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REVIEW

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Effects of ketogenic diets on polycystic ovary syndrome: a systematic review and meta-analysis

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Abstract

Background This systematic review and meta-analysis aimed to evaluate the effects of ketogenic diet (KD) and very-low-energy ketogenic therapy (VLEKT) protocols on various health outcomes in patients with polycystic ovary syndrome (PCOS) and increased body weight.

Methods A systematic search was conducted across Scopus, PubMed, Cochrane, and Embase databases from their inception through January 2025, using a predefined search strategy. Studies were selected based on the PICOS criteria. Data extraction focused on anthropometric measures, glycometabolic and lipid profiles, and hormone levels. Controlled studies were analyzed to evaluate the effects of high-fat KDs and VLEKT compared to low calorie diets (LCDs). Additionally, uncontrolled studies were included, and the outcomes following high-fat KDs or VLEKT were compared to baseline values (before-after study design). A sub-analysis was also performed to compare VLEKT with high-fat KDs. We assessed the quality of the evidence, as well as heterogenity, sensitivity, and publication bias.

Results A total of 10 studies were included in the analyses, comprising three randomized controlle studies (RCTs), one non-randomized intervention study, four cohort studies, and two case series. Two RCTs comparing VLEKT and high-fat KDs with LCDs found no significant effect on body weight. However, both high-fat KDs and VLEKT were associated with reductions in body mass index (BMI) and fat mass percentage in patients with PCOS. Significant improvements in weight, BMI, fat mass, and lean mass were observed following high-fat KDs or VLEKT interventions compared to baseline values, with no substantial differences between the two diet types. Regarding glycometabolic outcomes, both high-fat KDs and VLEKT reduced serum glucose levels and the homeostatic model assessment index compared to LCDs, with VLEKT showing slightly more favorable effects. In terms of the lipid profile, both high-fat KDs and VLEKT lowered total cholesterol and triglyceride levels, and VLEKT showing greater efficacy in triglyceride reduction. Hormonal analyses from two RCTs showed that both high-fat KDs and VLEKT were associated with lower serum luteinizig hormone (LH) levels compared to LCDs. Additionally, both high-fat KDs and VLEKT led to reductions in LH and total testosterone levels relative to baseline, with VLEKT showing a slight advantage in lowering LH and follicle-stimulating hormone levels.

Conclusions High-fat KDs and VLEKT show beneficial effects on weight, body composition, glycometabolic parameters, and hormone profile in women with PCOS. VLEKT may provide additional advantages, particularly in reducing

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fat mass and lowering triglyceride levels. Further studies with larger sample sizes and more robust study designs are needed to confirm these findings.

Keywords PCOS, Ketogenic diet, Very-low-calorie ketogenic diet, Hormones, Body weight, Glycolipid metabolism, Fat mass

Introduction

Polycystic ovarian syndrome (PCOS) is the most prevalent endocrine disorder affecting women of reproductive age worldwide. It is primarily characterized by hormonal imbalances and dysregulation of the hypothalamic-pituitary-ovarian axis, involving alterations in several hormones, including insulin, growth hormone (GH), ghrelin, leptin, gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), LH/FSH ratio, androgens, estrogens, anti-Müllerian hormone (AMH), and sex hormone-binding globulin (SHBG). These endocrine abnormalities contribute to mentrual dysfunction, infertility, and metabolic disturbances such as insulin-resistance (IR), obesity, and an increased risk of developing gestational diabetes mellitus and type 2 diabetes mellitus (T2DM). Additionally, PCOS is associated with reduced GH levels, elevated basal LH, an LH/FSH ratio > 2.5, increased androgen and estrogen levels, and impaired progesterone secretion, all of which contribure to the formation of multiple small antral follicles, a key factor in infertility [1].In addition to common symptoms such as menstrual irregularities, hirsutism, acne, and weight gain, women with PCOS may exhibit an increased percentage of fat mass even when their body mass index (BMI) is within the normal range [2].

The management of PCOS requires a comprehensive approach, with lifestyle modifications—encompassin dietary changes, physical activity, and behavioral interventions—serving as the first line of treatment. Dietary recommendations should be individualized based in body weight, physical activity levels, and energy requirements. Although the 2023 PCOS guidelines indicate insufficient evidence to support a specific dietary intervention [3], weight loss through dietary modifications remains a cornerstone of treatment, particularly for women with overweight or obesity. A 5–10% reduction in body weight has been shown to significantly improve metabolic function.

Research on dietary composition in women with PCOS has focused on both macro- and micronutrient intake, generally advocating for a reduced-carbohydrate diet that prioritizes complex carbohydrates, which are high in fiber and have a low glycemic index. This dietary pattern has been associated with improved insulin sensitivity, lower blood glucose levels, and modulation of the gut microbiome [4].

In recent years, ketogenic diets (KDs) have gained recognition as an effective and safe dietary approach for improving metabolic health and managing conditions such as IR. The term "ketogenic diet" (KD) has been generally employed for a high-fat, low-carbohydrate, and normal-protein diet, where fat typically constitutes more than 70% of total caloric intake. This diet induces hepatic production of ketone bodies, primarily acetoacetate and ß-hydroxybutyrate, as an alternative energy sources, leading to a catabolic state of ketosis (defined by blood ketone levels > 0.5 mM), which also suppresses appetite. Originally developed for the treatment of neurological disorders such as epilepsy, Parkinson's disease, and Alzheimer's disease, KDs are now widely recognized for their role in managing metabolic disorders, including obesity, T2DM, and non-alcoholic fatty liver disease–recently reclassified as metabolic dysfunction-associated steatotic liver disease (MASLD). Evidence suggests that KDs can effectively reduce body weight, fat mass, fasting hyperglycemia, IR, hyperinsulinemia, HbA1c, and triglyceride levels [5].

A more restrictive variation, the very low-calorie ketogenic diet (VLCKD), is characterized by a lower fat intake (approximately 15–30 g per day, primarily from extra virgin olive oil), a normal protein intake (1.2–1.5 g per kg of ideal body weight), and a very low carbohydrate intake (less than 30–50 g per day), providing only 500–800 kcal daily. The VLCKD is a rapid and highly effective intervention for significant weight loss, particularly in cases of severe obesity. It consists of six phases that incoporate specially formulated meal replacements. Due to its restrictive nature, the VLCKD requires strict medical supervision, including regular monitoring of hematological parameters, liver and kidney function, thyroid function, and lipid and glucose metabolism to prevent complications such as dehydration, electrolyte imbalances, and vitamin deficiencies, necessitating appropriate supplementation, especially in the early phases [6, 7]. Very recently, the acronym VLCKD was replaced with VLEKT (Very Low-Energy Ketogenic Therapy) to address the increasing confusion surrounding ketogenic diet nomenclature. The term VLCKD has been used to refer to various ketogenic diets with differing macronutrient compositions, which has led to ambiguity in the scientific literature. The new term, VLEKT, was introduced by the "KetoNut" panel

of experts from the Italian Society of Nutraceuticals (SINut) and the Italian Association of Dietetics and Clinical Nutrition (ADI). This new nomenclature aims to clearly differentiate very low-calorie ketogenic diets (providing < 800 kcal per day for medical weight loss) from other ketogenic diets, such as those used for the treatment of epilepsy or to support growth in children. This distinction is essential to reduce potential bias and misinterpretation within the scientific community, ultimately ensuring more accurate and effective application of ketogenic therapies [8].

For clarity, from this point onward, we will use the term "high-fat KD" to refer to KDs that are not calorie-restricted and typically have a high-fat, low-carbohydrate, and normal-protein profile. The term "KD", on the other hand, will be used to refer to KDs in general, without distinguishing between high-fat KDs and VLEKT.

Both high-fat KD and VLEKT have demonstrated significant benefits, including reductions in BMI, fat mass, waist circumference, and improvements in glucose metabolism (IR and HbA1c), and lipid profiles (reducing triglycerides and total cholesterol) [7]. Although limited, studies suggest that high-fat KDs and VLEKT may also positevely impact reproductive health by lowering serum LH levels, improving the LH/FSH ratio, increasing SHBG, reducing both free and total testosterone, and decreasing AMH levels [9–11]. Given these metabolic and hormonal benefits, high-fat KDs and VLEKT may serve as valuable dietary interventions for promoting weight loss and improving reproductive and metabolic parameters in PCOS women with overweight or obesity [12]. However, the existing literature presents conflicting findings, with studies showing variable outcomes. Moreover, there is a lack of high-quality, large-scale randomized controlled trials (RCT) evaluating the long-term efficacy and safety of these diets in PCOS patients.

This systematic review and meta-analysis aims to provide a comprehensive synthesis of the existing evidence, identify key variables influencing clinical outcomes, and offer clearer recommendations for clinical practice. The primary objective is to evaluate the effects of high-fat KDs and VLEKT on clinical outcomes in women with PCOS and overweight or obesity. This review includes a meta-analysis to quantify the impact of these diets on both metabolic and reproductive parameters. While current data suggest that both high-fat KDs and VLEKT are effective short-term weight loss interventions for patients with PCOS, it is crucial to identify potential confounders and moderating factors (e.g., diet duration, baseline metabolic health, and variability in diet composition across studies). A better understanding of these factors will provide more precise insights into the clinical applications of these diets and inform future research directions.

Methods

Search strategy

This meta-analysis was conducted following the MOOSE guidelines for observational studies [13] and the PRISMA-P framework for randomized controlled trials (RCTs) [14].

The search strategy was executed using the following query: TITLE-ABS-KEY(((pcos) OR (polycystic AND ovary AND syndrome)) AND ((vlckd) OR (diet) OR (ketogenic))) AND (LIMIT-TO (DOCTYPE,"ar"))".

This search encompassed the Scopus, Pubmed, Cochrane, and Embase databases, covering from their inception until January 2025. Only original human studies were included, with no restrictions on language. After duplicates were removed, the researchers reviewed the abstracts for eligibility.

Selection criteria

Eligible abstracts, including those in languages other than English, were retrieved in full text and translated into English when necessary. These articles were subsequently assessed for eligibility based on the PICOS criteria (Population, Intervention, Comparison/Comparator, Outcome, Study type) [15] (Table 1). The eligibility assessment process was conducted by three researchers (A.C., A.L., and M.R.). Each article was reviewed independently by two reviewers in an open manner. Initially, the titles and abstracts of the studies were screened independently for potential inclusion. In cases of uncertainty, the full text was reviewed to make a final decision. Disagreements between reviewers were resolved through discussion, and if consensus could not be reached, a third reviewer (R.C.) made the final determination. Articles meeting eligibility criteria were then subjected to data extraction.

Data extraction

The following data were collected: First author, year of publication, study design, presence of a control group, type of diet administered to patients (and to controls, if applicable), duration of follow-up, and the number of participants (as well as the number of controls, if applicable). For each of the following outcomes, data on the mean values and of standard deviations were collected for the patient group (and the control group, if appliable) before and after KDs: weight (kg), body mass index (BMI) (kg/m^2), lean mass (%), fat mass (%), glycemia (mg/dL), insulin (μU/mL), the homeostatic model assessment (HOMA) index, total cholesterol (mg/dL), HDL and LDL cholesterol (mg/dL), triglycerides (mg/dL), LH (IU/L), FSH (IU/L), 17β-estradiol (pg/mL), total testosterone (ng/dL), progesterone (ng/mL), AMH (ng/dL), other adrogens such as DHEAS (μg/dL) and androstenedione (ng/dL), and fertility outcomes.

Table 1 Selection criteria of the studies that were included in this systematic review and meta-analysis using the PICOS model

PICOS	Inclusion criteria	Exclusion criteria
Population	Patients with PCOS and obesity/overweight	Adolescent, hormonal treatment, major comorbidities
Intervention	KD (VLEKT or high-fat KD)	Weight lowering drugs or nutraceuticals
Comparison	Controlled studies: LCD Uncontrolled studies: before-KD parameters	-
Outcome	Antropometric parameters Body composition Glycometabolic profile Lipid profile Hormonal profile	-
Study Type	Observational studies, non-randomized trials, RCTs, case series	In vitro, animal studies, case reports, communications, proceedings, conference abstracts

Abbreviations LCD Low calorie diet, *KD* Ketogenic diet, *RCTs* Randomized controlled trials, *VLEKT* Very low energy ketogenic therapy

Quality assessment

Two investigators (A.C. and M.R.) evaluated the quality of evidence (QoE) for all included studies. Specifically, the Cambridge Quality Checklists [16] were used for the assessment of the non randomized controlled trials and for the uncontrolled trials. For randomized controlled trials (RCTs), the evaluation was conducted using the Cochrane Risk of Bias tool [17] to assess the potential for bias. Finally for case series the National institute of Health (NIH) Quality Assessment Tool for Case Series Studies (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools) was used for the evaluation.

Statistical analysis

Quantitative analysis was performed using two software tools: Comprehensive Meta-Analysis Software (Version 4) (Biostat Inc., Englewood, NJ, USA) and Review Manager (RevMan) Version 5.4. The mean difference (MD) was selected as the effect size to compare cases and controls, with a p-value of ≤ 0.05 considered statistically significant. To assess heterogeneity across studies, Cochran's Q test and the I^2 statistic were applied, with a p-value of <0.10 indicating significant heterogeneity. The I^2 value ranges from 0 to 100%, with values below 25% suggesting low heterogeneity, around 50% indicating moderate heterogeneity, and values above 75% pointing to high heterogeneity.

Both fixed-effect and random-effect models were used to calculate the pooled effect size, depending on the level of heterogeneity. The fixed-effect model was applied when heterogeneity was low, while the random-effect model was used in the presence of moderate to high heterogeneity. Subgroup analyses were conducted based on the type of diet used, including VLEKT with an intake of 600–800 kcal, and high-fat KDs, where calorie intake was not specified. Sensitivity analysis was performed by calculating the pooled effect size and confidence interval (CI) after sequentially excluding one study at a time; studies that notably influenced the results when removed were identified as "sensitive studies".

Publication bias was qualitatively assessed by examining funnel plot asymmetry, which indicated potential missing studies on one side. Additionally, quantitative analysis of publication bias was conducted using Egger's intercept test to assess its statistical significance.

Results

Using the aforementioned search strategy, a total of 2,674 abstracts were retrieved. After removing the duplicates, 2,058 records were screened based on the title and abstract examination. Following the exclusion of 1,838 abstracts, 220 full-text articles were assessed for eligibility. Of those, 199 were deemed unsuitable for inclusion in the study. Ten studies [11, 18–26] met the eligibility criteria and were therefore included in the quantitative synthesis (Fig. 1).

Among the 10 studies included in this meta-analysis, data were not in an extractable format for 3 studies [21, 23, 26]. Of the remaining, 3 were RCTs [18, 20, 24], 2 was a non-randomized intervention study (), 4 were cohort studies [11, 19, 21, 26], and 1 was a case-series [25].

A VLEKT protocol was used in 6 studies [18, 19, 21, 23, 24, 26], while the remaining studies employed a high-fat KDs protocol [11, 20, 22, 25]. Additionally, 4 studies included a control group treated with a mediterranean low calorie diet (LCD) (14, 8, 18, 22], and 7 studies provided data before VLCKD or high-fat KDs [11, 18–20, 22, 24, 25] (Table 2).

Data on fertility outcomes and hormones (AMH, DHEAS, and androstenedione) were not included in the analysis due to insufficient data across studies.

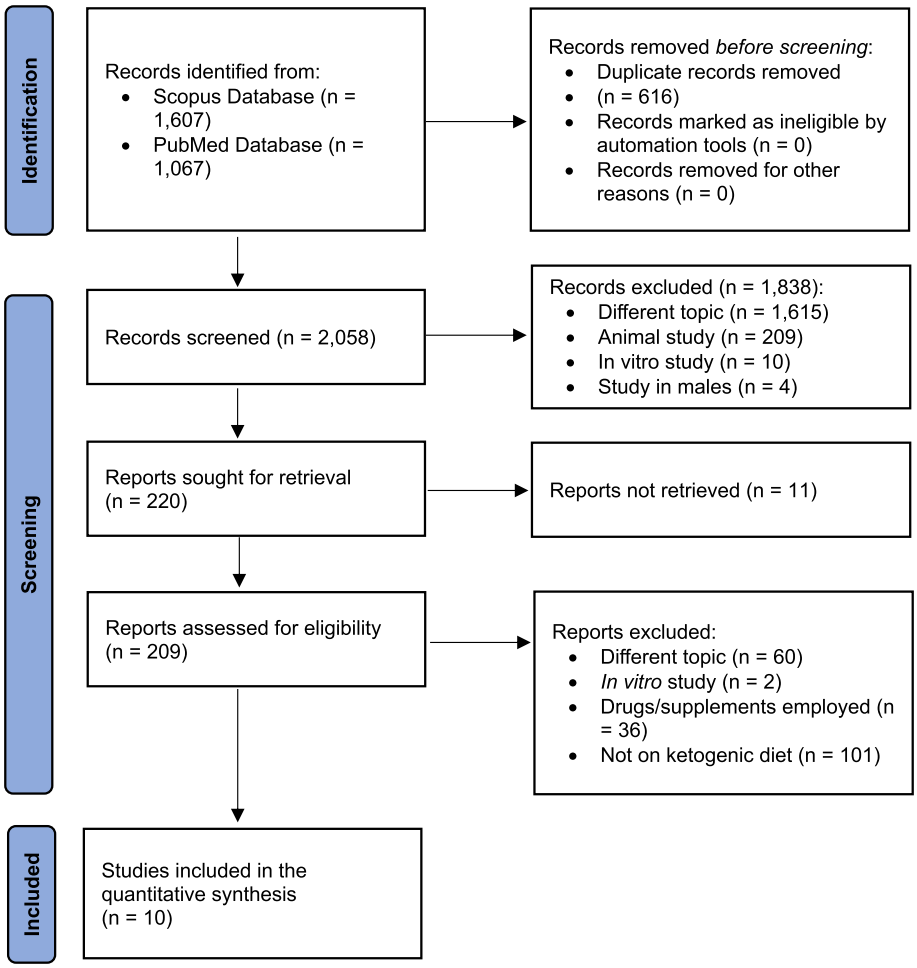

Fig. 1 PRISMA 2020 flow diagram of the included studies

Quality of evidence of included studies

Regarding the assessment of study quality, the evaluation of RCTs using the Cochrane Risk of Bias tool identified some concerns, primarily due to the lack of blinding in outcome assessment. However, this is unlikely to have impacted the reliability of the data. The only non-randomized clinical trial, assessed using Cambridge quality checklists, demonstrated had good overall quality due to its comparison with a well-selected control group. In contrast, the four uncontrolled intervention studies were of lower quality, primarily because they lacked a control group not treated with the KD, making it impossible to establish a definite cause-and-effect relationship. Lastly, the sole case series, evaluated with the NIH Quality Assessment Tool for Case Series Studies, was deemed to be of good quality (Table 3).

Anthropometric data and body composition

The analysis of controlled studies, which included two RCTs, revelaed no effect on body weight or fat mass percentage. However, a significant reduction in BMI was observed in PCOS patients on VLEKT or high-fat KDs compared to LCDs (Table 4). No significant differences were found across the studies in the subgroup analysis.

The pooled analysis of uncontrolled studies assessed the impact of VLEKT or high-fat KDs on various outcomes, using before diet as control values. This approach allowed for the inclusion of a larger number of studies and showed the efficacy of both VLEKT and high-fat KDs on all outcomes, including weight, BMI, fat and lean mass percentages, with no evidence of inter-study heterogeneity (Fig. 2). Subgroup analysis revelaed non significant differences between VLEKT and high-fat KDs.

Sensitivity analysis indicated that there were no sensitive studies affecting the conclusions for weight and BMI. However, the study by [24], was sensitive enough to change the conclusion regarding the effectiveness of KDs on fat mass reduction. Publication bias was absent for weight and BMI analyses, but was detected for fat mass (Supplementary Table 1).

Table 2 Characteristics of the included studies

First author	Year	Study design	Criteria used for PCOS diagnosis	Controlled study	Type of patients (controls)	n. of patients/ controls	Composition (%) of carbo, proteins, lipids and kcal of the administered diet	Available times of follow-up
Pandurevic et al., [24]	2023	Randomized controlled open-label trial study	National Institutes of Health (NIH) Criteria	Yes	Obese/overweight PCOS patients	15/15	NA—600–800 kcal/55%, 15%, 30%, on a 1200–1420 kcal diet	4 weeks/8 weeks/12 weeks
Cincione et al., [18]	2023	Randomized controlled open-label trial study	Rotterdam Criteria	Yes	Obese/overweight PCOS patients	73/71	20%, 35%, 45% on 600 kcal diet/55%, 20%, 25% on a 500 kcal deficit diet	45 days
Meneghini et al., [23]	2023	Non randomized intervention study	Rotterdam Criteria	Yes	Obese/overweight PCOS patients	42/42	20%,50%,30% on a 800 kcal diet/ 55%, 15%, 30% on a 1400 kcal diet	90 days/120 days
Yang et al., [26]	2022	Prospective cohort study	Rotterdam Criteria	Yes	Obese/overweight PCOS patients with different serum uric acid concentration	27/28	5–10%, 18–27%, 70–75% on a customized calculation of basal metabolism calories intake	6 weeks/12 weeks
Magagnini et al., [21]	2022	Retrospective uncontrolled study	Rotterdam Criteria	No	NA	25	8–10%, 36–48%, 18–24%, on 600–800 kcal diet during the first 4 weeks, followed by 1200–1500 LC Kcal diet for 4 weeks and then a 1500–2000 kcal balanced diet for the latter 4 weeks	12 weeks
Cincione et al., [19]	2021	Pre-post, single arm study	Rotterdam Criteria	No	NA	17	20%, 0,8% per kg, 45% on a 600 kcal diet	45 days
Li et al., [20]	2021	Randomized controlled open-label trial study	Revised Rotterdam Criteria	Yes	Obese/overweight PCOS patients with liver dysfunction	8/10	5–10%, 18–27%, 70–75% on a 1300–1500 kcal diet/ NA	12 weeks
Paoli et al., [11]	2020	Single arm trial study	Rotterdam Criteria	No	NA	14	4.8 ± 1.2%, 24.1 ± 5.6%, 71.0 ± 9.3% on a 1672 ± 90 kcal diet	12 weeks
Ula Abed et al., [25]	2018	Case series report	NA	No	NA	4	NA	6 months
Mavropoulos et al., [22]	2005	Pre-post single arm study	Diagnosis based on history of chronic anovulation and/or hyperandrogenemia	No	NA	5	NA	1 week/10 weeks/24 weeks

Abbreviations: *PCOS* Polycystic ovarian syndrome, *NA* Not available

Table 3 Evaluation of quality of the studies

Type of study	Author	Scale used for assessment							
		Cochrane Risk of Bias Toll 2							
		D1	D2		D3	D4	D5	Overall	
Randomized Controlled Trials	Cincione et al., [18]	Some concerns	Low		Low	Some concerns	Low	Some concerns	
	Li et al., [20]	Low	Low		Low	Some concerns	Low	Some concerns	
	Pandurevic et al., [24]	Low	Low		Low	Some concerns	Low	Some concerns	
		Cambridge Quality checklist							
Type of study	Author	Checklist for correlates		Checklist for risk factors		Checklist for causal risk factors		Total	
Non randomized controlled trials	Meneghini et al., [23]	2/5		3/3		6/7		11/15	
Uncontrolled trials	Cincione et al., [19]	2/5		3/3		3/7		8/15	
	Magagnini et al., [21]	2/5		3/3		3/7		8/15	
	Mavropoulos et al., [22]	2/5		3/3		3/7		8/15	
	Paoli et al., [11]	2/5		3/3		3/7		8/15	
	Yang et al., [26]	2/5		3/3		3/7		8/15	
		National Institute of Health (NIH) Quality Assessment Tool for Case Series Studies							
Type of study	Author	Q1	Q2	Q3	Q4	Q6	Q7	Q9	Overall judgment
Case series	Ula Abed et al., [25]	Yes	Yes	NA	Yes	Yes	Yes	Yes	Good quality

Abbreviation: *D* Domain, *Q* Question, *NA* Not available

Glycometabolic profile

The analysis of controlled studies inclued 3 RCTs for serum glucose levels and 2 RCTs for insulin levels and the HOMA index. Both VLEKT or high-fat KDs led to a reduction in serum glucose levels compared to LCDs, with a trend indicating higher efficacy for VLCKD over high-fat KDs. No effect on insulin was observed; however, the HOMA index was significantly lower in the VLEKT or high-fat KDs groups compared to the LCD group (Table 4).

The analysis of controlled studies also showed significantly lower serum glucose, insulin, and HOMA index in PCOS patients following VLEKT or high-fat KDs, compared to values before diets were started (Fig. 3). High heterogeneity was found across the studies. Subgroup analysis revealed no significant difference between VLEKT and high-fat KDs. Additionally, no sensitive studies were identified, and no publication bias was detected for any of the outcomes (Supplementary Table 1).

Lipid profile

A pooled analysis of controlled studies included 2 RCTs. Overall, neither VLEKT nor high-fat KDs had a significant impact on serum levels of total cholesterol, HDL cholesterol, LDL cholesterol, or tryglycerides. Intergroup comparisons revealed no differences between the VLEKT and high-fat KDs protocols (Table 4).

However, a pooled analysis of uncontrolled studies showed a significant reduction in serum total cholesterol and tryglyceride levels, with no detectable effect on HDL or LDL cholesterol (Fig. 4). Interestingly, subgroup analysis indicated that VLEKT protocol was more effective than the high-fat KDs protocols in lowering tryglyceride levels (Fig. 4, panel D). Significant inter-study heterogeneity was found for total cholesterol, HDL cholesterol, and LDL cholesterol, but not for tryglycerides. Sensitivity analysis identified 2 studies [11, 24] as influential for total cholesterol and one study [22] as influencial for LDL cholesterol, while no sensitive effects were detected for the remaining endpoints. Finally, no evidence of publication bias was found for any of the analyzed outcomes (Supplementary Table 1).

Hormonal profile

The analysis of controlled studies included 2 RCTs. The pooled analysis showed lower serum LH levels in patients following VLEKT or high-fat KDs compared to those on LCD, with no significant effects on FSH or total testosterone. No high or moderate inter-study heterogeneity was observed. Subgroup analysis did not show any difference between the VLEKT and the high-fat KDs protocols (Table 4).

In the analysis of uncontrolled studies, both serum levels of LH and total testosterone were significantly lower following the VLEKT of high-fat KDs protocols

Table 4 Analysis of controlled studies

Outcome	Number of studies	n patients/n controls	Overall MD (95% CI)	VLEKT MD (95% CI)	KD MD (95% CI)	Subgroup difference	Heterogeneity test	Sensitivity analysis	Publication bias analysis*
Weight (Kg)	2 [18, 20]	81/81	−0.52 (−4.35, 3.31)	−1.45 (−5.87, 2.97)	2.27 (−5.39, 9.93)	$Chi^2 = 0.68$, $p = 0.41$	$I^2 = 0\%$	No sensitive study	NA
BMI (Kg/m^2)	3 [18, 20, 24]	94/95	−1.97 (−3.21, −0.74)	−2.43 (−3.89, −0.96)	−0.87 (−3.16, 1.42)	$Chi^2 = 1.26$, $p = 0.26$	$I^2 = 0\%$; Q-test: 0.2; $p = 0.9$	Ciancione et al., [18]	$p = 1.0$
Fat mass (%)	3 [18, 20, 24]	94/95	−2.30 (−4.78, 0.18)	−4.41 (−7.79, −1.04)	0.19 (−3.47. 3.85)	$Chi^2 = 3.28$, $p = 0.07$	$I^2 = 42\%$; Q-test: 1.9; $p = 0.4$	No sensitive study	$p = 0.6$
Lean mass (%)	-	-	-	-	-	-	-	-	-
Glycemia (mg/dL)	3 [18, 20, 24]	94/152	−7.17 (−11.85, −2.50)	−9.40 (−11.93, −6.87)	0.0 (−8.32, 8.32)	$Chi^2 = 5.19$, $p = 0.07$	$I^2 = 61\%$; Q-test: 5.4; $p = 0.07$	Cincione et al., 2023; Pandurevic et al., 2023 [18, 24]	$p = 0.06$
Insulin (μU/mL)	2 [18, 24]	84/87	0.85 (−11.02, 12.73)	0.85 (−11.02, 12.73)	-	NA	$I^2 = 91\%$	Cincione et al., 2023 [18]	NA
HOMA index	2 [18, 24]	85/86	−1.74 (−0.91, −2.57)	−1.74 (−0.91, −2.57)	-	NA	$I^2 = 0\%$	Cincione et al., 2023 [18]	NA
Total cholesterol (mg/dL)	2 [20, 24]	24/21	9.65 (−11.77, 31.06)	14.0 (−12.83, 40.83)	2.0 (−33.55, 37.55)	$Chi^2 = 0.28$, $p = 0.60$	$I^2 = 0\%$	No sensitive study	NA
HDL cholesterol (mg/dL)	2 [20, 24]	21/24	−2.60 (−11.36, 6.16)	1–10 (−5.72, 7.92)	−8.0 (−18.30, 2.30)	$Chi^2 = 2.09$, $p = 0.15$	$I^2 = 52\%$	No sensitive study	NA
LDL cholesterol (mg/dL)	2 [20, 24]	24/21	5.61 (−13.33, 24.55)	14.0 (−9.01, 37.01)	−12.0 (−45.34, 21.34)	$Chi^2 = 1.58$, $p = 0.21$	$I^2 = 37\%$	No sensitive study	NA
Tryglycerides (mg/dL)	2 [20, 24]	24/21	54.43 (−40.18, 149.04)	24.0 (−8.37, 56.37)	131.0 (−10.47, 272.47)	$Chi^2 = 2.09$, $p = 0.15$	$I^2 = 52\%$	No sensitive study	NA
LH (IU/L)	2 [18, 20]	81/81	−4.67 (−6.79, −2.56)	−4.95 (−7.11, 2–79)	2.11 (−8.60, 12.82)	$Chi^2 = 1.60$, $p = 0.21$	$I^2 = 38\%$	Li et al., 2021 [20]	NA
FSH (IU/L)	2 [18, 20]	81/81	1.03 (−0.20, 2.25)	1.37 (−0.11, 2.85)	0.28 (−1.90, 2.46)	$Chi^2 = 0.66$, $p = 0.42$	$I^2 = 0\%$	Li et al., 2021 [20]	NA
17β-estradiol (pg/mL)	-	-	-	-	-	-	-	-	-
Total testosterone (ng/dL)	2 [18, 20]	81/81	3.77 (−0.07, 7.61)	3.96 (−0.90, 8.82)	3–45 (−2.81, 9.71)	$Chi^2 = 0.02$, $p = 0.90$	$I^2 = 0\%$	No sensitive study	NA

* Calculated with the Egger's test statistics; *BMI* body mass index, *FSH* follicle-stilumating hormone, *LH* luteinizing hormone, *NA* not applicable

compared to baseline values, with no significant effects on serum FSH or 17β-estradiol levels (Fig. 5). Notably, subgroup analysis showed a trend toward greater efficacy of the VLEKT protocols in reducing LH levels over the high-fat KDs protocols (Fig. 5**,** panel A). Additionally, a significant difference was found between the VLEKT and high-fat KDs protocols in FSH levels, with VLEKT leading to a signficant increase in FSH (Fig. 5, panel B). Inter-study heterogeneity was found for both FSH and 17β-estradiol. Sensitivity analysis identified one study [18] as influential for LH outcomes, two studies [18, 20] as influential for FSH outcomes, and one study [20] as influential for 17β-estradiol. Finally, no evidence of publication bias was detected for any of the endpoints (Supplementary Table 1).

Discussion

This systematic review and meta-analysis examined the effects of KDs on metabolic and reproductive parameters in PCOS patients with obesity/overweight. Overall,

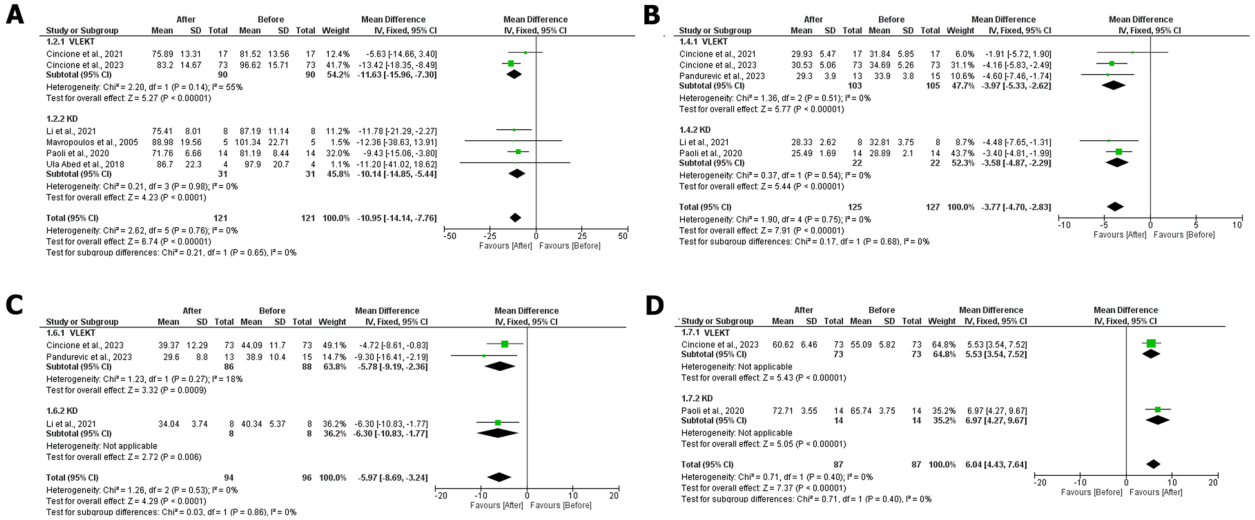

Fig. 2 Forest plots showing weight **A**, body mass index **B**, fat mass **C** and lean mass **D** percentages in patients with overweight or obesity and polycystic ovary asyndrome. who underwent very-low-energy ketogenic therapy (VLEKT) or high-fat ketogenic diets (KDs). Post-diet data were compared with baseline values recorded before the dietary intervention

we found that KDs improve both anthropometric and metabolic parameters, as well as the sex hormone profile. Notably, superior outcomes were observed with VLEKT compared to high-fat KDs. However, it is important to note that most of the studies included in this review had short-term follow-up periods, indicating that the long-term effects and sustainability of these improvements remain uncertain.

Our analysis included both RCTs and uncontrolled studies (observational cohort studies and case series). While this introduced some heterogeneity degree, it allowed for a larger sample size, given the limited number of eligible RCTs available in the literature. Ten studies were included in the meta-analysis, three of which were RCTs comparing VLEKT or high-fat KDs to a LCD. In the remaining uncontrolled studies, a before-after analysis was conducted to assess changes in the aforementioned parameters before and after the dietary intervention. Two RCTs featured follow-up at two different time points: 8 and 16 weeks [24] and 4 and 12 weeks [20]. For consistency and to align with other studies, we included only the longer follow-up period in the statistical analysis.

The analysis of controlled studies revealed significant reduction in BMI, serum glucose levels, the HOMA index, and LH levels. No significant effects were found on the lipid profile. VLEKT demonstrated greater reductions in fat mass and more substantial improvements in the glycometabolic profile compared to high-fat KDs. The before-after analysis of uncontrolled studies showed reductions in weight, BMI, fat mass percentage, serum glucose levels, insulin levels, the HOMA index, total cholesterol, triglycerides, LH and total testosterone. Subgroup analysis revealed no significant differences between VLEKT and high-fat KDs, except for higher FSH levels, and lower LH and triglyceride levels in the VLEKT group.

To the best of our knowledge, this is the first study to compare the outcomes of VLEKT to standard KDs. This comparison is particularly important given the impact of high-fat KDs on lipid metabolism. In some animal models, long-term high-fat KDs use has been associated to the development of MASLD, impaired glucose tolerance, steatosis and liver fibrosis [6]. In this context, VLEKT may be more appropriate approach than high-fat KDs, which could be excessively high in protein and/or fat.

Our results align with previous systematic reviews on the effects of KDs on PCOS, while also providing new and valuable insights. Regarding reproductive hormonal parameters, Khalid and colleagues reported a significant reduction in the LH/FSH ratio and an increase in SHBG following KD intervention [10]. Similarly, Eshaghhosseiny and colleagues found significantly lower LH and higher FSH levels, along with a reduction in total testosterone, with SHBG significantly increasing only in the subgroup analysis of RCTs [27]. Our analysis supports these findings, confirming a reduction in LH in both the RCT analysis and the before-after analysis of uncontrolled studies. Additionally, total testosterone levels were significantly reduced following KD intervention.

Furthermore, Khalid et al. observed significant weight loss [10], which was also reported by Xing and colleagues, who noted reductions in various anthropometric parameters, including BMI, waist circumference, and fat mass [28]. Similar outcomes were observed in our study,

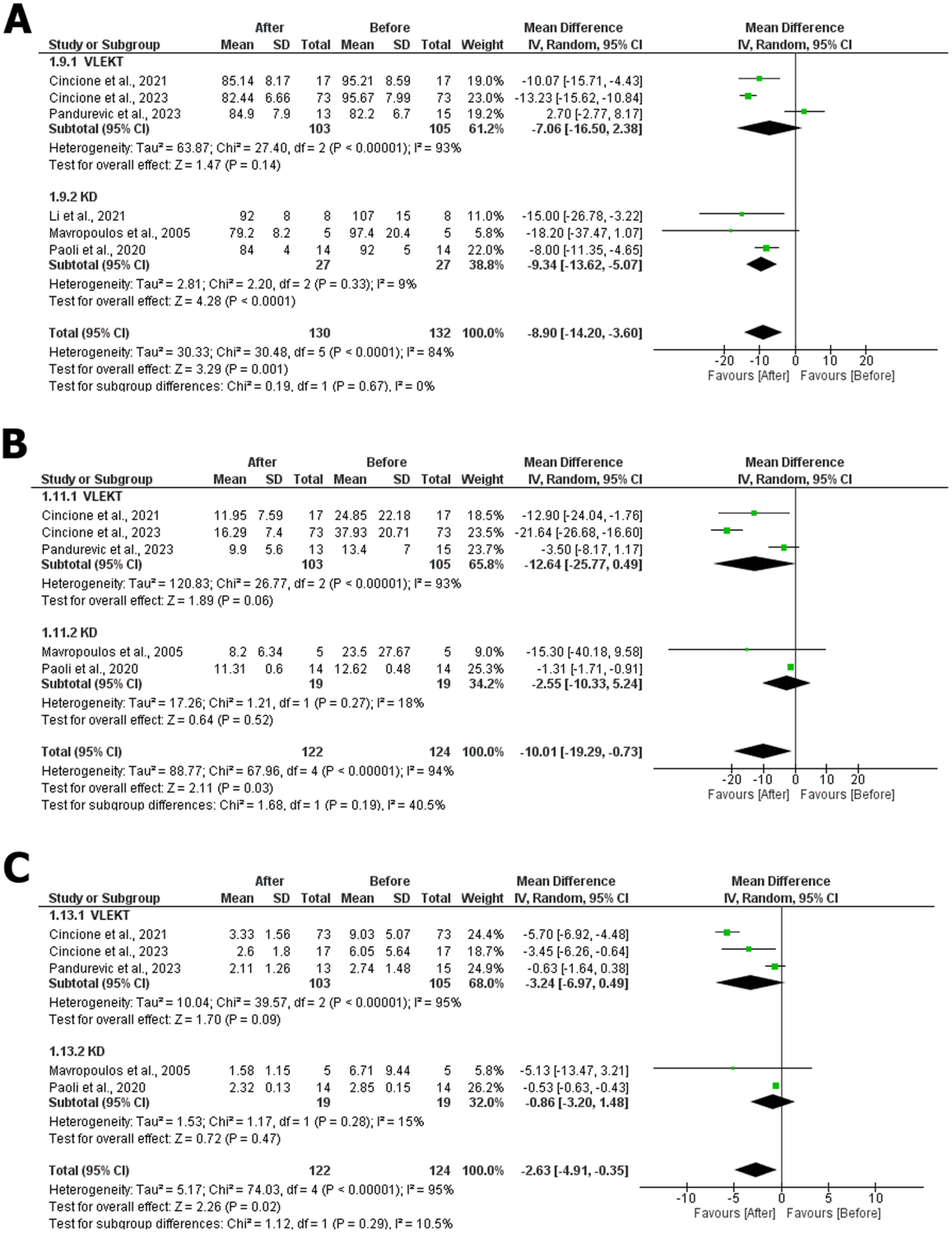

Fig. 3 Forest plots showing glycemia **A**, insulin **B**, and the HOMA index **C** in patients with overweight or obesity and polycystic ovary asyndrome who underwent very-low-energy ketogenic therapy (VLEKT) or high-fat ketogenic diets (KDs). Post-diet data were compared with baseline values recorded before the dietary intervention

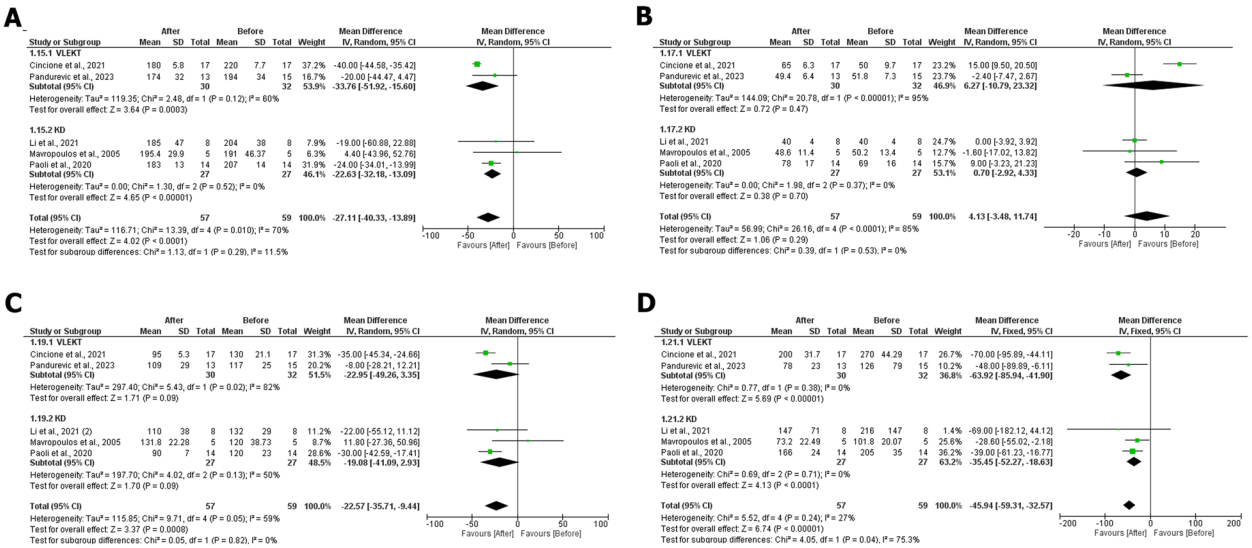

Fig. 4 Forest plots showing changes in total cholesterol **A**, HDL cholesterol **B**, LDL cholesterol **C**, and triglycerides **D** in patients with overweight or obesity and polycystic ovary asyndrome who underwent very-low-energy ketogenic therapy (VLEKT) or high-fat ketogenic diets (KDs). Post-diet data were compared with baseline values recorded before the dietary intervention

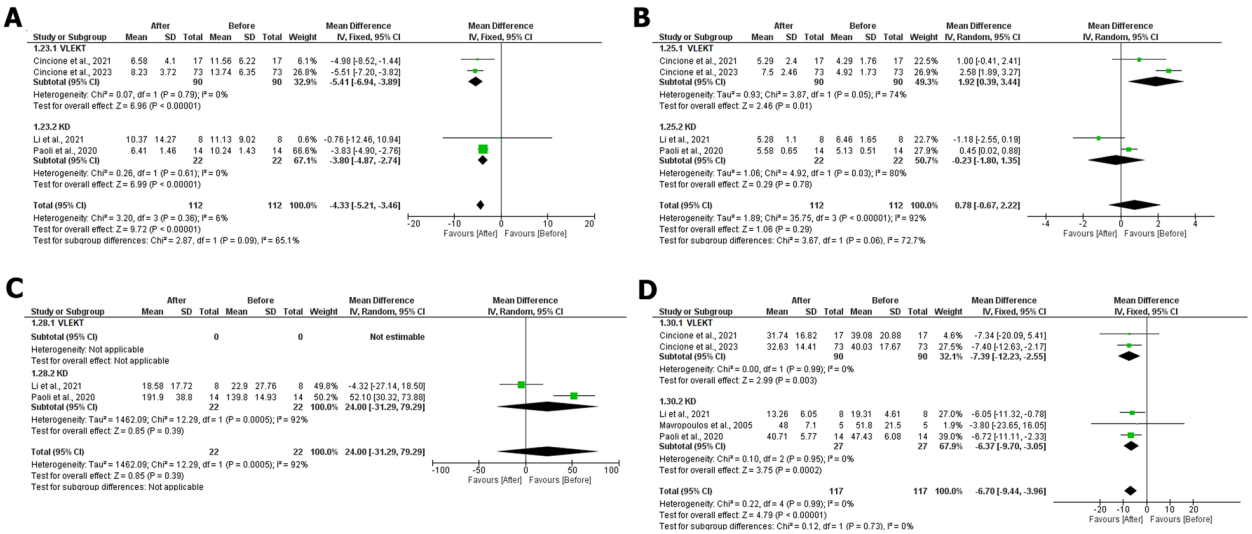

Fig. 5 Forest plots showing changes in luteinizing hormone **A**, follicle-stimulating hormone **B**, 17β-estradiol **C**, and total testosterone **D** in patients with overweight or obesity and polycystic ovary syndrome who underwent very-low-energy ketogenic therapy (VLEKT) or high-fat ketogenic diets (KDs). Post-diet data were compared with baseline values recorded before the dietary intervention

although data on waist circumference were unavailable. Eshaghhosseiny further assessed metabolic biomarkers, reporting decreases in triglycerides, total cholesterol, LDL, fasting glucose, and the HOMA index—findings consistent with our analysis, except for LDL levels [27].

This comparison suggests that our analysis offers a more comprehensive approach by simultaneously exploring anthropometric, metabolic, and reproductive hormonal parameters.

Many of these results are already well-established in other context, such as obesity and diabetes mellitus (in both males and females). For instance, a systematic review and meta-analysis on VLEKT for obesity management in the European guidelines demonstrated the long-term efficacy of VLEKT in reducing weight, BMI, waist circumference, fat mass, glycemic levels, HbA1c, HOMA index, total cholesterol, LDL, and triglycerides [7]. VLEKT has also been shown to be superior to other

dietary interventions, particularly LCD and very low calorie diet, in terms of weight loss, waist circumference, fat mass, HOMA index, total cholesterol, and triglycerides [7]. Numerous studies have also evaluated the effects of KDs on T2DM. A meta-analysis of RCTs confirmed reductions in body weight, waist circumference, HbA1c, and triglycerides in patients with T2DM who followed with a KD compared to tjose on a control diet [5].

Overall, these outcomes can be explained by the physiological mechanisms triggered by KDs. Compared to standard KD, the VLEKT is characterized by a normal fat intake, while maintaining low carbohydrates and adequate protein intake. In contrast, standard KD, which is typically isocaloric or slightly hypocaloric, may risk excessive intake of fats or proteins. The primary feature common of all KDs is the severe restriction of carbohydrate consumption, which induces a fasting-like state that leads to the production of ketone bodies and the onset of ketosis.

In this context, the primary target appears to be IR and hyperinsulinemia, which are central mechanisms underlying the development of PCOS. Reduced carbohydrate intake lowers blood glucose levels, preventing excessive insulin production. This, in turn, increases glucagon secretion, promoting a lipolytic effect rather than lipogenetic one [29]. Loss of fat mass, particularly visceral adipose tissue, contributes to a reduction in the acyclic production of estrogens via the aromatization of excess androgens. This leads to improved FSH levels relative to LH and a better LH/FSH ratio [19]. Another mechanism through which the KDs improve insulin sensitivity involves the activation of adenosine monophosphate-activated protein kinase and silent mating type information regulation 2 homologue 1, both of which play important roles in regulating glucose homeostasis [9].

Resolving IR and hyperinsulinemia is a critical aspect of managing PCOS, as these conditions contribute directly and indirectly to hyperandrogenism. Insulin, together with LH, stimulates the proliferation of ovarian theca cells and stimulates steroidogenesis. This process also inhibits hepatic SHBG synthesis, resulting in elevated free androgen levels in the plasma [30]. Moreover, hyperinsulinemia may interfere with progesterone's inhibitory effect on the GnRH pulse generator and enhance adrenal responsiveness to ACTH, thereby promoting adrenal steroidogenesis [31]. Hyperinsulinemia, coupled with aberrant adipose tissue storage and excessive carbohydrate intake, establishes a chronic low-grade inflammatory state and oxidative stress, which contribute to both metabolic and hormonal disorders in women with PCOS. These factors also increase cardiovascular risk [29, 32]. It is noteworthy that in these patients, glucose ingestion can induce an inflammatory response independent of obesity or excessive abdominal adiposity [33]. Women with PCOS typically exhibit elevated levels of circulating lymphocytes, monocytes, eosinophilic granulocytes, and higher cytokine levels, including tumor necoris facto-α and interleukin-6, which promote IR, androgen production, and disrrpt the function of the hypothalamic-pituitary-ovarian axis [11].

In this context, KDs, with their distinct limitation on carbohydrate intake, plays a significant role not only by modulating glycemic and insulin levels but also through weight loss and reduction of visceral fat [34]. Additionally, KDs may reduce inflammation through the production of ketone bodies, particularly ß-hydroxybutyrate, which has been shown to suppress the activation of the NLRP3 inflammasome [34, 35]. Recently, Zhao and colleagues observed in a letrozole-induced PCOS mouse model that hyperandrogenism may induce ovarian dysfunction through the activation of the cGAS-STING pathway, contributing to granulosa cell inflammation and apoptosis. However, letrozole-treated mice fed with a KD showed that ß-hydroxybutyrate inhibited the cGAS-STING pathway both in vitro, in testosterone-treated KGN cells, and in vivo, by downregulating the pathway compared to letrozole-treated mice on a control diet [36].

To date, PCOS guidelines have not specifically recommended KDs as a therapeutic approach for treating patients. The most recent guidelines emphasized the importance of lifestyle management, particularly highlighting the clinical importance of weight loss in PCOS women with overweight/obesity [3]. However, these guidelines suggest that dietary interventions should be personalized based on the individual needs and characteristics of patients, without identifying any single dietary regimen as superior to others [3]. Our findings suggest that, at least in the short term, KDs, particularly VLEKT, may be effective in managing weight, adiposity, IR, and hyperandrogenism. Based on these results, we recommend considering the initiation of a KD in PCOS patients with obesity. However, further research with longer follow-up periods is needed to better understand the long-term impact of VLEKT on these health outcomes.

These results are consistent with the latest consensus statement from the Italian Society of Endocrinology (SIE) regarding VLEKT and metabolic diseases. This statement recommends VLEKT for improving IR, ovulatory dysfunction, and hyperandrogenism in patients with overweight/obesity, particularly after other standardized diets have failed [6]. The consensus advises caution in prescribing VLEKT as a first-line therapy due to the limited evidence available. Our review contributes to the growing body of evidence supporting the benefits of KDs diet in managing PCOS and suggests their potential as an initial

therapeutic approach, while still emphasizing the need to tailor the diet to individual patient characteristics.

Patients who may benefit most from this approach are women with obesity, dysglycemia and IR. However, it is important to consider the controindications for the VLEKT, including type 1 diabetes mellitus, pregnancy, breastfeeding, and kidney failure [6]. Additionally, caution should be exercised in patients with low adherence to restrictive dietary regimens, those with a BMI below the obesity threshold, and those at high risk for gallstones or cholecystitis, as rapid weight loss may exacerbate these risks [7].

The strengths of our study lie in the rigorous systematic review process and statistical analysis. This article provides a comprehensive synthesis of the available evidence, incorporating both RCTs and uncontrolled, single-arm studies. Notably, it is the first systematic review to compare the outcomes of the standard KDs to VLEKT, in PCOS patients with overweight/obesity. Our findings confirm and expand upon previous research, offering new insights into the differences between standard KDs and VLEKT, suggesting that the latter may demonstrate superior efficacy. Furthermore, the analysis of publication bias and sensitivity analysis frequently yielded negative results, which strengthens the overall quality and reliability of the study.

However, this systematic review and meta-analysis has some limitations. Due to the limited number of studies available for inclusion, both RCTs and uncontrolled studies were considered, which resulted in significant heterogeneity that complicated the comparison of different studies. The variability in study designs, patient characteristics, and KD/VLEKT protocols contributed to this heterogeneity. In total, 10 studies were included, a number consistent with previous research, but the small sample size limits the ability to draw definitive general conclusions. Additionally, due to the short duration of the included studies, our results primarily reflect short-term effects. As a results, many questions remain regarding the long-term sustainability, safety, and efficacy of KDs.

These limitations underscore the need for further research. Future studies should aim to address the issue of small sample sizes and short follow-up periods to extend the validity and generalizability of the findings. Specifically, the number of RCTs should be increased, with studies designed around standardized KD or VLEKT protocols and clearly defined outcome measures. A particular focus should be placed on reproductive hormone outcomes, as many key parameters, including 17β-estradiol, SHBG, AMH, and adrenal androgens (DHEAS and androstenedione), are absent in several studies. Moreover, investigating fertility outcomes (e.g., pregnancy rate, live birth rate, and miscarriage rate) would provide valuable insights into the broader implications of KDs for women with PCOS.

It is also essential to continue exploring the impact of KDs across different PCOS populations, including those with overweight or obesity and IR, as well as the less commonly studied lean phenotype with IR. This wil help to better understand the effects of carbohydrate restriction (e.g., isocaloric KD) even in the absence of higher body weight, providing a more comprehensive understanding of how this dietary approach affects women with diverse clinical presentations of PCOS.

Concluding remarks

In conclusion, both high-fat KDs and VLEKT show promising effects for women with PCOS who suffer from overweight or obesity. Our study further demonstrates that KDs, particularly the VLEKT, can positively influence female reproductive hormones, suggesting their potential role as antiandrogenic therapy. Given the limited number of studies on this topic, further research is needed to better elucidate the underlying mechanisms and to develop new therapeutic options for managing PCOS across various phenotypes and clinical settings.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12958-025-01411-1.

Supplementary Material 1

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None.

Clinical trial number
Not applicable.

Attestation statement
The subjects in this study have not concomitantly been involved in other randomized trials. Data regarding any of the subjects in the study has not been previously published unless specified. Data will be made available to the editors of the journal for review or query upon request.

Data sharing statement
Data will be made available upon request.

Authors' contributions
R.C. conceived the study, performed the statistical analysis, wrote the method and result section, drafted the figures, and revised the manuscript. M.R., A.C., A.Ca., F.B. and A.L. assessed the articles' eligibility, extracted the data, evaluated the quality of evidence, drafted the tables, and wrote the first draft of the manuscript. S.L.V. critically revised the manuscript. A.E.C. conceived the study and critically reviewed the manuscript. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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