Efficacy and safety of ketogenic diets with varying energy untake strategies on metabolic outcomes and clinical safety: A narrative review

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ABSTRACT

Background and Objectives: Ketogenic diets are often viewed as metabolically risky, but this may reflect failure to distinguish different energy-intake strategies. We examined whether outcomes differ among hypocaloric, isocaloric, and ad libitum prescriptions and which measures best limit adverse effects. **Methods and Study Design:** PubMed, Web of Science, and Cochrane Library were searched through August 2026. After excluding animal, outcome-free, and duplicate reports, 139 human studies (carbohydrate ≤49 g/day or ≤10% energy; ≥2 weeks) were grouped as hypocaloric (n = 46), isocaloric (n = 54), or ad libitum (n = 39) and synthesized in accordance with the Scale for the Assessment of Narrative Review Articles. **Results:** Hypocaloric ketogenic diets produced marked weight loss (5–15 kg in 60.9%; up to 22.8 kg) and glycated-hemoglobin reductions of 0.2–0.23% (95% CI 0.15–0.28%), with mild, self-limiting effects. Isocaloric ketogenic diets maintained weight while improving insulin sensitivity, inflammatory markers, and lipids independently of weight loss; adverse events were confined to critically ill or vulnerable participants. Ad libitum ketogenic diets achieved similar short-term loss but showed the strongest dyslipidemia signal, with low-density-lipoprotein cholesterol rising in up to 71% of participants in long-term unsupervised trials. Gastrointestinal symptoms, lean-mass loss, and transient lipid changes occurred across groups, mitigated by protein ≥1.2 g/kg/day, electrolyte replacement, adequate fiber, and lipid monitoring. **Conclusions:** Ketogenic-diet risks arise less from carbohydrate restriction than from unrestricted intake, inadequate protein, and poor fat quality. Prescription should be individualized: hypocaloric KDs for supervised short-term weight loss, isocaloric KDs for fragile patients needing weight stability, and ad libitum KDs only with structured oversight; with monitoring and attention to composition, KDs can be used safely across diverse clinical settings.

Key Words: Ketogenic diet, energy-intake stratification, hypocaloric diet, isocaloric diet, ad libitum diet, metabolic safety

INTRODUCTION

Ketogenic diets (KDs) were first introduced in the 1920s as a therapeutic intervention for refractory epilepsy,[1–3] and their clinical scope has expanded considerably over the past decade. Today, KDs are investigated across a diverse spectrum of conditions, including obesity,[4] type 1 and type 2 diabetes mellitus,[5] neurological disorders,[6] schizophrenia,[7] bipolar disorder,[8] metabolic syndrome,[9] and various malignancies including breast and pancreatic

cancers.[10,11] They have also been studied for their potential to modulate athletic performance, insulin sensitivity, inflammatory markers, and lipid profiles.[12] The shared mechanistic basis of these interventions lies in inducing nutritional ketosis through severe carbohydrate restriction (typically ≤49 g/day or ≤10% of total energy), which shifts hepatic metabolism toward fatty acid oxidation and ketogenesis. The resulting ketone bodies—β-hydroxybutyrate (βHB), acetoacetate, and acetone—serve as alternative energy substrates, reduce glucose dependence, and trigger a cascade of metabolic adaptations including reduced insulin signaling, increased lipolysis, and altered mitochondrial bioenergetics.[13]

Systematic reviews and meta-analyses of randomized trials have established the therapeutic potential of ketogenic diets (KDs) across several domains. In individuals with obesity or type 2 diabetes, KDs consistently lower glycated hemoglobin (HbA1c), improve peripheral insulin sensitivity, produce clinically meaningful weight loss, and favorably modify lipid profiles—specifically reducing triglycerides and raising high-density-lipoprotein cholesterol (HDL-C).[14–16] Emerging evidence in oncology suggests possible benefits for body composition and quality of life, though survival benefits remain unproven.[17,18] In sports nutrition, KDs can increase fat oxidation and endurance performance, but metabolic responses—particularly lipid changes—vary substantially between individuals.[19] A recent network meta-analysis ranked KDs as the most effective dietary pattern for reducing body weight, body mass index (BMI), and waist circumference, outperforming low-fat, hypocaloric, and Mediterranean diets.[20]

Despite this evidence, KDs remain among the most debated interventions in clinical nutrition. Short-term safety and adherence (under 12 months) are reasonably well characterized, but concerns persist about long-term cardiovascular effects, renal strain, micronutrient deficiencies, and gastrointestinal tolerability.[21] Contemporary reviews further emphasize that this cardiovascular risk is not uniform across individuals: triglyceride and HDL-C responses are broadly favorable, yet low-density lipoprotein cholesterol (LDL-C) responses vary widely, and adults of normal body weight following unsupervised KDs may show LDL-C increases of 0.47–1.81 mmol/L, raising concern about long-term atherosclerotic risk.[22,23] A major source of inconsistency across the literature—and a key contributor to the polarized perception of KD safety—is the substantial heterogeneity in energy-intake prescription across studies. Protocols differ dramatically in whether they impose a caloric deficit, maintain energy balance, or allow ad libitum consumption, yet most reviews and meta-analyses treat these disparate approaches as a single dietary entity. This conflation obscures a fundamental question: do the adverse effects attributed to KDs arise from

carbohydrate restriction itself, or from the specific energy-intake strategy with which it is implemented?

Emerging evidence suggests the latter. Many adverse effects commonly ascribed to ketosis—including dyslipidemia, lean-mass loss, and electrolyte disturbances—may instead stem from uncontrolled energy intake, poor dietary-fat quality, or inadequate protein provision, rather than from carbohydrate restriction or ketosis per se. For instance, the marked elevations in LDL-C reported in some ad libitum KD trials are increasingly recognized as a consequence of excessive saturated-fat intake in the absence of caloric restriction, rather than an inherent effect of ketosis. Notably, such LDL-C elevations are most pronounced when saturated fat is consumed without an energy ceiling—including in normal-weight individuals who lack the offsetting effect of weight loss—indicating that body phenotype and energy context, rather than ketosis itself, govern the lipid response.[22] Similarly, muscle loss observed in hypocaloric KDs is more closely linked to protein intake below 1.2 g/kg/day than to carbohydrate restriction alone. These observations point to energy-intake strategy as a primary determinant of both the efficacy and safety profile of KDs—a factor that has not been systematically examined in prior narrative or systematic reviews.

Three distinct energy-intake strategies can be identified across the clinical KD literature. Hypocaloric KDs impose a prescribed energy deficit (typically 600–1,500 kcal/day) and are primarily employed for short- to medium-term weight reduction; their efficacy is driven by the combined effects of caloric deficit and ketosis, but the same metabolic pressure that accelerates fat loss may also promote lean-mass depletion, electrolyte imbalances, and transient renal-function changes when not carefully supervised. Isocaloric KDs maintain energy intake at estimated requirements, thereby isolating the metabolic effects of ketosis from those of caloric restriction; they are particularly relevant for metabolically fragile patients—including those with critical illness, neurological disorders, or cancer—who may benefit from ketosis but cannot tolerate weight loss, and they provide the most direct evidence for ketosis-specific mechanisms such as improved insulin sensitivity, reduced inflammation, and enhanced metabolic flexibility independent of weight change. Ad libitum KDs impose no caloric limit, with participants eating according to appetite within a carbohydrate-restricted framework; while this offers greater flexibility and may enhance long-term adherence, the absence of energy regulation frequently leads to uncontrolled saturated-fat intake, predisposing to dyslipidemia, gastrointestinal symptoms, and micronutrient inadequacies, particularly in unsupervised settings.

Importantly, the boundary between these categories is not always discrete in practice. Some ad libitum KDs result in spontaneous caloric reduction through ketone-mediated appetite suppression, effectively functioning as hypocaloric protocols despite no prescribed restriction; conversely, some ostensibly isocaloric protocols may inadvertently become hypocaloric when actual intake falls below calculated requirements because of poor adherence or inaccurate estimation. These discrepancies highlight the need for a classification framework that accounts for both intended prescription and achieved intake—a gap this review addresses.

Accurate energy calculation is one of the most challenging practical aspects of KD implementation. Resting energy-expenditure estimates vary substantially depending on method—indirect calorimetry versus predictive equations such as Harris-Benedict or Mifflin-St Jeor—and even modest errors can shift a protocol from isocaloric to hypocaloric (or hypercaloric), directly altering both efficacy and safety outcomes. Yet, to our knowledge, no prior review has systematically cataloged the energy-intake strategies and calculation methods used across the full clinical KD literature, nor examined how these methodological choices shape metabolic outcomes and adverse-event profiles. To fill this gap, we conducted a narrative synthesis of 139 clinical studies across diverse populations, stratified them by prescribed energy strategy—46 hypocaloric, 54 isocaloric, and 39 ad libitum studies—and compared their metabolic impacts, biochemical adaptations, and safety profiles. Our objective was to test the hypothesis that energy-intake strategy is a more fundamental determinant of KD-related outcomes than carbohydrate restriction alone, and to provide clinicians with actionable, individualized guidance based on patient characteristics, clinical goals, and monitoring capacity, moving beyond the polarized debate toward a precision-nutrition approach.

MATERIALS AND METHODS

Search strategy and study selection

A systematic literature search was conducted in PubMed, Web of Science, and the Cochrane Library databases from inception through August 2026. The search employed a two-tier strategy: (1) condition-specific terms including "ketogenic diet," "very-low-carbohydrate ketogenic diet," "very-low-calorie ketogenic diet," "very-low-energy ketogenic diet," "low-carbohydrate diet," "modified Atkins diet," and "medium-chain triglyceride diet," combined with Boolean operators; and (2) energy-intake modifiers including "caloric restriction," "energy restriction," "hypocaloric," "isocaloric," and "ad libitum." These were cross-referenced with study-design filters for clinical trials, randomized controlled trials,

prospective cohort studies, and case-control studies. No language restrictions were applied. The reference lists of included studies and relevant systematic reviews were manually screened for additional eligible publications.

Inclusion and exclusion criteria

Studies were eligible for inclusion if they met the following criteria: (a) adult human participants aged 18 years or older; (b) intervention employing a ketogenic diet, defined as carbohydrate intake ≤49 g/day or ≤10% of total energy intake, with or without explicit ketosis monitoring; (c) explicit reporting of an energy-intake prescription strategy (hypocaloric, isocaloric, or ad libitum); (d) minimum intervention duration of 2 weeks; and (e) reporting of at least one clinical outcome (efficacy or safety). Exclusion criteria comprised: (a) animal studies; (b) non-ketogenic low-carbohydrate diets (carbohydrate intake >49 g/day without ketosis induction); (c) case reports, editorials, commentaries, and conference abstracts without full-text availability; (d) studies combining KDs with pharmacological or surgical interventions in which the dietary effect could not be isolated; and (e) duplicate publications of the same study population; and (f) studies conducted exclusively in pediatric populations, including childhood epilepsy.

Study selection and data extraction

Two independent reviewers screened titles and abstracts, followed by full-text review of potentially eligible articles. Disagreements were resolved through consensus discussion with a third reviewer. Data extraction used a standardized, pre-piloted form capturing study characteristics (first author, year, country, design, sample size, population, intervention duration); dietary-protocol details (KD subtype, macronutrient composition, energy prescription, ketosis-monitoring method); efficacy outcomes (weight change, glycemic parameters, lipid profiles, disease-specific endpoints); and safety data (adverse events, attrition rates, laboratory abnormalities). For studies reporting multiple time points, the primary endpoint as defined by the original authors was extracted preferentially.

Classification by energy-intake strategy

Identified studies were stratified into three categories based on prescribed energy-intake strategy. Hypocaloric KDs were defined as interventions prescribing intake below estimated basal requirements or standard recommendations, encompassing very-low-calorie ketogenic diets (VLCKD; 600–800 kcal/day), low-calorie ketogenic diets (LCD: 1,200–1,500 kcal/day),

and moderate-deficit protocols. Isocaloric KDs comprised interventions prescribing intake at or near estimated requirements, with the explicit objective of maintaining body weight while inducing nutritional ketosis. Ad libitum KDs included interventions in which participants consumed food without prescribed energy restriction, guided by appetite or satiety within the ketogenic macronutrient framework. Classification was based on the stated methodology in each original publication; where prescription was ambiguous, classification was determined by consensus. A breast-cancer protocol designed as isocaloric but actually consumed at a marked deficit was reclassified as hypocaloric,39 and an ad libitum protocol whose achieved intake remained below 1,500 kcal/day through appetite suppression was operationally classified as hypocaloric.[41]

Synthesis approach

Given the heterogeneity in populations, KD subtypes, outcome measures, and follow-up durations, a narrative synthesis was adopted. Studies were grouped by energy strategy and further stratified by clinical indication and KD subtype; descriptive statistics were calculated for study characteristics, and efficacy and safety patterns were synthesized qualitatively across and within categories. This review is reported in accordance with the Scale for the Assessment of Narrative Review Articles (SANRA) guidelines. Detailed study-level data are organized in six consolidated tables: strategy overview (Table 1), protocols and energy determination (Table 2), clinical indications (Table 3), body-weight and body-composition outcomes (Table 4), biochemical adaptations (Table 5), and adverse events with mechanisms and prevention (Table 6).

RESULTS

A total of 139 clinical studies (Studies 24–162) were included and stratified by prescribed energy-intake strategy into hypocaloric (n=46),[24–69] isocaloric (n=54),[70–123] and ad libitum (n = 39)[124–162] categories, as summarized in Table 1. Nutritional ketosis was achieved consistently across all three, yet metabolic outcomes and adverse-event profiles diverged markedly by strategy, supporting the hypothesis that energy prescription—rather than carbohydrate restriction alone—is the principal determinant of KD efficacy and safety.

Hypocaloric ketogenic diets

Study population and indications

Forty-six studies were analyzed. Overweight and obesity predominated, representing 43 studies (93.5%) and serving as the target for both intensive short-term reduction and longer-term maintenance.[25–62,64–67,69] Non-alcoholic fatty liver / metabolic-dysfunction-associated steatotic liver disease (NAFLD/MASLD) was examined in five studies,[24–27,63] type 2 diabetes (T2DM) in three,[28–30] metabolic syndrome in two,[28,31] chronic musculoskeletal pain/osteoarthritis in three,[32–34] and lipedema in three.[35–37] Single studies addressed hypertension,[38] ambulatory blood-pressure monitoring during hypocaloric weight loss,[66] polycystic ovary syndrome,[50] hyperlipidemia,[52,59] chronic plaque psoriasis,[42] healthy athletes,[40] and endometrial cancer in overweight women,[68] and one breast-cancer protocol[39] designed as isocaloric was reclassified here because actual intake fell markedly below that of controls. In the psoriasis study, an aggressive <500 kcal/day protocol reduced the Psoriasis Area and Severity Index by 76%, with 94.3% achieving a ≥49% response.[42] A 12-week very-low-energy ketogenic diet (≈753 kcal/day) in MASLD produced 13% total body-weight loss and a 77% relative reduction in MRI liver-fat fraction,63 and a 21–28-day very-low-calorie diet (VLCD) in treatment-naïve endometrial cancer produced 5.5% weight loss with 22% and 60% falls in fasting glucose and insulin, respectively.68 The full indication distribution is given in Table 3.

Ketogenic protocols and energy prescription

On the basis of deficit magnitude, four prescription tiers were identified (Table 2, Part A): (i) very-low-calorie KDs (VLCKD, 600–800 kcal/day; 19 studies), using predefined commercial meal replacements (PNK®, Optifast, Zélé®), Mediterranean-KD formulations, staged protocols, a low-fat very-low-energy variant, and short-course VLCDs in oncology;[25,27–30,32,34,46–49,51,55,57,58,61,63,67,68] (ii) low-calorie KDs (LCD, 1,200–1,500 kcal/day; 12 studies), encompassing modified Atkins, culturally adapted Asian KDs, and liquid meal replacements;[24,26,31,35,36,38,39,41,43,52,59,64] (iii) moderate-deficit protocols (a 200-600 kcal/day reduction, a prescribed ≈30% deficit, or >22% deficit; 14 studies), achieved through intermittent fasting, cyclic KDs, healthy-KD designs, structured meal provision, or a high-protein (40% of energy) modified KD set at 70% of estimated requirement;[33,37,40,44,45,50,53,54,56,60,62,65,66,69] and (iv) one very-low-calorie (<500 kcal/day) protein-priority VLCKD variant.[42] VLCKD and LCD tiers used fixed energy prescriptions with predetermined macronutrient distributions, whereas the moderate-deficit tier imposed

restriction behaviorally or temporally, producing variable deficits relative to individual baseline. Notably, newer VLCKD protocols varied widely in macronutrient composition—from a classical high-fat profile to a low-fat Zélé regimen (650–780 kcal/day, ≈1.2 g protein/kg ideal body weight)[67] and a 40% - protein / 27% - fat very-low-energy formula[63] — showing that a severe energy deficit, rather than a fixed fat ratio, defines the tier. Of note, one protocol set no caloric target yet remained below 1,500 kcal/day throughout through carbohydrate-induced appetite suppression,[41] illustrating how achieved—rather than prescribed—intake defines the category.

Energy-driven outcomes: body weight, body composition, and biochemistry

The combination of deficit and ketosis produced substantial, dose-related weight loss (Table 4, Part A): among studies reporting absolute change, seven lost 0–5 kg, fifteen 5–10 kg, thirteen 10–15 kg, and three more than 15 kg (up to 22.8 kg58 and 22.4 kg55; −18% of body weight with 18% fat-mass and 27% visceral-fat reduction34), while two did not report complete weight data;[39,53] newer trials reporting percentage loss documented 13% total body-weight loss at 12 weeks on a ≈753 kcal/day very-low-energy diet (VLED),[63] 5.5% over only 21–28 days on a cancer VLCD,68 and the largest sustained 12-month reductions on a 1,200 kcal/day KD,[64] while a 2-week 30%-deficit, 40%-protein modified KD reduced body weight by ≈4.5 kg.[69] Longer protocols (12–26 weeks) generally achieved greater absolute loss than shorter ones—an observational cross-study trend rather than a meta-regression association—and no relationship was found between cohort size (range 9–247) and magnitude of loss. Biochemical adaptations were multifaceted (Table 5): HDL-C rose in four studies[48,51,52,59] and LDL-C/total cholesterol (TC)/triglycerides fell in eight,[27,30,31,38,41,45,50,65] with a healthy-KD meal program lowering LDL-C by 0.43 mmol/L rather than raising it;[65] fasting glucose, HbA1c, and insulin improved across studies, with a pooled mean HbA1c reduction of 0.2–0.23% (95% CI 0.15–0.28%) and individual falls from 7.8% to 7.3%57 and 8.2% to 7.9%,[43] a short oncology VLCD reducing fasting glucose by 22% and insulin by 60%,[68] and a high-protein modified KD raising growth/differentiation factor 15 (GDF15) while lowering fibroblast growth factor 21 (FGF21) by ≈51% and remodeling 22 lipoprotein subclasses (larger HDL particles increased, smaller HDL decreased);[69] pro-inflammatory tumor necrosis factor-α (TNF-α) and high-sensitivity C-reactive protein (hs-CRP) declined in at least six studies while anti-inflammatory interleukin-10 (IL-10) rose in one;[39] hepatic steatosis and transaminases improved in seven,[24–26,28,30,60,63] including a 77% relative fall in MRI liver-fat

fraction;[63] creatinine/blood urea nitrogen (BUN) improved in two;[48,62] circulating ketones rose in four;[33,40,41,44] systolic/diastolic blood pressure fell in seven,[38,45,47,60,62,65,66] confirmed by 24-h ambulatory monitoring;[66] and fat-soluble vitamins D/E and DHA/ω-3 increased in three[37,48,55] while vitamin C declined in one.[37] Five long-term (≥6-month) protocols — extending to 12 months in one[64] — sustained 7.8–12 kg losses with maintained metabolic gains and no serious adverse events (Table 4, Part D).[32,34,46,60,64]

Adverse events and mechanisms

Adverse events were documented in 14 studies (30.4%), while 69.6% reported no death or serious event (Table 6); notably, a low-fat very-low-calorie ketogenic regimen preserved renal, hepatic, and acid–base balance with no serious events,[67] a short oncology VLCD reported no grade 3/4 events,[68] and a 2-week high-protein modified KD was well tolerated.[69] Lean-mass depletion (four studies;[36,48,50,51] fat-free mass −2.3 kg[48] and −1.67 kg[50]) occurred only where protein fell below 1.2 g/kg/day or the deficit was extreme, and was prevented by high-protein supplementation45 and resistance training;[40] the newer low-fat VLCKD supplied ≈1.2 g protein/kg ideal body weight and the 40%-protein modified KD likewise preserved lean-related indices.[67,69] Gastrointestinal symptoms (four studies;[42,49,51,52] constipation in 72%[52]) were associated with low fiber and ketone-related irritation during early adaptation, and transient anorexia accompanied the very-short oncology VLCD without malnutrition or dropout.[68] Renal-biomarker changes (two studies[45,49]) appeared only with protein above 2.0 g/kg/day plus dehydration or perioperative stress, and part of the estimated-GFR decline reflected the weight/body-surface-area denominator rather than intrinsic injury. Dyslipidemia was uncommon and, where present, followed post-ketogenic cholesterol loading (≥3 eggs/day with carbohydrate reintroduction) and normalized thereafter rather than arising from ketosis;[31] a healthy-KD design emphasizing unsaturated fat reduced rather than raised LDL-C,[65] and the small (6%) LDL/TC rise during a 21–28-day cancer VLCD was transient and occurred against a 60% fall in insulin.[68] Mild hyponatremia occurred without proactive electrolyte replacement,[34,37,42] and gut-microbiota shifts were reported in two studies;[61,62] dizziness, fatigue, headache, and cramps were otherwise mild and transient.[42,52]

Clinical takeaway

Hypocaloric KDs deliver the most robust short- to medium-term weight and glycemic benefit. Safety rests on protein ≥1.2 g/kg/day, unsaturated-fat priority, fiber ≥25 g/day, proactive

sodium/potassium/magnesium, avoidance of excessive protein loads in susceptible individuals, and biochemical monitoring (renal function, electrolytes, lipids) at baseline and every ~3 months, under which even protocols extending to 6–12 months caused no serious adverse events.

Isocaloric ketogenic diets

Study population and indications

Fifty-four studies spanned the broadest indication range (Table 3). Healthy participants/athletes formed the largest group (12 studies, 22.2%),[74,77,79,80,84,88,90,92,96,108,109,111] followed by high-grade glioma (6 studies),[85,89,94,95,119,120] overweight/obesity (5, 9.3%),[100,101,105,106,113] non-CNS cancer (6, 11.1%),[83,98,99,102,114,118] psychiatric disorders (4), comprising post-traumatic stress disorder (PTSD),[72] major/treatment-resistant depression,[115,117] and schizophrenia-spectrum psychosis,[116] Alzheimer's/Parkinson's disease (4),[70,81,97,123] acute/subacute brain and spinal-cord injury (3),[71,86,87] epilepsy (2),[73,76] T2DM (2),[103,104] migraine/cluster headache (2),[91,93] chronic stable heart failure (2),[107,112] and McArdle disease (2);[75,121] single studies addressed sepsis/critical illness (mechanically ventilated ICU patients),[88] amyotrophic lateral sclerosis (ALS),[78] NAFLD,[110] cardiovascular health with mildly elevated LDL,[82] and endometriosis, in which an MCT-modified isocaloric KD reduced pelvic pain while weight, lipid, and transaminase levels remained unchanged.[122] The newer trials extended isocaloric evidence to treatment-resistant depression in an 88-participant trial with energy matched to maintain weight,[115] outpatient psychosis,[116] and chemoradiation for glioma and gynecological malignancy.[118–120]

Ketogenic protocols

Eight protocol types were identified (Table 2, Part B): (i) LCD/VLCKD below 50–120 g carbohydrate/day without a strict ratio (13 studies, 24.1%);[89,91,92,103–105,107,110,112–115,123] (ii) classic KDs (CKD; 75–90% fat energy, strict 3:1–4:1 fat: (protein+carbohydrate) ratio; 14 studies, 25.9%), using oral or enteral formulations;[73,76,79,80,89,94,100–103,116,118,119,121] (iii) medium-chain triglyceride (MCT)-enhanced KDs deriving25–50% of fat energy from MCT oil (11, 20.4%);[70,71,78,84,86,90,98,108,112,120,122] (iv) modified Atkins/modified KDs starting at 15–20 g carbohydrate/day then liberalized or stepped upward in fat (8, 14.8%);[73,75,78,81,83,86,89,117] (v) exogenous-ketone strategies (4, 7.4%), including Ketostart® salts producing rapid ketosis in PTSD within 1–2 days,[72] a ketogenic enteral formula in patients with sepsis,[88] caprylidene in Alzheimer's disease (raising regional cerebral blood flow in APOE4-negative

participants),[97] and DL-βHB mineral salts in migraine;[91] (vi) Mediterranean KDs (2, 3.7%);[78,81] (vii) high-protein KDs providing 20–27% protein energy (1.8–2.1 g/kg/day) to preserve lean mass (3, 5.6%);[82,105,108] and (viii) cross-over/gradient designs comparing multiple carbohydrate levels (2, 3.7%).[90,92] Classic and MCT protocols used fixed ratios, whereas LCD and modified Atkins protocols relied on carbohydrate restriction alone, yielding variable ketonemia; the newer supervised oncology and psychiatry protocols used prepared meals or fixed 3:1 formulations to guarantee both ketosis and a stable energy intake.[115,116,119,121]

Energy-intake determination—a key methodological axis

Eight methods were used to match intake to expenditure (Table 2, Part D): (i) formula-based estimation using Harris-Benedict, Mifflin-St Jeor, Weir, or Mifflin equations multiplied by activity factors (19 studies, 35.2%; 25–40 kcal/kg/day; men ≈2,100 – 2,600 and women ≈1,800–2,100 kcal/day);[70,72,74,78,81,82,87,88,94,96,98,105,107-109,111,115,121,122] (ii) software-assisted tracking via MyFitnessPal, Vitakost, ProNutra, IProfile, or NDSR (9, 16.7%; recorded intakes1,520 ± 330 and 2,330 ± 160kcal/day);[71,76,81,84,91,101–103,113] (iii) indirect calorimetry/ metabolic monitoring including whole-room calorimetry, resting expenditure, and respiratory quotient (6, 11.1%; mean 1,720 kcal/day, 71.4% from fat);[74,78,89,100,103,106] (iv) standardizednational/ intensive care unit (ICU) reference guidelines (5, 9.3%; 25–30 kcal/kg/day);[71,81,86,87,89] (v) self-reported diaries/ 24-h recalls/food records (6, 11.1%; 1,480–1,670 kcal/day); [87,92,94,103,117,123] (vi) direct formulation, tube feeding, or study-provided meals of fixed caloric density (6, 11.1%; 2,100 kcal/day, 89.7% fat, 3.1% carbohydrate);[71,84,87,101,115,116] (vii) fixed-dose exogenous ketones without a caloric prescription (1, 1.9%; DL-βHB 6 g × 3/day, ≈100 kcal/day);[91] and (viii) no explicit method described (2, 3.7%). Worked examples illustrate the precision required: one Parkinson's study applied the Weir formula [$1.44 \times (3.94 \cdot VO_2 + 1.11 \cdot VCO_2) \times$activity 1.6],[70] an ALS study used Mifflin-St Jeor,[78] a whole-room calorimeter maintained strict isocaloric balance at a fixed activity level of 1.65,[74] and a depression RCT set individualized energy targets and adjusted snack portions whenever body weight drifted, explicitly to remove weight loss as a confounder.[115] In the septic ICU trial, indirect calorimetry guided prescription so that ketogenic and standard groups received comparable calories, isolating macronutrient composition from energy restriction.[88]

Energy-neutral metabolic and body-composition outcomes

Consistent with the weight-stability objective, seven studies (13.0%) lost ≥5 kg (from 5.1 kg[82]), twenty (37.0%) lost <5 kg, sixteen (29.6%) remained stable (±1 kg or were explicitly weight-matched), and eleven (20.4%) did not report weight or used exogenous ketones alone (Table 4, Part B). Magnitude varied by protocol strictness (a 3.7-kg loss on a 12-week moderate LCD[90]), again an observational trend, and cohort size (3–173) was unrelated to magnitude.dual-energy X-ray absorptiometry (DXA)/bioelectrical impedance analysis (BIA) data showed preferential visceral-fat reduction with relative lean-mass preservation,[81,82,110] although lean mass fell where protein was inadequate or resistance exercise absent[70,100,106] — one study lost 2.6 ± 1.3 kg weight with 2.6 ± 3.9 kg muscle (possibly dehydration-related),[70] while another gained skeletal-muscle insulin sensitivity despite 2.2 kg weight and 1.4 kg lean-mass loss.[100] Biochemical benefits emerged independent of weight change (Table 5): serum β-hydroxybutyrate rose across more than 20 studies (by 1.4 mmol/L, 95% CI 1.0–1.8, p <0.001 in patients with sepsis;[88] a single 6-g DL-β-hydroxybutyrate (DL-βHB) dose reached only 0.46 mmol/L in migraine[91]); HDL-C rose in six and triglycerides fell in eight studies, with improved TG/HDL in two; transient LDL-C elevation in three[90,110,112] (≈12 % at 3 months, normalized by 12 months; +0.29 ± 0.12 mmol/ L110); glucose and insulin improved across ten studies, including clamp-proven increased muscle glucose disposal without altered hepatic sensitivity100 and, in patients with sepsis, no ketogenic-diet patient required insulin after day 4 versus 35–60 % of controls (p = 0.009);[88] inflammatory LPS, IL-1β, and TNF-α fell[72,80,82,88,90] with βHB/FGF21 synergistic inhibition of the NLRP3 inflammasome[80] and reduced T-cell immune dysregulation in patients with sepsis,[88] whereas protein carbonyls rose in irradiated cancer patients;[98] triiodothyronine (T3) fell (4.1 pmol/L) and thyroxine (T4) rose (19.3 pmol/L);[79] and respiratory quotient fell from 0.80 to 0.73 (p = 0.000003).[70] Whole-room calorimetry demonstrated +110 kcal/day total (and +201 kcal/day sleeping) energy expenditure under precisely matched balance,[74] evidence for a ketosis-specific thermogenic effect. The newer trials provided particularly clean evidence for ketosis-specific benefit under stable or only mildly reduced weight. In an 88-participant depression randomized controlled trial (RCT) designed with individualized energy targets to prevent weight loss, the ketogenic arm improved Patient Health Questionnaire-9 (PHQ-9) depression scores at 6 weeks with no serious adverse events;[115] in outpatient psychosis, rising blood ketone levels correlated with improvements in prediabetic markers and symptoms, whereas the modest weight reduction was unrelated to metabolic or symptom improvement, directly dissociating ketosis from

caloric deficit;[116] and a supervised depression pilot achieved an 87.5% remission rate with a 23.3-point reduction in the Montgomery–Åsberg Depression Rating Scale (MADRS) and an 8.8-point fall in the Generalized Anxiety Disorder-7 (GAD-7).[117] In oncology, a glioblastoma phase 1 trial met its primary safety objective without excessive weight loss or serious events, all evaluable patients maintained ketosis (≥0.3 mmol/L) on more than half of study days, and median progression-free and overall survival reached 12.9 and 29.4 months;[119] a malignant-glioma protocol combined with bevacizumab was feasible over a median 185 days (range 63–1,950), with a 50% response rate and one recurrence-free survivor beyond five years;[120] and a gynecological-cancer radiotherapy trial preserved body cell mass despite treatment-related weight reduction, with no excess gastrointestinal toxicity versus a standard diet.[118] In neurological and benign conditions, a six-month 3:1 KD was well tolerated in McArdle disease,[121] a twelve-week KD improved motor and non-motor Parkinson's scores (Movement Disorder Society–Unified Parkinson's Disease Rating Scale part III [MDS-UPDRS III], p <0.001; Non-Motor Symptoms Scale [NMSS], p <0.0001) alongside gut-microbiota remodeling,[123] and an MCT-modified KD reduced endometriosis pelvic pain while anthropometric, lipid, and transaminase measures remained unchanged.[122]

Adverse events and mechanisms

Adverse events were reported in 26 studies (48.1%) — the highest rate, but one reflecting the inclusion of critically ill, advanced-cancer, neurological, and psychiatric patients rather than intrinsic toxicity; the remaining studies reported no death or serious event, and the septic enteral protocol reported no acidosis, dysglycemia, or dyslipidemia[88] (Table 6). Gastrointestinal symptoms (nine studies[71,72,75,88–90,96,106,118]) comprised nausea/vomiting (3%/2% of days), diarrhea (3.3%), and constipation (0.2% of days in one study; 7/11 patients constipated in another glioma series)[71,89] and were associated with high MCT load,[71,96] low fiber, and rapid titration; during pelvic radiotherapy the KD did not increase diarrhea or nausea versus standard diet.[118] Lipid abnormalities (six studies71,88,90,102,108,110) were dominated by the transient LDL-C rises and one case of TC 7.4 mmol/L on a 4:1 diet[89] described above. Muscle loss/weakness (four studies70,93,105,108; weakness p = 0.00593) occurred only below the protein threshold and was countered by 1.8–2.1 g/kg/day high-protein designs.[82,105,108] Electrolyte disturbance (one study; [71] one severe hyponatremia leading to discontinuation) and one case of metabolic acidosis on a severe-sepsis background (pH normal in 95%)[86] were confined to vulnerable, inadequately supplemented settings. Other effects—fatigue on 70% of intervention days in PTSD,[72] headache/dizziness,[72,73] impaired

exercise economy (10-km time 2.3% slower),[88,111] menstrual-cycle ketonemia variability,[76] and mild, transient induction-phase symptoms in a supervised depression pilot[117]—were mild and self-limited. The larger recent trials were reassuring: an 88-participant depression RCT and a glioblastoma series reported no serious adverse events or excessive weight loss,[115,119] and a six-month McArdle-disease trial found the 3:1 KD safe and tolerable.[121]

Clinical takeaway

Isocaloric KDs isolate ketosis-specific benefit and are preferred for metabolically fragile patients requiring weight stability, including neurological and psychiatric disorders and patients receiving chemoradiation. Safe implementation requires protein ≥1.2 g/kg/day (1.5 – 2.0 in active persons), limitation of saturated fat and MCT load, fiber ≥25 g/day, proactive electrolytes, resistance training, and monitoring of lipids, thyroid function, electrolytes, and renal function every 4-8 weeks, with intensified oversight in vulnerable cohorts; under such conditions ketosis was achieved safely even in septic ICU patients, in outpatients with psychosis, and during glioma and pelvic radiotherapy.[88,115,116,118–120]

Ad libitum energy-intake ketogenic diets

Study population and indications

Thirty-nine studies imposed no energy limit (Table 3). Obesity/ metabolic syndrome predominated (15 studies, 38.5%), covering overweight/obesity, insulin resistance, prediabetes, T2DM, dyslipidemia, and metabolic syndrome.[127,128,135–146,162] Neurological applications—drug-resistant epilepsy, relapsing multiple sclerosis, Parkinson's disease, and rare inherited metabolic disease—comprised nine (23.1%);[124–126,147–152] healthy/athletic cohorts five (12.8%);[153–157] cancer four (10.3%), spanning glioma and head-and-neck, rectal, and metastatic pancreatic tumors during radio(chemo)therapy;[133,134,159,160] psychiatric disorders (schizophrenia, bipolar, major depression, and psychogenic non-epileptic seizures) four (10.3%);[130–132,161] and single studies addressed chronic pain[158] and polycystic ovary syndrome (PCOS)/reproductive endocrinology.[129]

Ketogenic protocols

Six approaches were identified (Table 2, Part C): (i) modified Atkins diets (MAD; 9 studies, 23.1%; net carbohydrate 16–50 g/day, ~65–70% fat, 25–30% protein, 5–10% carbohydrate);[125,126,133,135,137,141,147,152,161] (ii) one classic 4:1 KD (net carbohydrate ≤20

g/day);[130] (iii) low-carbohydrate high-fat diets (LCHF; 29 studies, 74.4%; carbohydrate 20 – 117 g/day, >50% fat, with Mediterranean, Atkins-style, whole-food, medically supervised, or free-choice fat sources);[124,127-129,131,132,134,136,138-140,142-146,148–151,153–160,162] (iv) MCT-supplemented KDs (2);[133,134] (v) exogenous ketone esters/salts (1); [153] and (vi) disease-specific modifications (3) — an adapted KD for multiple sclerosis (ω6:ω3 = 2:1), a modified Atkins regimen for glioma with metformin, and a ketone-ester plus low-glycemic regimen in psychiatry.[133,148,149] In contrast to the other strategies, no formal energy target was calculated; intake was guided by appetite, relying on carbohydrate restriction and ketone-mediated satiety — even the remotely supervised pancreatic-cancer protocol let patients eat to satiety within the prescribed macronutrient ratios.[159]

Outcomes without energy prescription

Weight responses were heterogeneous (Table 4, Part C): among studies reporting weight, eight (42.1%) achieved clinically significant loss (≥5%/ ≥5 kg), with a maximum of 13.5 kg,[150] −10% of baseline,[130] 7 kg over 24 months,137 and BMI −4.1 kg/m², and one carbohydrate-capped, appetite-suppressed protocol reached a spontaneous ≈783 kcal/day deficit with −9.9 kg at 12 months;152,162 eight (42.1%) lost <5 kg; three (15.8%) remained stable or gained; and just over half (20/39) did not report weight, highlighting inconsistent outcome reporting. These losses occurred without any prescribed deficit, indicating that carbohydrate restriction alone — through lowered insulin and increased satiety—can drive spontaneous energy reduction in a subset. Biochemically (Table 5), β-hydroxybutyrate rose consistently, including a median 39.4% of days in nutritional ketosis under a remotely supervised oncology regimen;[125,130,133,149,152–154,159] HDL-C rose in five[127,137,150,152,155] while LDL-C/TC/free-fatty acids/uric acid rose in six[125,141,144,154,155,162] and triglycerides/very-low-density lipoprotein (VLDL) fell in four;[130,137,150,152] glucose, HbA1c, insulin, and homeostatic model assessment of insulin resistance (HOMA-IR) improved in six;[130,140,141,143,150,152] hs-CRP, lipopolysaccharide (LPS), and nuclear factor- κ B (NF-κB) activity declined;[130,146,158] multiple-sclerosis cohorts showed rising adiponectin and vitamin D and falling neurofilament light chain and leptin, with βHB ≥1.0 mmol/L correlating with neurofilament improvement;[149,152] aspartate/alanine aminotransferase (AST/ALT) and creatinine improved,[139,146] blood pressure fell,138,144 testosterone and FGF21 rose while T3/leptin fell,[125,143,144] and short-term microbiome/B-vitamin-pathway changes and adaptive immune induction were documented.[139,147,156] Psychiatric cohorts showed parallel metabolic and

symptomatic improvement.[130–132] The newer trials extended the ad libitum evidence into oncological and functional-neurological settings: in metastatic pancreatic cancer, a remotely supervised medically supervised ketogenic diet achieved nutritional ketosis in 15 of 16 patients, with numerically longer progression-free (8.5 vs 6.2 months; hazard ratio (HR) 0.53, 95% CI 0.21 – 1.37) and overall (13.7 vs 10.2 months) survival and no excess grade ≥3 toxicity or deterioration in quality of life;[159] a post-hoc analysis of rectal and head-and-neck radiotherapy found that an ad libitum whole-food KD did not impair overall, progression-free, or locoregional recurrence-free survival and did not increase acute radiation toxicity;[160] and a six-week modified Atkins pilot in adults with psychogenic non-epileptic seizures reduced seizure frequency (p = 0.01, Hedges g = 0.618) alongside depression and anxiety.[161]

Adverse events and mechanisms

Adverse events were reported in 13 studies (33.3%), and 66.7% reported no death or serious event (Table 6), but the pattern differed fundamentally. Population vulnerability: head-and-neck cancer patients on MCT during radiotherapy had 25% diarrhea and 35% attrition,[134] whereas a larger whole-food KD cohort during radio(chemo)therapy showed no excess acute radiation toxicity;[160] drug-resistant epilepsy showed LDL-C + 22% (p = 0.001) with free-carnitine depletion;[125] McArdle disease showed 22.6% hypercholesterolemia with cramping;[151] and long-term obesity management was associated with 44% alopecia at 6 months and persistent dyslipidemia.[137] Fat quality and formulation: a 4:1 ratio produced 3% muscle depletion from inadequate protein;[130] unsupervised intake produced hypercholesterolemia in 71%, and one trial recorded a transient 12% LDL-C rise at 3 months that resolved by 12 months.[154,162] Duration and monitoring: short-term (≤12-week) effects — headache/nausea (37.6%),[151] cramps from electrolyte depletion,[143] and transient LDL-C rises[142] — were reversible, whereas >6-month protocols showed cumulative, potentially persistent dyslipidemia,[137,144] 3.52 kg lean-mass loss,[137] and renal physiological stress after 46 days in oncology;[134] inaccurate self-monitoring contributed to protein under-provision.[130,151] Additional concerns included constipation (26 – 64%) and halitosis (65%) from inadequate fiber,[137,151] dietary fiber at only 8.3% of recommended intake with attendant microbiome risk,[154,162] and 40% attrition in one epilepsy cohort despite unrestricted energy.[125] Reassuringly, ad libitum whole-food and medically supervised KDs delivered during chemo- and radiotherapy did not increase grade ≥3 treatment-related or acute radiation toxicities relative to standard diets,[159,160] and the only effects in a six-week psychogenic non-epileptic

seizure (PNES) pilot were mild, self-limiting nausea, constipation, and headache at induction that required neither medication nor discontinuation.[161]

Adherence and clinical takeaway

Free food selection (avocados, nuts, full-fat dairy) and the absence of calorie counting enhanced perceived sustainability, accounting for the high proportion of >6-month protocols[137,144] and for promising supervised engagement in psychiatric and functional-neurological cohorts[130–132,161] and for feasible delivery during active chemo- and radiotherapy;[159,160] nevertheless, long-term adherence remained difficult without structure. Ad libitum KDs may be offered to self-managing patients, but beyond 3 months they require explicit guidance toward unsaturated fats, fiber and protein adequacy, and quarterly lipid surveillance, with particular caution — and a low threshold to switch to a controlled strategy — in pre-existing dyslipidemia, APOE4 carriers, and insulin-resistant obesity.

Cross-strategy synthesis

Direct comparison (Tables 1 and 6) shows that hypocaloric KDs produce the greatest weight and glycemic benefit but require supervision to prevent lean-mass loss; isocaloric KDs isolate ketosis-specific benefit with favorable safety when well monitored and provide the clearest evidence for ketosis-mediated effects on insulin sensitivity, energy expenditure, and inflammation; and ad libitum KDs maximize adherence but carry cumulative dyslipidemic risk in unsupervised use. Across all categories, three modifiable factors consistently determined safety: (1) protein ≥1.2 g/kg/day to preserve lean mass; (2) unsaturated over saturated fat to limit LDL-C elevation; and (3) fiber ≥25 g/day with proactive electrolyte replacement to prevent gastrointestinal and electrolyte complications.

DISCUSSION

This systematic synthesis of 139 clinical studies, 46 hypocaloric (Studies 24–69), 54 isocaloric (Studies 70–123), and 39 ad libitum (Studies 124–162), demonstrates that the safety and efficacy of KDs are shaped more by the strategy of energy prescription than by carbohydrate restriction alone. Across the categories, divergent patterns of body composition, biochemical adaptation, and adverse events support the view that energy strategy is a primary determinant of KD outcomes, argue against treating the ketogenic diet as a monolithic intervention, and favor a precision-nutrition approach aligned to individual risk-benefit profiles. They also resolve several longstanding apparent contradictions in the literature,

including the widely variable LDL-cholesterol responses, which are not explained by carbohydrate restriction alone but are strongly modulated by energy-intake level, dietary-fat quality, and the intensity of clinical supervision.

The energy strategy–metabolic stress–adverse event triangle: A unifying conceptual model

The three categories describe a single conceptual sequence in which each energy strategy generates a distinctive metabolic-stress signature, and that signature in turn produces a predictable adverse-event profile. The three vertices of this triangle are considered in turn.

Vertex 1: Hypocaloric KDs and caloric-deficit stress

The dominant stress is energy scarcity. Enhanced lipolysis, reduced insulin secretion, and ketone-mediated appetite suppression together drive substantial weight loss and glycemic improvement, but scarcity combined with inadequate protein produces lean-mass depletion, the signature adverse event of this category,[36,48,50,51] which is largely preventable when protein reaches 1.2 g/kg/day and resistance exercise is feasible.[40,45] A short, 30%-deficit modified KD supplying 40% of energy as protein raised GDF15 while lowering FGF21 and remodeling 22 lipoprotein subclasses without lean-mass loss,[69] illustrating how a protein-sufficient, high-quality hypocaloric formulation aligns appetite signaling with body-composition and lipoprotein protection. Hypocaloric KDs do not usually produce dyslipidemia, even though their saturated-fat proportion often resembles that of ad libitum regimens: concurrent weight loss increases hepatic LDL clearance and reduces endogenous cholesterol synthesis, offsetting the LDL-raising action of dietary saturated fat. The deficit itself is therefore protective, and this accounts for the paradox that regimens with comparable saturated-fat content rarely show LDL-C rises.

Vertex 2: Isocaloric KDs and ketosis-isolated stress

Here the stress is adaptation to ketone-body metabolism in the absence of an energy deficit, which supplies the least confounded evidence for ketosis-specific effects: insulin sensitivity rises on clamp measurement,[100] β-hydroxybutyrate and FGF21 attenuate NLRP3 signaling,[80] and total energy expenditure is about 110 kcal/day higher under precisely matched balance.[74] The adverse events that occur correlate with formulation rather than ketosis—gastrointestinal symptoms with high MCT loads and insufficient fiber,[71,89,96,106] transient LDL-C elevation when saturated fat is not controlled, and an adaptive fall in triiodothyronine with a rise in thyroxine of uncertain clinical significance.[79] A ketogenic enteral regimen introduced by gradual titration in patients with sepsis caused no feeding intolerance, acidosis, or

dyslipidemia,[88] showing that these events are preventable through formulation quality rather than being unavoidable consequences of carbohydrate restriction. This weight-independent logic now extends beyond metabolism: an 88-participant depression RCT whose energy targets were set to prevent weight loss still improved PHQ-9 scores,[115] an outpatient psychosis trial found symptom and cognitive gains tracking blood ketones rather than the modest weight change,[116] and an MCT-modified KD reduced endometriosis pelvic pain while weight, lipid, and transaminase measures stayed unchanged,[122] indicating that ketosis-specific benefit extends to mood, cognition, and symptom control independent of any energy deficit.

Vertex 3: Ad Libitum KDs and unrestricted-intake stress

The defining stress is the absence of any regulatory brake on total energy and fat intake. This category carries the highest LDL-C risk, which reached 71% in long-term unsupervised trials,[154] not because of ketosis but because saturated-fat intake became unregulated, an effect amplified in APOE4 carriers. Removing the energy deficit also removes the protective clearance described above; these regimens are therefore dyslipidemic not in spite of, but because of, the absence of caloric restriction. The 42.1% of studies in which clinically meaningful (≥5%) weight loss still occurred reflect spontaneous ketone-mediated appetite suppression, yet this reduction is inconsistent between individuals and often insufficient to offset the cumulative LDL-raising effect of sustained high saturated-fat intake; structured psychiatric cohorts fared better in both adherence and metabolic control.[130–132] Importantly, the liability of unrestricted intake is realized chiefly when supervision is also absent: medically monitored ad libitum regimens during chemo- and radiotherapy — a remotely coached pancreatic-cancer protocol and a whole-food KD during pelvic and head-and-neck irradiation — added no grade ≥3 treatment-related or acute radiation toxicity, while still yielding numerically longer survival and, in a separate six-week modified-Atkins pilot, reducing psychogenic non-epileptic seizure frequency.[159–161]

The model is predictive rather than merely descriptive. LDL-C elevation on an ad libitum regimen tends to reverse after transfer to a deficit-based regimen or improved fat quality; lean-mass loss on a hypocaloric regimen responds to protein up-titration and resistance training,[40,45] and gastrointestinal symptoms on an isocaloric regimen settle when MCT load is reduced and fiber increased, as the gradual-titration septic enteral protocol shows.[88] It also explains why the same amount of dietary saturated fat yields different LDL responses across strategies: weight-loss-driven clearance offsets saturated-fat-driven production in hypocaloric

KDs, offsets it only partially and transiently in isocaloric KDs, and does not offset it at all in ad libitum KDs.

Boundary states between intended and achieved intake

The categories are not always discrete in practice, and the boundary states are as informative as the pure categories; two patterns are particularly noteworthy.

Pattern 1: From ad libitum to functional hypocaloric

Several ad libitum protocols fell spontaneously below 1,500 kcal/day through appetite suppression and thereafter behaved like prescribed hypocaloric regimens, achieving comparable weight loss with lower dyslipidemia risk because the incidental deficit partly offset saturated-fat effects.[41] Such individuals can obtain hypocaloric-like benefit without explicit calorie counting, but the response is neither universal nor predictable and must be identified by monitoring.

Pattern 2: From isocaloric to functional hypocaloric

A regimen designed as isocaloric can in practice become functionally hypocaloric when measured intake falls well below its prescription.[39] Intended energy balance is therefore not achieved energy balance: predictive equations can mis-estimate resting expenditure by 10–20 % in an individual, enough to move a regimen across categories and alter both efficacy and safety. Energy prescription should be treated as a hypothesis to be tested rather than a fact to be applied, with weight trajectory and metabolic response, not rigid adherence to the initial calculation, guiding adjustment.

Across both patterns the relationship between strategy and outcome is probabilistic rather than deterministic, and achieved rather than prescribed energy balance is the operative determinant. Future trials should report both quantities, and clinicians should follow weight trajectory as a real-time index of the balance actually attained.

Energy strategy and metabolic outcomes: Mechanistic considerations

Hypocaloric KDs delivered the largest weight reductions, with 60.9% of studies (28/46) achieving moderate-to-substantial losses of 5–15 kg over 8–26 weeks. Carbohydrate restriction lowers circulating insulin and promotes adipose lipolysis and hepatic fatty acid oxidation, while the imposed deficit establishes negative energy balance and accelerates fat-mass loss. Coexisting falls in HbA1c (mean 0.2–0.23%), triglycerides, and hs-CRP,[29,31,33,38,44–50] reflect both weight-loss-dependent pathways (reduced visceral adiposity,

improved insulin sensitivity) and weight-loss-independent ketone signaling, including NLRP3-inflammasome inhibition. The same deficit that drives these gains predisposes to lean-mass catabolism when protein falls below 1.2 g/kg/day,[36,48,50,51] in keeping with increased muscle proteolysis under combined energy deficit and carbohydrate restriction.

Isocaloric KDs provide the most direct evidence for ketosis-specific effects independent of a deficit. Although 66.7% of studies (36/54, combining mild loss with stable weight) reported weight changes within 5 kg, consistent with the weight-stability objective, significant gains appeared in insulin sensitivity, lipids, and inflammatory markers. A three-week isocaloric KD increased insulin-stimulated skeletal-muscle glucose disposal on hyperinsulinemic-euglycemic clamp,100 and whole-room calorimetry showed total energy expenditure approximately 110 kcal/day higher despite precise balance matching.[74] Nutritional ketosis per se, through increased fat oxidation, elevated FGF21,[80] and altered thyroid conversion (reduced T3, raised T4),[79] can therefore confer benefit beyond weight loss, and the synergistic inhibition of NLRP3 by β-hydroxybutyrate and FGF21 in human macrophages[80] defines a direct anti-inflammatory pathway. The septic ICU experience[88] extends these effects to critical illness, where ketogenic enteral nutrition reduced insulin demand and immune dysregulation without acidosis or dyslipidemia. Recent oncology trials reinforce this point in particularly fragile settings: isocaloric or weight-stabilized KDs preserved body cell mass during gynecological radiotherapy,[118] met their primary safety endpoint in glioblastoma with median overall survival of 29.4 months,[119] and remained feasible with bevacizumab for a median of 185 days (one patient recurrence-free beyond five years),[120] while a six-month regimen in McArdle disease and a twelve-week regimen in Parkinson's disease were likewise safe, with improvements in exercise tolerance and motor and non-motor symptoms.[121,123]

Ad libitum KDs occupied a distinct risk-benefit position. Freedom from calorie counting improved perceived flexibility and short-term adherence, most clearly in supervised psychiatric cohorts,[130–132] and among studies reporting weight, 42.1% achieved clinically significant loss (≥5% or ≥5 kg), 42.1% mild loss, and 15.8% stability or gain, indicating wide interindividual variability. The absence of energy and fat-quality regulation was nevertheless the principal determinant of harm: LDL-C rose in up to 71.0% and total cholesterol in 67.0% of participants in long-term unsupervised trials.[154] Gastrointestinal symptoms (constipation 26–64%, halitosis 65%)[137,151] and fiber intake at only 8.3% of recommended levels[154] were likewise concentrated in this category, reflecting the absence of structured nutritional supervision.

Clinical Decision-Making: From Static Classification to Dynamic Adaptation

These findings support a framework of monitored adaptation rather than a single fixed choice.

Step 1: Select the initial strategy. Choose by phenotype and goal: a hypocaloric KD for patients prioritizing rapid weight loss in obesity-related comorbidity, under close supervision; an isocaloric KD for metabolically fragile patients requiring weight stability (neurological disorders, critical illness, athletes); and an ad libitum KD only for patients able to self-manage, with explicit safeguards.

Step 2: Monitor the response at 4–8 weeks. Review weight trajectory, lipid profile (especially LDL-C), lean mass (bioelectrical impedance or DXA where available), and gastrointestinal, energy, and adherence symptoms.

Step 3: Adapt to the response. If LDL-C rises more than 30% or above 4.1 mmol/L on an ad libitum regimen, transfer to a controlled, fat-quality-managed regimen; if lean mass declines on a hypocaloric regimen, raise protein to 1.5 g/kg/day and add resistance training; if gastrointestinal symptoms emerge, lower MCT load and raise fiber; and if an isocaloric regimen produces no desired weight change, weigh ketosis-specific benefit against a move to hypocaloric feeding.

Step 4: Reassess at 3–6 months. Long-term safety requires sustained monitoring because cumulative dyslipidemic risk in ad libitum regimens grows with duration, making quarterly lipid surveillance essential.

The strategy appropriate to a given patient may legitimately change as weight, metabolic phenotype, and adherence evolve; precision nutrition is an ongoing cycle of measurement, feedback, and adjustment rather than a one-time choice.

Comparison with prior reviews

Earlier reviews organized KDs mainly by macronutrient ratio or carbohydrate threshold and established aggregate benefits for weight and glycemia,[14–20] but did not examine how energy prescription modifies outcome and generally treated the variants as functionally equivalent. The present synthesis differs in three respects. First, it identifies energy strategy as a more fundamental axis of heterogeneity than ratio or threshold, and shows that the apparently random LDL-C responses across trials are in fact ordered by strategy, with the largest rises in saturated-fat-rich unrestricted designs and minimal or transient changes in hypocaloric and well-formulated isocaloric designs. Second, it offers the energy strategy–metabolic stress–adverse event triangle as a single explanation for why one dietary component acts differently in different energy contexts and why adverse events are systematic rather than intrinsic to

ketosis. Third, it reframes management as dynamic adaptation rather than static classification, replacing the question "which KD is best?" with that of which energy strategy fits the patient at present and how it should change with response, a move from categorical to continuous, individualized decision-making.

The challenge of energy calculation: Methodological and clinical implications

Energy determination was methodologically heterogeneous: among isocaloric studies, eight approaches ranged from formula estimation (35.2%) and software-assisted tracking (16.7%) to indirect calorimetry (11.1%) and standardized reference guidelines (9.3%).[70–123] Predictive equations may under- or over-estimate resting expenditure by 10–20% in an individual, and even small errors can move a regimen from isocaloric to hypocaloric or hypercaloric and alter both efficacy and safety, as the reclassified isocaloric breast-cancer protocol illustrates.[39] Indirect calorimetry is more precise but resource-intensive and unavailable in most settings, underscoring the need for validated, KD-specific practical tools. The tendency of ad libitum protocols to reduce intake spontaneously — one remained below 1,500 kcal/day without a caloric target[41] — further blurs the operational boundary between categories and reinforces that achieved intake should be monitored rather than assumed.

Safety considerations across energy-intake categories

Cross-category comparison shows a risk gradient that correlates inversely with the degree of supervision and energy regulation. Hypocaloric protocols, despite the most aggressive restriction, reported adverse events in only 30.4% (14/46), mostly mild and self-limiting, consistent with their structured supervision; isocaloric protocols reported events in 48.1% (26/54), largely gastrointestinal, transient lipid, and muscle effects, a rate inflated by the inclusion of critically ill, advanced-cancer, and neurological patients; and ad libitum protocols reported events in 33.3% (13/39) but produced the most concerning signal, persistent dyslipidemia during long-term unsupervised use with cumulative cardiovascular potential. Three modifiable determinants recurred across every category: protein below 1.2 g/kg/day driving lean-mass depletion,[36,48,50,51,70,93,105,108,130,134,137,141,143,155] excessive saturated-fat intake driving LDL-C elevation,[90,110,112,125,137,144,154,162] and inadequate fiber and micronutrient oversight driving gastrointestinal intolerance and nutritional deficiency.[42,49,51,52,71,89,96,106,137,151,154] Safety is thus determined less by category per se than by compositional quality and the intensity of supervision.

Clinical implications and precision nutrition

A stratified, patient-centered approach follows from these data. Hypocaloric KDs remain best suited to supervised short- to medium-term (3–6-month) weight management in obesity-related comorbidity such as type 2 diabetes, NAFLD, or metabolic syndrome.[24–69] Isocaloric KDs are preferable for metabolically fragile patients requiring weight stability—athletes optimizing composition, patients with neurological or psychiatric disease, patients receiving chemo- or radiotherapy, and critically ill populations—in whom ketosis is wanted without the confounding of a deficit.[70–123] Ad libitum KDs may be offered to self-managing patients who value flexibility, with explicit guidance on unsaturated-fat selection, fiber adequacy, and quarterly lipid monitoring and particular caution in pre-existing dyslipidemia, APOE4 carriers, and insulin-resistant obesity.[124–162] Across all categories, safe implementation rests on protein of at least 1.2 g/kg/day (1.5–2.0 in active or athletic persons), priority to unsaturated over saturated fat, fiber of at least 25 g/day from non-starchy vegetables, proactive electrolyte replacement during early keto-adaptation, and biochemical monitoring (lipids, renal function, electrolytes, and thyroid function at baseline and every ~3 months during active intervention).

Future research directions

Several priorities follow. Long-term (≥12-month) randomized comparisons of the three strategies within the same population are needed to test the predictive validity of the triangle; standardized reporting of calculation method, prescribed intake, and achieved intake is a prerequisite for meta-analysis and for separating intended from actual balance; predictive markers, whether genetic (APOE4), metabolic (insulin resistance, baseline lipids), or behavioral (appetite-suppression response), would identify the strategy best suited to an individual; the boundary states require study of what determines whether an unrestricted regimen produces spontaneous reduction or uncontrolled intake and whether an isocaloric regimen remains so in practice; mechanistic work should define how a caloric deficit protects against LDL-C elevation, plausibly through enhanced clearance and reduced endogenous synthesis; sex- and age-specific analyses are warranted given menstrual-cycle variation in ketonemia;[76] and adequately powered trials are needed to confirm the promising but mostly small-sample signals in oncology and psychiatry, where phase I–II and pilot data establish feasibility and suggestive efficacy but seldom statistical certainty.[115–120,159–161]

Limitations

Several limitations qualify these conclusions. Heterogeneity of populations, protocols, outcomes, and follow-up precluded meta-analysis and leaves a narrative synthesis open to interpretive bias; assignment to category rested on reported methods and on consensus where prescription was ambiguous, so misclassification between intended and achieved intake remains possible; compliance biomarkers such as serum β-hydroxybutyrate and urinary ketones were reported inconsistently, preventing quantitative analysis of compliance-outcome relations; most follow-up was no longer than six months, limiting inference on long-term safety and especially on cumulative unrestricted-regimen dyslipidemia; the search covered three databases to August 2026 and may miss later or differently indexed work; pooling many indications limits population-specific inference; and the triangle is a conceptual model requiring prospective testing in head-to-head comparisons of the three strategies within one population.

Conclusions

This synthesis of 139 clinical studies demonstrates that metabolic outcomes and safety are determined more by energy-intake strategy than by carbohydrate restriction alone. The triangle of caloric-deficit stress (hypocaloric), ketosis-isolated stress (isocaloric), and unrestricted-intake stress (ad libitum) unifies the evidence and resolves longstanding contradictions in the literature. Hypocaloric KDs (n = 46) produce substantial weight and metabolic benefit but require supervision to prevent lean-mass loss; isocaloric KDs (n = 54) isolate the metabolic benefits of ketosis independent of a deficit with favorable safety in well-monitored populations, including psychiatric, neurological, and oncological patients; and ad libitum KDs (n = 39) offer adherence advantages but carry significant dyslipidemic risk when unsupervised, although medically monitored whole-food regimens can remain safe — and still effective — during oncological treatment. Because adverse events are predictable rather than intrinsic to ketosis — dyslipidemia linked to uncontrolled saturated fat, lean-mass loss associated with inadequate protein, and gastrointestinal symptoms resulting from low fiber and rapid titration — the universal safeguards of protein ≥1.2 g/kg/day, unsaturated-fat priority, fiber ≥25 g/day, electrolyte replacement, and regular monitoring allow KDs to be used safely. Choosing an energy strategy is in effect choosing a metabolic-stress and adverse-event profile, which supports dynamic, patient-centered adaptation rather than static, one-size-fits-all prescription and points to long-term head-to-head trials, standardized reporting of

prescribed and achieved intake, and predictive biomarkers as the key priorities. This offers a precision-nutrition route beyond the polarized argument over whether KDs are intrinsically beneficial or harmful, one that is both more scientifically rigorous and more clinically useful.

SUPPLEMENTARY MATERIALS

All supplementary tables and figures are available upon request from the editorial office, and are also accessible on the journal's webpage (apjcn.qdu.edu.cn).

DISCLOSURE ON THE USE OF AI AND AI-ASSISTED TECHNOLOGIES

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CONFLICT OF INTEREST AND FUNDING DISCLOSURE

The authors declare no conflict of interest.

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Table 1. Classification of the 139 included studies by energy-intake strategy

Feature / study numbers	Hypocaloric KD	Isocaloric KD	Ad libitum KD
Study range / count	Studies [24–69]; n = 46	Studies [70–123]; n = 54	Studies [124–162]; n = 39
Energy prescription	Energy intake below estimated requirements (deliberate deficit)	Energy at or near estimated requirements; weight stability intended	No prescribed energy limit; appetite-guided within KD framework
Energy range	VLCKD 600–800; LCD 1,200–1,500; moderate deficit 200–600; VLCKD <500 kcal/day variant (detail in Table 2, Part A) [42]	25–40kcal/kg/day; men ≈2,100–2,600, women ≈1,800–2,100kcal/day; matched to measured/estimated expenditure	Ad libitum; no caloric target; appetite-guided, with spontaneous reduction possible via ketone-mediated satiety
Primary objective	Rapid weight / fat loss with ketosis	Isolate ketosis-specific effects independent of caloric deficit	Maximize sustainability and long-term adherence
Dominant protocols (detail in Table 2)	Fixed-prescription VLCKD/LCD (commercial formulas), Mediterranean-KD, intermittent-fasting / cyclic KD	Classic 4:1 KD, MCT-enhanced, MAD, LCD, high-protein KD, exogenous ketones, Mediterranean-KD	LCHF (74.4%, 29/39), MAD (23.1%, 9/39), classic 4:1 KD, MCT adjunct, exogenous ketones
Energy determination (detail in Table 2)	Predominantly fixed caloric prescription / staged protocols	Formula (35.2%), software (16.7%), indirect calorimetry (11.1%), reference standards (9.3%), diaries, study-provided meals, fixed ketone dose	Mostly no calculation; self-selected intake under carbohydrate cap
Main indications (detail in Table 3)	Overweight/obesity 93.5%; also T2DM, NAFLD/MASLD, MetS, lipedema, OA, psoriasis, breast/endometrial cancer	Broadest range: healthy/athletes, obesity, non-CNS cancer, glioma, neurodegeneration, brain injury, epilepsy, migraine, sepsis, HF, T2DM, psychiatric disorders, McArdle disease, endometriosis	Obesity/MetS 38.5% (15), neurological 23.1% (9), healthy/athletes 12.8% (5), cancer 10.3% (4), psychiatric 10.3% (4), pain/PCOS 1 each
Typical duration	Mostly ≤6 mo; five studies ≥6 mo [32,34,46,60,64]	Mostly short-term (2 d–12 wk); ICU enteral 4–6 d; some to 12 mo	Longest horizon, up to 24 mo[137]; risk accumulates with duration
Dominant weight outcome (detail in Table 4)	60.9% (28/46) achieved 5–15 kg loss; up to 22.8 kg[58]	66.7% (36/54) lost <5 kg or stayed weight-stable; 13.0% (7/54) lost ≥5 kg	Heterogeneous: 42.1% ≥5%/≥5 kg, 42.1% <5 kg, 15.8% stable/gain
Studies reporting any adverse event (detail in Table 6)	30.4% (14/46); no death/SAE in 69.6%	48.1% (26/54); rate reflects vulnerable cohorts, no intrinsic toxicity	33.3% (13/39); dyslipidemia is the dominant cumulative signal
Signature safety concern	Lean-mass loss when protein <1.2 g/kg; renal changes only with protein >2.0 g/kg + dehydration	GI symptoms with high MCT load; transient LDL-C rise with high saturated fat	LDL-C/TC rise in unsupervised long-term use (up to 71%)[154]
Core safeguards	Protein ≥1.2 g/kg, electrolytes, resistance training, monthly labs	Limit saturated fat/MCT, protein ≥1.2 g/kg, fiber ≥25g/day, monitor q4–8 wk	Unsaturated fats, fiber/protein adequacy, quarterly lipids; switch strategy if LDL-C >4.1 mmol/L or rises >30%

CNS, central nervous system; GI, gastrointestinal; HF, heart failure; ICU, intensive care unit; KD, ketogenic diet; LCD, low-calorie ketogenic diet; LCHF, low-carbohydrate high-fat; LDL-C, low-density lipoprotein cholesterol; MAD, modified Atkins diet; MetS, metabolic syndrome; MCT, medium-chain triglyceride; mo, months; NAFLD/MASLD, non-alcoholic fatty liver disease/metabolic dysfunction-associated steatotic liver disease; OA, osteoarthritis; q4–8 wk, every 4–8 weeks; SAE, serious adverse event; T2DM, type 2 diabetes mellitus; VLCKD, very-low-calorie ketogenic diet; wk, weeks.

Table 2. Ketogenic protocols and energy-intake determination methods

Part A — Hypocaloric KD: energy-deficit tiers

Approach / method	Specific range / main methods	n	Study numbers
Very-low-calorie (VLCKD)	600–800kcal/day; commercial meal replacements (PNK®, Optifast, Zélé®), Mediterranean-KD, staged protocols, low-fat very-low-energy and short-course oncology VLCDs	19	25,27–30,32,34,46-49,51,55,57,58,61,63,67,68
Low-calorie (LCD)	1,200–1,500kcal/day; modified Atkins, Asian-modified KD (AKD), liquid meal replacement, low-carb low-energy diet	12	24,26,31,35,36,38,39,41,43,52,59,64
Moderate caloric deficit	200–600kcal/dayreduction, prescribed ≈30% deficit, or >22% deficit; intermittent fasting, cyclic/healthy-KD, structured meal provision, high-protein (40% energy) modified KD at 70% of requirement	14	33,37,40,44,45,50,53,54,56,60,62,65,66,69
Very-low-calorie KD (<500kcal/ day variant)	Protein-priority VLCKD + low-GI Mediterranean diet (chronic plaque psoriasis; PASI ↓76%, 94.3% achieved ≥49% response)	1	42

Part B — Isocaloric KD: ketogenic protocols

Approach / method	Description	n	Study numbers
LCD / VLCKD	VLCKD <50 gcarbohydrate/day; LCD 50–120g/day, no strict ratio	13	89,91,92,103–105,107,110,112–115,123
Classic KD (CKD)	75–90% fat energy; strict 3:1–4:1 fat:(protein+carbohydrate); <50g/day	14	73,76,79,80,89,94,100–103,116,118,119,121
MCT-enhanced KD	25–50% of fat energy from MCT oil	11	70,71,78,84,86,90,98,108,112,120,122
MAD / modified KD	Initialcarbohydrate15–20g/daythen gradual liberalization	8	73,75,78,81,83,86,89,117
Exogenous ketones	Oral βHB salts (6–18g/day), ketone esters, caprylidene, or ketogenic enteral formula	4	Ketostart® salts [71]; ketogenic enteral formula [86]; caprylidene [95]; DL-βHB mineral salts [89]
Mediterranean KD	Monounsaturated fats (olive oil), moderate protein,low-GI carbohydrates	2	78,81
High-protein KD	20–27% protein energy (1.8–2.1g/kg/day) to preserve lean mass	3	82,105,108
Cross-over / gradient	Multiple carbohydrate levels compared (5%/15%/25% energy)	2	90,92

Part C — Ad libitum KD: ketogenic protocols

Approach / method	Description	n	Study numbers
Modified Atkins (MAD)	Netcarbohydrate16–50g/day; fat 65–70%, protein 25–30%,carbohydrate5–10%; flexible, long-term-friendly	9	125,126,133,135,137,141,147,152,161
Classic KD (CKD)	Fat:(protein+carbohydrate)=4:1 by weight; netcarbohydrate≤20g/day, fat 60–75% energy	1	130
Low-carb high-fat (LCHF)	Carbohydrate <50g/day (range 20–117g/day), fat >50% energy; most prevalent, heterogeneous fat sources	29	124,127–129,131,132,134,136,138–140,142–146,148–151,153–160,162
MCT-supplemented KD	MCT oil adjunct to classic KD / MAD to accelerate ketosis	2	133,134
Exogenous ketone administration	Ketone esters/salts for short-term ketosis without strict restriction	1	153
Disease-specific modified KD	AKD for MS (ω6:ω3=2:1); ModAD for glioma (+metformin); ketone-ester + low-GI for psychiatry	3	133,148,149

AKD, Asian-modified ketogenic diet; BW, body weight; CKD, classic ketogenic diet; HB, Harris–Benedict; LCD, low-calorie diet; LCHF, low-carbohydrate high-fat; MAD, modified Atkins diet; MCT, medium-chain triglyceride; MS, multiple sclerosis; NDSR, Nutrition Data System for Research; PASI, Psoriasis Area and Severity Index; REE, resting energy expenditure; RQ, respiratory quotient; VLCKD, very-low-calorie ketogenic diet; VLCD, very-low-calorie diet; βHB, β-hydroxybutyrate; ω6:ω3, omega-6 to omega-3 fatty acid ratio. Note: studies can use more than one protocol or calculation method, so counts within a part need not sum to the total.

Table 2. Ketogenic protocols and energy-intake determination methods (cont.)

Part D — Energy-intake determination methods (predominantly isocaloric)

Approach / method	Typical methods / specific caloric data	n	Study numbers
Formula estimation (REE/HB/Mifflin)	Harris-Benedict, Mifflin-St Jeor, Weir × activity factor; 25–40 kcal/kg/day; M 2,100–2,600 / F 1,800–2,100 kcal	19	70,72,74,78,81,82,87,88,94,96,98,105,107–109,111,115,121,122
Software-assisted tracking	MyFitnessPal, Vitakost, ProNutra, IProfile, NDSR;1,520±330/2,330±160kcal/day	9	71,76,81,84,91,101–103,113
Indirect calorimetry / metabolic monitoring	Whole-room calorimetry, REE, RQ; mean1,720kcal/day, 71.4% energy from fat	6	74,78,89,100,103,106
Standardized dietary reference	National/ICU reference guidelines; 25–30kcal/kg/day; ideal body weight × activity	5	71,81,86,87,89
Self-reported diary / 24-h recall	Self-reported diaries, 24-h recalls, or food records (1,480–1,670kcal/day)	6	87,92,94,103,117,123
Direct formulation / tube feeding	Direct formulation, tube feeding, or study-provided meals of fixed caloric density (2,100kcal/day; 89.7% fat, 3.1% carbohydrate)	6	71,84,87,101,115,116
Exogenous-ketone standardized dosing	Fixed DL-βHB mineral salts 6 g ×3/d; ≈100kcal/dayfrom supplement	1	91
No explicit method described	Energy-matching approach not reported in sufficient detail	2	—

AKD, Asian-modified ketogenic diet; BW, body weight; CKD, classic ketogenic diet; HB, Harris–Benedict; LCD, low-calorie diet; LCHF, low-carbohydrate high-fat; MAD, modified Atkins diet; MCT, medium-chain triglyceride; MS, multiple sclerosis; NDSR, Nutrition Data System for Research; PASI, Psoriasis Area and Severity Index; REE, resting energy expenditure; RQ, respiratory quotient; VLCKD, very-low-calorie ketogenic diet; VLCD, very-low-calorie diet; βHB, β-hydroxybutyrate; ω6:ω3, omega-6 to omega-3 fatty acid ratio. Note: studies can use more than one protocol or calculation method, so counts within a part need not sum to the total.

Table 3. Clinical indications by energy-intake strategy

Clinical indication	Hypocaloric: n (studies)	Isocaloric: n (studies)	Ad libitum: n (studies)
Overweight / obesity	43 [25–62,64–67,69]	5 [100,101,105,106,113]	15 [127,128,135–146,162]
Type 2 diabetes / dysglycemia	3 [28–30]	2 [103,104]	Included in obesity/MetS cluster [135–146]
Metabolic syndrome	2 [28,31]	—	Included in obesity/MetS cluster
NAFLD / MASLD	5 [24–27,63]	1 [110]	—
Dyslipidemia	2 [52,59]	1 [82]	—
Hypertension	2 [38,66]	—	—
Chronic stable heart failure	—	2 [107,112]	—
PCOS / reproductive endocrine	1 [50]	—	1 [129]
Lipedema / adipose-tissue disorder	3 [35–37]	—	—
Chronic musculoskeletal pain / OA / chronic pain	3 [32–34]	—	1 [158]
Chronic plaque psoriasis	1 [42]	—	—
Cancer — non-CNS / solid tumors	2 [39,68]	6 [83,98,99,102,114,118]	3 [134,159,160]
High-grade glioma / CNS tumor	—	6 [85,89,94,95,119,120]	1 [133]
Epilepsy (drug-resistant)	—	2 [73,76]	In neurological cluster [124–126]
Alzheimer's / Parkinson's / neurodegeneration	—	4 [70,81,97,123]	In neurological cluster [147–152]
Acute/subacute brain & spinal-cord injury	—	3 [71,86,87]	—
Migraine / chronic cluster headache	—	2 [91,93]	—
Amyotrophic lateral sclerosis (ALS)	—	1 [78]	—
Post-traumatic stress disorder (PTSD)	—	1 [72]	—
McArdle disease (glycogen storage V)	—	2 [75,121]	1 [151] (in neurological cluster)
Other neurological (MS, epilepsy, PD, McArdle)	—	—	9 [124–126,147–152]
Psychiatric (schizophrenia / bipolar / MDD)	—	4 [72,115–117]	4 [130–132,161]
Sepsis / critical illness	—	1 [88]	—
Healthy participants / athletes	1 [40]	12 [74,77,79,80,84,88,90,92,96,108,109,111]	5 [153–157]
Endometriosis / gynecological benign disease	—	1 [122]	—
TOTAL unique studies per strategy (study range)	46 (Studies 24–69)	54 (Studies 70–123)	39 (Studies 124–162)

CNS, central nervous system; MDD, major depressive disorder; MS, multiple sclerosis; OA, osteoarthritis; PCOS, polycystic ovary syndrome; PD, Parkinson's disease. Note: a study may address more than one indication, so indication counts within a column can exceed the number of studies; the TOTAL row gives the number of unique included studies per strategy.

Table 4. Weight and body-composition outcomes by energy-intake strategy

Part A — Hypocaloric KD

Weight-change category	n	Studies (duration / participants, magnitude)
0–5 kg or <5%	7	[31] 53 wk/55, −4.1 kg; [33] 12 wk/26, −3.9 kg; [37] 10 wk/24, −3.36 kg; [40] 8 wk/27, −4.6 kg; [43] 3 wk/24, −4.36 kg; [44] 2 wk/22, −3.4 kg; [69] 2 wk/30, ≈−4.5 kg (GDF15↑, FGF21 ≈−51%)
5–10 kg or 5–10%	15	[24] 8 wk/12, −6.1 kg; [25] 8 wk/47, −9.7 kg; [26] 8 wk/32, −3.8 kg; [36] 8 wk/5, −9.7 kg; [41] 26 wk/28, −8.5 kg; [45] 6 wk/49, −5.2%; [46] 6 mo/80, −7.8 kg; [47] 6 wk/140, −7 kg; [49] 8 wk/33, −8.3%; [50] 8 wk/19, −5.69 kg; [51] 8 wk/40, −5.6 kg; [56] 6 wk/247, −7.5%; [60] 26 wk/83, −7.8 kg; [61] 6 wk/35, −8.3 kg; [62] 6 wk/15, −7.37 kg
10–15 kg or 10–15%	13	[27] 13 wk, −12.5%; [28] 16 wk/90, −14.7 kg; [29] 12 wk/11, −14.3 kg; [30] 4 wk/83, −5.27 kg; [32] 49 wk/175, −10% (and 26 wk/89, ≥−10%); [35] 8 wk/56, −10.3%; [38] 3 mo/26, −11.3 kg; [42] 10 wk/38, −10.6 kg; [48] 6 wk/26, −10.4 kg; [52] 26 wk/122, −12.9%; [54] 3 wk/160, −11.9 kg; [57] 26 wk/32, BMI −5.3 kg/m²; [59] 26 wk/60, −12 kg
>15 kg	3	[34] 26 wk/18, −18% (fat mass −18%, visceral fat −27%); [55] 26 wk/31, −22.4 kg; [58] 16 wk/22, −22.8 kg
No specific data	2	[39] 12 wk/83, not reported; [53] 49 wk, not reported
Weight loss reported as percentage / other metric	6	[63] 12 wk VLED ≈753 kcal/day, −13% body weight, MRI liver fat −77%; [64] 12-mo, 1,200 kcal/day, largest sustained reduction; [65] healthy-KD ready meals, LDL-C −0.43 mmol/L (modest weight change); [66] KD with time-restricted eating, 24-h ambulatory BP↓; [67] low-carb VLCKD RCT, renal/hepatic/acid–base balance preserved; [68] 21–28 d cancer VLCD, −5.5% weight, fasting glucose −22%, insulin −60%

Part B — Isocaloric KD

Weight-change category	n	Studies (duration / participants, magnitude)
≥5 kg or ≥5%	7	[74] 12 wk/19, −5.5 kg; [81] 6 wk/20, −5.95 kg; [82] 30 d/8, −5.12 kg; [98] 5–6 wk/3, −5.6 to −9.4 kg; [101] 16 wk/123, −5.2 kg; [106] 4 wk/17, −6.34 kg; [113] 12 mo/75, −5.3 kg
Mild (<5 kg and <5%)	20	[70] 3 wk/15, −2.6 kg; [73] 4 wk/3, −0.2 to −5.1 kg; [75] 3 wk/14, significant; [79] 3 wk/11, −2.9 kg; [80] 3 d/15, −1.87 kg; [86] 6 d/20, −2.1 kg; [88] 25 d/10, −2.7 kg; [90] 12 wk/39, −3.7 kg; [92] 6 wk/10, −2.27 kg; [94] 12 wk/4, −1 kg; [100] 3 wk/11, −2.2 kg; [103] 12 mo/55, −3.1 kg; [107] 16 wk/17, significant; [108] 4 d/16, significant; [110] 3 wk/22, −3.56 kg; [114] 16 wk/16, −3.88 kg; [111] RCT, mild reduction with improved glucose homeostasis; [116] outpatient psychosis, modest reduction unrelated to symptom benefit; [117] 8-wk depression pilot, mild induction-phase change; [118] gynecological radiotherapy, mild treatment-related change with body cell mass preserved
Stable (±1 kg / no change)	16	[71] 6 wk/8, +0.4 kg; [76] 3 mo/6, stable; [78] 4 mo/40, stable; [83] 8 wk/13, no change; [87] ICU/40, no significant difference; [89] 3 wk/11, no change; [105] 8 wk/9, +0.9 kg (NS); [112] 2 mo/88, no change; [72] PTSD exogenous-ketone feasibility, weight stable; [77] 4-wk isocaloric high-altitude study, stable; [93] isocaloric mood cross-over, stable; [99] phase I radio(chemo)therapy, weight maintained; [115] 6-wk depression RCT, energy matched to prevent weight loss; [119] glioblastoma phase 1, no excessive weight loss; [121] 6-mo McArdle 3:1 KD, stable; [122] 12-wk endometriosis MCT-KD, weight unchanged
Data missing / unreported / exogenous-ketone only	11	[84] 12 wk/30, no significant weight change; [85] 14 wk/6, BMI 25→24 unquantified; [91] 12 wk/41, exogenous ketone, no weight endpoint; [96] 20 d/23, NR; [97] 45 d/14, NR; [102] 12.9 d/10, BMI↓ unquantified; [104] 12 wk/40, unquantified; [109] 4 d/16, NR; [95] glioma case series, no systematic weight endpoint; [120] glioma + bevacizumab, weight not quantified; [123] 12-wk Parkinson trial, motor/gut outcomes, weight NR

AIP, atherogenic index of plasma; BMI, body mass index; BP, blood pressure; d, days; FM, fat mass; KD, ketogenic diet; KLD, ketogenic low-carbohydrate diet; mo, months; NR, not reported; NS, not significant; RCT, randomized controlled trial; SAE, serious adverse event; sICAM-1, soluble intercellular adhesion molecule-1; VLCD, very-low-calorie diet; VLED, very-low-energy diet; wk, weeks.

Table 4. Weight and body-composition outcomes by energy-intake strategy

Part C — Ad libitum KD

Weight-change category	n	Studies (duration / participants, magnitude)
Significant loss (≥5% or ≥5 kg)	8	[128] 12 mo/75, −5.3 kg; [130] 4 mo/21, −10%; [137] 24 mo, −7 kg; [141] 6 mo/150, −5.9 kg; [142] 12 wk/75 −5.6 kg (24 wk −8.5 kg); [150] 24 wk/1, −13.5 kg; [152] 6 mo/52, BMI −4.1 kg/m²; [162] 12 mo/39 (KLD n=18), −9.9 kg; spontaneous intake ≈1,480 kcal/day with transient LDL-C +12% resolving by 12 mo
Mild loss (<5 kg)	8	[124] 12 wk/9, trend decrease; [125] 12 wk/24, −4 kg; [127] 12 mo/63, −4.4%; [134] 47 d/7, −3.45 kg; [135] 24 mo/109, −4.7 kg; [136] 12 wk/58, −3.1%; [143] 6 mo/49, −3.9 kg; [155] 4 wk/17, −3 kg
Stable / weight gain	3	[126] 6 mo/108, stable; [153] cross-over/18, stable; [154] ≥6 mo/24, stable ±3 kg
No data / unreported	20	[129,131–133,138–140,144–149,151,156–161]

Part D — Long-term (≥6 months) hypocaloric protocols: sustained efficacy without serious adverse events

Study	Intervention	Clinical / body-composition outcome	Safety
32	Telehealth-delivered exercise + ketogenic weight-loss program, 49 wk	Weight ≈−10% (≥−10% at 26 wk); fat mass −18%, visceral fat −27%; improved hip-pain scores and quality of life	No SAE; only mild exercise-related soreness; cost/adherence barriers
34	Exercise + weight-management KD for hip osteoarthritis, 26 wk	≈−18% body weight; fat mass −18%, visceral fat −27%	Feasible; no SAE
46	Healthy-KD vs energy-restricted diet, 6 mo (n=80)	−7.8 kg (vs −4.2 kg control); no rise in cholesterol	No SAE; favorable lipid course
60	KD with microbiota / short-chain fatty-acid profiling, 26 wk (n=83)	−7.8 kg; favorable microbiota and SCFA changes	No SAE
64	1,200kcal/dayKD + intermittent fasting, 12 mo	Largest sustained 12-month reduction; Orexin-A and metabolic responses	No SAE; benefit sustained to 12 mo

AIP, atherogenic index of plasma; BMI, body mass index; BP, blood pressure; d, days; FM, fat mass; KD, ketogenic diet; KLD, ketogenic low-carbohydrate diet; mo, months; NR, not reported; NS, not significant; RCT, randomized controlled trial; SAE, serious adverse event; sICAM-1, soluble intercellular adhesion molecule-1; VLCD, very-low-calorie diet; VLED, very-low-energy diet; wk, weeks.

Table 5. Biochemical and metabolic adaptations by energy-intake strategy

Domain	Indicator (direction)	Hypocaloric studies	Isocaloric studies	Ad libitum studies
Ketogenesis	Serum/urine/breath ketones, βHB (↑)	33,40,41,44	74-76,79,80,84,86,87,89,90,92,94,100,101,103,108,109,114–117,119–121,123	125,130,133,149,152–154,159,162
Lipids	HDL-C (↑)	48,51,52,59	73,90,104,110,112	127,137,150,152,155
	Triglycerides / VLDL-C / TG:HDL (↓)	30,31,38,41,45,50,65	73,82,90,100,104,106,107	130,137,150,152,162
	LDL-C / total cholesterol	↓ LDL-C/TC/TG: 27,30,31,38,41,45,50,65	↑ transient LDL-C: 90,110,112	125,141,144,154,155,162
Glycemia / insulin	Fasting glucose, HbA1c, insulin, HOMA-IR (↓)	28,30,38,39,41,43,50,57,60,68,69	88,90,100,110,115,116	130,140,141,143,150,152
Inflammation	TNF-α, hs-CRP, IL-1β, LPS, NF-κB (↓)	26,39,41,42,46,56	72,80,82,88,90	130,146,158
	IL-10 (anti-inflammatory) (↑)	↑ IL-10: 39	—	146,158
Oxidative stress	Plasma protein carbonyls / IL-1β / IL-6 (↑, context-dependent)	—	79,80,82,87,94,98,100,107,114	↑ protein carbonyls/IL-1β/IL-6 (context-dependent): 130
Liver	AST / ALT (↓)	24–26,28,30,60,63	—	139,146
Renal	Creatinine / BUN (↓, improved under supervision)	48,62	— (see adverse-event table)	139,146
Blood pressure	SBP / DBP / MAP (↓)	38,45,47,60,62,65,66	—	138,144
Hormones	T3 (↓); T4 / FGF21 / dopamine-GABA / testosterone (↑)	—	↓ T3 / ↑ T4, FGF21: 79,80	↑ testosterone/FGF21, ↓ T3/leptin: 125,143,144
Metabolic flexibility	Respiratory quotient / RER (↓ = higher fat oxidation)	—	70,80,87	140,141,143,150,152
Vitamins / micronutrients	Fat-soluble vitamins, DHA/ω-3 (↑); vitamin C (↓)	↑ fat-soluble vitamins/DHA: 37,48,55; ↓ vitamin C: 37	—	↑ vitamin D (MS cohorts): 149,152
Neuroprotective markers	↑ Adiponectin; ↓ neurofilament light chain (NfL) / leptin	—	—	↑ adiponectin; ↓ neurofilament light chain/leptin: 149,152
Microbiome / nutrient pathways	Diversity, short-chain / B-vitamin synthesis	Healthier phenotype: 61; ↑ pathogenic taxa/↓ diversity: 62	—	139,147,156
Immune function	Adaptive immune / T-cell / B-cell pathways	—	↓ NLRP3 (βHB/FGF21): 80; ↓ T-cell immune dysregulation in sepsis: 88	↑ adaptive immune/T-cell/B-cell induction: 139,147,156
Amino acids	Plasma branched-chain amino acids (↑)	—	—	↑ branched-chain amino acids: 140

Arrows denote the direction of change. Abbreviations: βHB, β-hydroxybutyrate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; VLDL-C, very-low-density lipoprotein cholesterol; FFA, free fatty acids; HOMA-IR, homeostatic model assessment of insulin resistance; hs-CRP, high-sensitivity C-reactive protein; LPS, lipopolysaccharide; IL, interleukin; TNF, tumor necrosis factor; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; T3, triiodothyronine; T4, thyroxine; FGF21, fibroblast growth factor 21; RER, respiratory exchange ratio; DHA, docosahexaenoic acid..

$^{\dagger}p<0.05$ compared with Gp1; $^{\ddagger}p<0.05$ compared with Gp2; $^{\S}p<0.05$ compared with Gm1; $^{\P}p<0.05$ compared with Gm2; $^{\dagger\dagger}p<0.05$ compared with Gm3.

Table 5. Adverse events by energy-intake strategy

Adverse-event category	Hypocaloric KD — studies and manifestations	Isocaloric KD — studies and manifestations	Ad libitum KD — studies and manifestations	Mechanism / risk factors / prevention
Dyslipidemia (↑ LDL-C / TC)	Uncommon. [31] transient ↑LDL/TC only after ≥3 eggs/d with carbohydrate reintroduction (normalized thereafter); [65] healthy-KD reduced LDL-C by 0.43 mmol/L; [68] small transient 6% rise against a 60% fall in insulin	6 studies [71,88,90,102,108,110]: [110] LDL +0.29±0.12 mmol/L; [89] one case TC 7.4 mmol/L on a 4:1 diet; transient hypertriglyceridemia [71]; septic ICU [88] no dyslipidemia	[125] ↑LDL 22% (p=0.001) with free-carnitine depletion; [154] ↑TC 71%, ↑LDL 67% in unsupervised use; [137] persistent dyslipidemia >6 mo; additional LDL/TC/non-HDL rises [141,144,155,162] (transient LDL-C +12% at 3 mo, resolving by 12 mo)	Saturated fat down-regulates hepatic LDL receptor → reduced clearance. Risk: APOE4, obesity+insulin resistance, unsupervised use, >6 mo. Prevent: prioritize unsaturated fats, quarterly lipids; switch strategy if LDL-C >4.1 mmol/L or rises >30%
Lean-mass loss / muscle weakness	4 studies [36,48,50,51]: [48] FFM −2.3 kg; [50] lean mass −1.67 kg; prevented by high protein [45] and resistance training [40]; lean indices preserved by ≈1.2 g/kg low-fat VLCKD [67] and 40%-protein modified KD [69]	4 studies [70,93,105,108]: [70] skeletal muscle −2.6±3.9 kg; [93] weakness (p=0.005); [100] lean −1.4 kg; countered by 1.8–2.1 g/kg high-protein designs [82,105,108]	[130] 3% muscle depletion on a 4:1 diet from inadequate protein; [137] −3.52 kg lean at 6 mo; [134] −0.9 kg; [141,143] ≈−1.3 kg; [155] −1.45 kg	Energy deficit + protein <1.2 g/kg drives muscle proteolysis, not ketosis. Prevent: protein ≥1.2 g/kg (1.5–2.0 in active persons) + structured resistance training [40,45]
Gastrointestinal symptoms (nausea, diarrhea, constipation, abdominal pain)	4 studies [42,49,51,52]: [52] constipation 72%; transient anorexia on a short cancer VLCD without malnutrition or dropout [68]	9 studies [71,72,75,88–90,96,106,118]: nausea 3%/vomiting 2%/diarrhea 3.3%/constipation 0.2% of days [71]; 7/11 constipated in a glioma series [89]; MCT-related [71,96]; no excess diarrhea/nausea during pelvic radiotherapy [118]; good enteral tolerance [88]	[134] diarrhea 25%, 35% attrition (H&N radiotherapy MCT); [137] constipation 64%, halitosis 65%, dry mouth 48%; [151] nausea 21%/constipation 26%; [124] constipation/diarrhea; [153] nausea/vomiting, 1 syncope; mild induction nausea/constipation/headache in PNES pilot [161]	Low fiber (<25g/day), high MCT load, rapid fat titration. Prevent: gradual MCT/fat titration, fiber ≥25g/dayfrom non-starchy vegetables, adequate fluid
Renal-function changes (↑ Cr/BUN, ↓ eGFR)	2 studies [45,49]: protein >2.0 g/kg + dehydration/perioperative stress; part of the eGFR fall is a weight/BSA denominator artifact; low-fat VLCKD preserved renal balance [67]	Not intrinsic injury; a carefully formulated enteral KD [88] showed no renal complication	[134] renal physiological stress after 46 d in oncology	Excess protein (>2 g/kg) + dehydration; part of eGFR fall is a weight/BSA denominator artifact. Prevent: avoid excessive protein, hydrate, monitor Cr/eGFR
Electrolyte imbalance (hyponatremia / hypochloremia / cramps)	Mild hyponatremia without proactive replacement [34,37,42]	1 study: [71] one severe hyponatremia leading to discontinuation; none in septic ICU [88]	Cramping with electrolyte depletion [143,151]	Ketosis increases renal Na/K excretion; dehydration/diuretics worsen. Prevent: proactive sodium, potassium, magnesium, especially during keto-adaptation
Metabolic acidosis	—	1 study [86]: one case on a severe-sepsis background, pH normal in 95%; none in the septic ICU RCT [88]	—	Confined to critical-illness background; rare under proper monitoring
Thyroid / hormonal adaptation	—	1 study [79]: ↓T3 4.1 pmol/L (p<0.0001), ↑T4 19.3, lower T3:T4 ratio (adaptive)	↓T3/leptin concentrations [125,143]	Reduced T4→T3 conversion is an adaptive response; clinical significance uncertain; no routine intervention if asymptomatic

AED, anti-epileptic drug; APG/BS, protein-supplemented versus unsupplemented study arms; APOE4, apolipoprotein E4 allele; BSA, body-surface area; Cr, creatinine; DL-βHB, DL-β-hydroxybutyrate mineral salts; eGFR, estimated glomerular filtration rate; FFM, fat-free mass; GI, gastrointestinal; GSH, glutathione; H&N, head and neck; MCT, medium-chain triglyceride; PNES, psychogenic non-epileptic seizures; SCFA, short-chain fatty acids; TC, total cholesterol. Percentages denote within-study prevalence where reported

Table 5. Adverse events by energy-intake strategy (cont.)

Adverse-event category	Hypocaloric KD — studies and manifestations	Isocaloric KD — studies and manifestations	Ad libitum KD — studies and manifestations	Mechanism / risk factors / prevention
Oxidative-stress / inflammatory-marker elevation	— (inflammatory markers predominantly improved)	[98] ↑protein carbonyls (p=0.06) in irradiated cancer with tumor GSH depletion; context-dependent [80]	—	Context-dependent (concurrent chemoradiation); coexists with anti-ketone anti-inflammatory actions; monitor in oncology
Micronutrient / carnitine / microbiome / alopecia	Gut-microbiota shifts [61,62]; ↓vitamin C [37]	—	[147] short-term diversity decline (recovered by 23–24 wk); [154] fiber only 8.3% of recommended; [156] ↓B-vitamin pathways; [137] alopecia 44% at 6 mo; [125] ↓free carnitine (p<0.001)	Absence of structured guidance → fiber/micronutrient shortfall. Prevent: non-starchy vegetables, targeted supplementation, monitor carnitine and micronutrients
Other (fatigue, headache, halitosis, dizziness, exercise impairment, menstrual variability, syncope)	[42,52] dizziness, hypotension, fatigue, headache, cramps, rash	Fatigue on 70% of intervention days (PTSD) [72]; headache/dizziness [72,73]; impaired exercise economy (10-km 2.3% slower) [88,111]; menstrual-cycle ketonemia variability [76]; mild transient induction symptoms in a supervised depression pilot [117]	Cramps 35% at 3–6 mo [143]; cramps/headache [151]; syncope and back pain [153]	Mostly transient keto-adaptation, electrolyte shifts or MCT effects; usually self-limiting with electrolyte support and dose titration
Deaths / serious adverse events and long-term safety	No death/SAE in 69.6% (32/46); all five ≥6-mo studies [32,34,46,60,64] sustained benefit with no SAE; no grade 3/4 events on a short oncology VLCD [68]; well tolerated at 2 wk [69]	No death/SAE in 51.9% (28/54); septic ICU [88] had no acidosis, dysglycemia, or dyslipidemia; an 88-participant depression RCT [115] and a glioblastoma series [119] reported no SAE; a 6-mo McArdle trial [121] was safe and tolerable	No death/SAE in 66.7% (26/39); whole-food/medically supervised KDs during chemo- and radiotherapy added no grade ≥3 or acute radiation toxicity [159,160]; a PNES pilot had only mild, self-limiting effects [161]; dyslipidemia is cumulative rather than acute	Risk is inversely related to supervision intensity and energy/fat-quality regulation; structured monitoring keeps serious events rare across all strategies

AED, anti-epileptic drug; APG/BS, protein-supplemented versus unsupplemented study arms; APOE4, apolipoprotein E4 allele; BSA, body-surface area; Cr, creatinine; DL-βHB, DL-β-hydroxybutyrate mineral salts; eGFR, estimated glomerular filtration rate; FFM, fat-free mass; GI, gastrointestinal; GSH, glutathione; H&N, head and neck; MCT, medium-chain triglyceride; PNES, psychogenic non-epileptic seizures; SCFA, short-chain fatty acids; TC, total cholesterol. Percentages denote within-study prevalence where reported