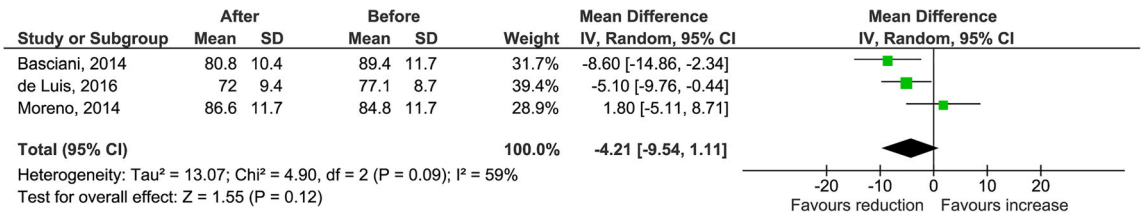

Fig. 4 Forest plot of meta-analysis for change in body weight from the end of ketogenic phase to the last available follow-up on VLCKD

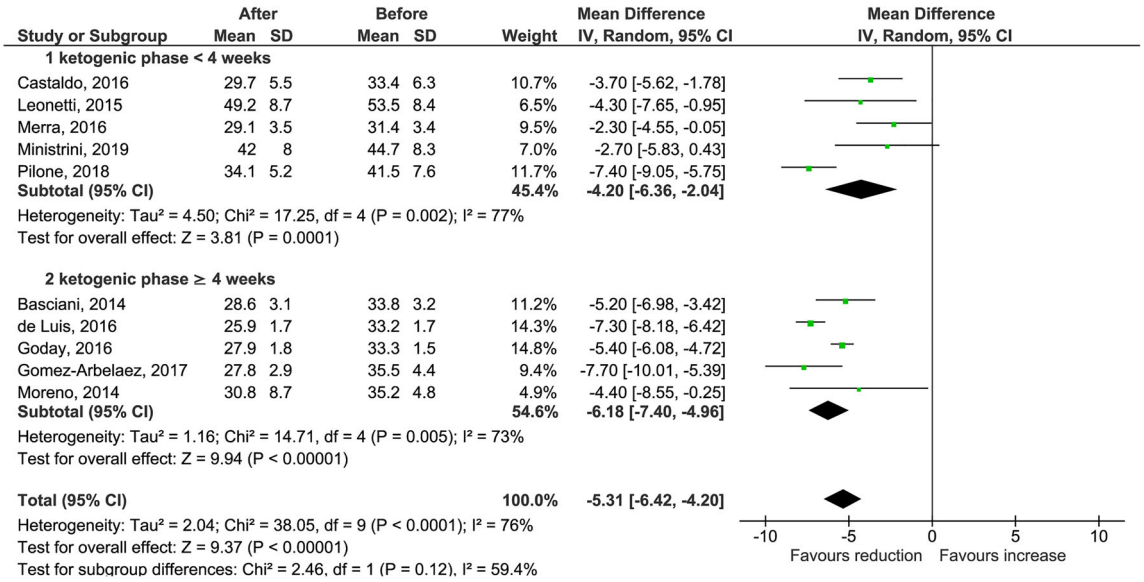

Fig. 5 Forest plot of meta-analysis for change in body mass index from baseline to the last available follow-up on VLCKD

changes in each subgroup (Fig. 2). Also, results obtained early were stable during a follow-up up to two years. Thus, VLCKD should be considered as a reliable intervention to achieve a significant weight loss in a short period of time. Depending on the target to be reached, a different duration of the ketogenic phase should be planned. Particularly, in patients for whom a bariatric surgery is considered, protocols based on a ketogenic phase only for few weeks can be preferred, while longer protocols including all phases of VLCKD should be chosen for the remaining patients.

In the former group of patients, a strategic issue is represented by the preoperative weight loss since it is associated with reduction of hepatomegaly, improved accessibility to the abdominal cavity, shorter duration of operations and lower rates of complications [39]. Then, several strategies have been proposed to achieve this goal, including intragastric balloon (IGB) and lifestyle interventions [46–48]. It should be noted that IGB is associated with a mean 13.2% (95%CI 12.3-14.0) total body weight loss at six months, while the present meta-analysis found VLCKD to be associated with a mean weight loss of 14% in studies with a ketogenic phase up to 12 weeks [49]. Also, three studies were performed specifically focusing on this indication. Albanese et al. found VLCKD to be associated with a shorter hospital stay ($p = 0.04$), higher postoperative hemoglobin levels ($p = 0.04$) and lower drainage output ($p = 0.03$) compared to VLCD [31]. Pilone et al. reported a 30% reduction in liver volume on VLCKD, in line with a previous work [33, 35]. These results, as well as the non-invasive nature of this intervention, strongly support the use of VLCKD in this context. Combination therapies have also been proposed.

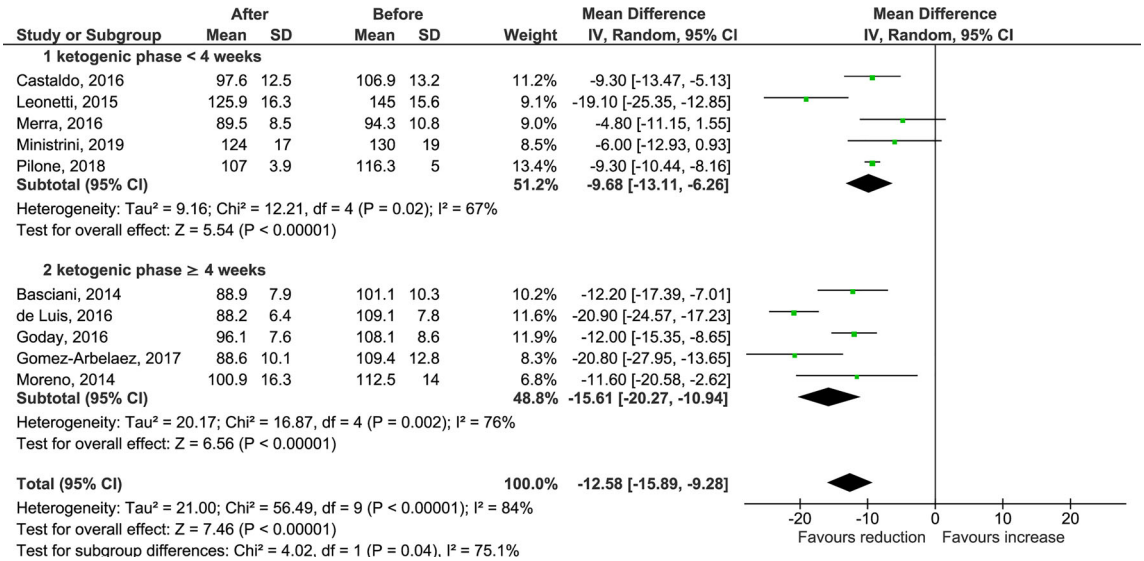

Fig. 6 Forest plot of meta-analysis for change in waist circumference from baseline to the last available follow-up on VLCKD

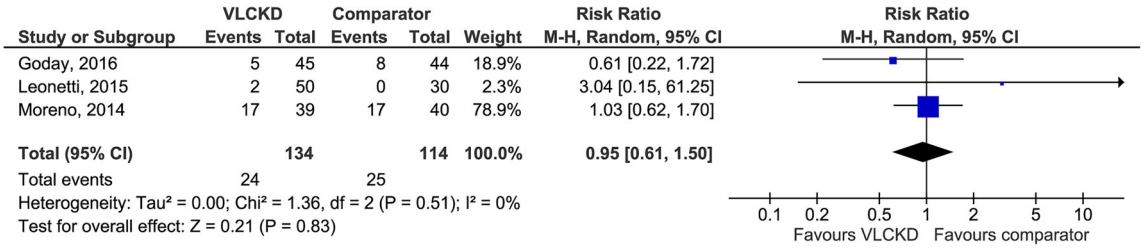

Fig. 7 Forest plot of meta-analysis for relative risk of discontinuation on VLCKD versus other diets

It is common experience that in patients with IGB the largest amount of body weight loss is recorded in the first four months. Then, a study randomized 80 patients to VLCKD or LCD in the last two months before IGB removal. Additional body weight was lost, and it was significantly greater in the VLCKD group. The overall body weight lost during the six-month period in patients on IGB and VLCKD was of about 18.3 kg; whether different results would have been reached if patients were treated with VLCKD only is unclear [50].

A number of comorbidities is associated with overweight and obesity, including hypertension, dyslipidemia, T2DM, NAFLD, and obstructive sleep apnea (OSA). According to current guidelines significant improvements of these are achieved following weight loss. A maintenance of a healthy body weight (BMI of approximately 20-25 kg/m^2 in people <60 years of age; higher in older patients) and waist circumference (<94 cm for men and < 80 cm for women) is recommended for non-hypertensive individuals to prevent hypertension, and for hypertensive patients to reduce blood pressure [51]. Even a modest body weight reduction of 5-10% improves lipid profile [52]. Achieving and maintaining a weight loss of at least 5% is recommended in T2DM patients, in order to slow the progression of the disease, improve glycemic control, reduce medication use, and induce disease remission. Also, very-low-calorie diets and total meal replacements may be prescribed for carefully selected patients in order to reach these targets [53]. A 7-10% weight loss is associated with improvements of liver enzymes and histology in patients with NAFLD, including non-alcoholic steatohepatitis [54, 55]. A weight loss of at least 7% to 11% or more is recommended in patients with OSA to achieve a significant improvement in its severity [40, 56]. Since VLCKD was found to be associated with a consistent weight loss, a positive effect on the above comorbidities or their markers should be expected. It is worth noting that drugs for hypertension and diabetes were discontinued before VLCKD in some studies [32], and drug consumption at the end of the study was reduced in a number of them [21, 32, 33]. Then, changes in blood pressure, lipids and HbA1c should be interpreted in view of this data as well. Also, an improvement in the liver steatosis pattern was reported in three papers, in line with changes of liver enzymes [23, 33, 35]. Finally, one study found an improvement in sleepiness in patients with OSA, consistently with the reported reduction in neck circumference [19, 33]. All in all, VLCKD was associated with a favorable change in most of major risk factors for cardiovascular disease.

A major concern when using VLCKD is represented by the safety issues. VLCKD is contraindicated in patients with type 1 diabetes mellitus, recent cardiovascular or cerebrovascular events, severe hepatic insufficiency, any type of renal insufficiency, gout episodes, kidney stones, hydroelectrolytic alterations, severe depression or any other psychiatric disease, abuse of narcotics or alcohol, and women with child-bearing potential, pregnant, breast-feeding, intending to become pregnant, or not using adequate contraceptive methods [15, 20]. Also, an adequate micronutrient supplementation should always be warranted, given their deficiency in restricted-calorie diets [57]. The risk of acidosis connected to ketones has been raised. A paper specifically focusing on this outcome was published and overall results were reassuring; this was not included in the meta-analysis due to overlap in patients [58]. The majority of papers described VLCKD as being well-tolerated with mild symptoms of short duration (e.g. nausea, vomiting, constipation, diarrhea, headache), and a risk of discontinuation similar to LCD was reported. However, the present meta-analysis found an increase in serum sodium, possibly related to the intense water loss that occurs in the first phase of any VLCKD [17]. Although statistically significant, the clinical relevance of this results may be limited given the absolute serum sodium level at the last available follow-up (140.1 ± 3.0 mEq/l) and sodium supplementation should always be assured given the increased natriuresis during ketosis [59]. Thus, it is worth to underline that this intervention, as all VLCD, should be not be routinely used as first line therapy for overweight and obesity management, but should be only considered in properly selected patients, as a part of a multicomponent strategy, and under strict medical supervision [60]. Another issue may be represented by the risk of weight regain following a sharp weight loss. Of note, a study found that fast weight losers obtained greater weight reduction and long-term maintenance and were not more susceptible to weight regain than gradual weight losers [61].

Limitations of the present paper should be discussed. First, a limited number of studies and usually with a short-term follow-up was found. As already stated, VLCKD can be used in two scenarios: 1) in a bariatric preoperative setting; 2) in a

lifestyle intervention. While current literature may be deemed sufficient for the former, further studies are needed for the latter. Particularly, a comparison with VLCD should be performed to assess additional benefits, if any. One possible advantage could be represented by reduced hunger associated with ketones [33]. Protocols for VLCKD differed between studies, and this is a second limitation. However, a consistent body weight loss with no heterogeneity was found despite the differences in calories and macronutrients composition. Forth, given that the 80% of body weight loss is achieved during the ketogenic phase and that it takes three to five days to reach this phase, an adequate patient compliance to the diet protocol is needed in order for the results to be replicable [62]. Lastly, even if the ketogenic phase was no longer than 12 weeks, there was no or limited evidence supporting the safety of VLCKD other than what has been the reported one (e.g. the effects on bone are unknown).

5 Conclusions

VLCKD proved to be a reliable option to achieve a significant weight loss in overweight and obese patients. Results were early obtained during the ketogenic phase and were stable over a follow-up of up to two years. In addition, VLCKD was associated with significant improvements in comorbidities, including hypertension, dyslipidemia, T2DM, and NAFLD. However, an increase in serum sodium was found. VLCKD should thus be regarded as an effective intervention to be proposed to properly selected patients, as a part of a multicomponent strategy, and under strict medical supervision.

Data accessibility The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Author Contributions MC and PT conceived the meta-analysis, developed the search strategy and provided statistical expertise. MC, EC, AC, and PT drafted the manuscript. All Authors contributed to the development of the selection criteria, the risk of bias assessment strategy and data extraction criteria. All Authors read, provided feedback, and approved the final manuscript.

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Compliance with ethical standards

Ethical approval These systematic review and meta-analysis were in accordance with the principles of the Declaration of Helsinki. Analyses were performed on data extracted from published papers.

Conflict of interest MC, EC, AC, SP, AG, LG, FG, and PT declare that they have no conflict of interest.

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