RESEARCH PAPER | REVISION 1 | PREPRINT

L-Carnitine L-Tartrate and Skeletal Muscle Androgen Receptor Protein: A Critical Evidence Map with an Unresolved Testosterone Therapy Hypothesis

A formulation-aware appraisal of exposure, muscle carnitine, receptor function, and an untested testosterone interaction

Critical narrative review, curated evidence map, and translational hypothesis paper

Not a treatment protocol. Not a clinical recommendation. No TRT interaction has been established.

Kamil Khoury

RESEARCHER | AUTHOR | ARCHITECT

Evidence cutoff: 30 July 2026

Status: Preprint; not peer reviewed

A bounded analysis of what is observed, what is inferred, and what still requires direct testing.

1. Evidence boundary

Observed. This paper evaluates a narrow chain of propositions concerning L-carnitine L-tartrate, abbreviated LCLT, oral levocarnitine exposure, skeletal muscle carnitine biology, a reported skeletal muscle androgen receptor protein signal, and a possible interaction with prescribed testosterone. These propositions do not share a common level of evidentiary maturity. The material can be defined chemically, several disposition processes have been measured with free levocarnitine or other formulations, selected muscle metabolic or tissue effects have been observed under specific coexposure conditions and in one LCLT-alone crossover in volunteers with impaired glucose tolerance, and one small crossover study reported a difference in total androgen receptor protein [18,24]. No controlled LCLT-by-testosterone study was identified through the evidence cutoff.

Inferred. A defensible assessment therefore requires an evidence ladder. Material identity must precede exposure inference. Plasma exposure must not be substituted for muscle uptake. Muscle uptake must not be substituted for pathway flux. Total receptor protein must not be substituted for receptor function. Receptor function must not be substituted for muscle adaptation or clinical response. Each transition is a causal edge that needs its own measurement and falsification test.

Hypothesized. LCLT could alter an androgen-dependent muscle outcome only if a verified LCLT exposure changes a relevant tissue state, that state changes functional androgen receptor signaling, and the resulting signaling change modifies a prespecified functional endpoint under a defined testosterone exposure. This is a research hypothesis, not a demonstrated interaction, adjunct rationale, or human-use recommendation.

Unknown. It remains unknown whether the total androgen receptor protein signal reported in ten young resistance-trained men is reproducible, whether it reflects a within-person change rather than carryover or analytical variation, whether it changes receptor activity, and whether it modifies any response to prescribed testosterone.

Inferred. This manuscript does not provide dosing, titration, route, meal-timing, exercise-timing, or treatment instructions. Descriptions of exposures are historical study descriptors only. Findings from free levocarnitine, prescription levocarnitine, acetyl-L-carnitine, propionyl-L-carnitine, mixed carnitine products, or LCLT combined with carbohydrate are not treated as interchangeable with LCLT alone. Safety observations are formulation, population, exposure, and duration specific. Regulatory status is not represented as evidence of efficacy.

2. Structured abstract

Background

Observed. LCLT is registered and structurally described as a 2:1 salt of levocarnitine and tartaric acid [1-3]. Levocarnitine has established physiological roles in long-chain acyl-group transport and acetyl-group buffering. These roles do not by themselves establish that supplementation increases pathway flux in carnitine-replete humans [12-14,20,21].

Inferred. Applying registry molecular masses to the ideal anhydrous 2:1 composition gives a theoretical levocarnitine mass fraction of 68.23%. The calculation does not establish the assay value, hydration state, purity, or stability of a particular lot [1-3].

Objective

Observed. The objective was to construct a formulation-aware evidence map from verified LCLT material to oral disposition, skeletal muscle uptake, metabolic effects, total androgen receptor protein, receptor function, muscle outcomes, and any interaction with testosterone therapy.

Methods

Observed. A curated search through 30 July 2026 used PubMed, PubMed Central, publisher records, Crossref, ClinicalTrials.gov, PubChem, DailyMed, the US Food and Drug Administration GRAS inventory, European Food Safety Authority records, EUR-Lex, and correction or retraction notices. Primary human studies and official records were prioritized. Data were separated by material, route, population, coexposure, endpoint, and analytical model. Each proposition was classified as Observed, Inferred, Hypothesized, or Unknown. This was a critical narrative review and curated evidence map, not a systematic review or meta-analysis.

Results

Observed. Small oral studies of free levocarnitine or prescription formulations reported absolute availability values of approximately 5% to 16%, with the estimate varying by formulation and exposure [6,7,51]. A small liquid free levocarnitine study reported a maximum plasma concentration time of 3.4 ± 0.46 hours, which cannot be generalized to LCLT [9]. Human skeletal muscle accumulation has been demonstrated in selected contexts involving insulin or prolonged carbohydrate coadministration [15-17,19]. In a separate 36-day crossover in 11 volunteers with impaired glucose tolerance, the primary report found no significant fasting-biopsy difference in free carnitine or acetylcarnitine, while magnetic resonance measurements showed enhanced afternoon and exercise-associated acetylcarnitine formation and metabolic flexibility without improved peripheral insulin sensitivity [18]. A later report characterized the underlying total-pool values as a numeric increase of approximately 12%, from about 8.5 to 9.5

mmol/kg dry mass, but the primary report did not establish a statistically significant total-carnitine treatment effect [18,19]. The pivotal androgen receptor study was a balanced randomized double-blind crossover experiment in ten resistance-trained men. After 21 days per condition and a 7-day washout, the indexed abstract reported preexercise vastus lateralis total androgen receptor protein values of 12.9 ± 5.9 arbitrary units with LCLT and 11.2 ± 4.0 arbitrary units with placebo, $P < 0.05$, without naming the dispersion statistic [24]. The inspected corrigendum replaced Figure 2, corrected the free androgen index equation, and corrected one procedural word; the corrected Figure 2 caption states that plotted values are means ± standard error and retains significance markers [25]. The study did not measure muscle carnitine, receptor localization, ligand occupancy, transcriptional activity, muscle protein synthesis, hypertrophy, or response to testosterone therapy. The paired uncertainty around the 1.7-arbitrary-unit difference cannot be reconstructed because the within-person covariance and paired-difference variance were not reported. No independent replication or controlled LCLT-by-testosterone experiment was identified through the evidence cutoff.

Interpretation

Inferred. The androgen receptor result is a hypothesis-generating total-protein signal with substantial measurement, multiplicity, carryover, sponsorship, and external-validity limitations. It is not evidence of increased androgen sensitivity or improved response to testosterone. Exercise-recovery trials provide formulation-specific signals in soreness, biochemical markers, and selected performance measures, but they do not establish tissue repair, hypertrophy, or a receptor-mediated mechanism [22,23,26-28].

Conclusion

Unknown. The clinical meaning of LCLT-associated total androgen receptor protein remains unresolved. A defensible next experiment requires verified material, direct tissue exposure measurement, receptor-state assays, prespecified functional endpoints, adequate washout or a parallel design, and a factorial testosterone interaction estimand. Until those bridges are measured, synergy and therapeutic benefit remain unestablished.

Keywords: L-carnitine L-tartrate; levocarnitine; skeletal muscle; androgen receptor; testosterone therapy; pharmacokinetics; carnitine transport; TMAO; evidence map; causal inference

3. Plain-language summary

Inferred. LCLT is a salt for which dissociation into levocarnitine and tartrate species is chemically expected under relevant aqueous conditions. The extent and local speciation can still depend on formulation, matrix, concentration, pH, and ionic environment. Levocarnitine is necessary for normal energy metabolism, but necessity does not mean that more oral levocarnitine will automatically increase muscle energy production. The body already synthesizes carnitine, obtains it from food, transports it into tissues,

reabsorbs most filtered carnitine in the kidney at ordinary concentrations, and permits gut microorganisms to transform a variable fraction of an oral exposure [7-14,31-37].

Observed. The central androgen receptor claim comes from one study of ten young men. The study found a difference in total receptor protein measured in muscle homogenate. It did not show that the receptor moved into the nucleus, bound testosterone, recruited the required coregulators, bound DNA, changed target-gene expression, increased muscle protein synthesis, or produced more muscle. It also did not include people receiving testosterone therapy [24,25].

Inferred. A larger amount of measured receptor protein can matter only if the additional protein is correctly localized, ligand responsive, biochemically competent, and connected to a meaningful downstream response. Those conditions cannot be assumed from a Western blot result.

Hypothesized. A controlled study could ask whether verified LCLT exposure changes a functional androgen receptor response under controlled testosterone exposure. That question is scientifically testable.

Unknown. Current evidence cannot tell a clinician, patient, or consumer whether LCLT improves, reduces, or leaves unchanged the effects or risks of testosterone therapy. This paper therefore maps what is known, what is merely inferred, and which measurements would decide the question.

4. Research question

The primary research question is:

Hypothesized. Does verified exposure to LCLT cause a reproducible change in functional skeletal muscle androgen receptor signaling, and does that change modify a prespecified functional response to a controlled testosterone exposure?

This question is decomposed into nine ordered subquestions:

1. **Required measurement:** Is the administered material analytically verified as the intended 2:1 LCLT salt?
2. **Required measurement:** What levocarnitine exposure follows from that material in the studied population?
3. **Required measurement:** Does plasma exposure produce a measurable change in skeletal muscle carnitine or acylcarnitine pools?
4. **Required measurement:** Does the tissue change alter a defined metabolic state or flux?
5. **Required measurement:** Is total androgen receptor protein changed in an independently replicated assay?
6. **Required measurement:** Is receptor localization, occupancy, coregulator recruitment, chromatin binding, or transcription changed?

7. **Required measurement:** Is a receptor-state change connected to protein synthesis, muscle architecture, strength, symptoms, or another prespecified functional endpoint?
8. **Hypothesized:** Does the effect differ under controlled testosterone exposure?
9. **Unknown:** Are any benefits or harms durable, clinically meaningful, and acceptably characterized in the intended population?

Inferred. The questions are intentionally ordered. A positive answer at one level cannot substitute for data at the next.

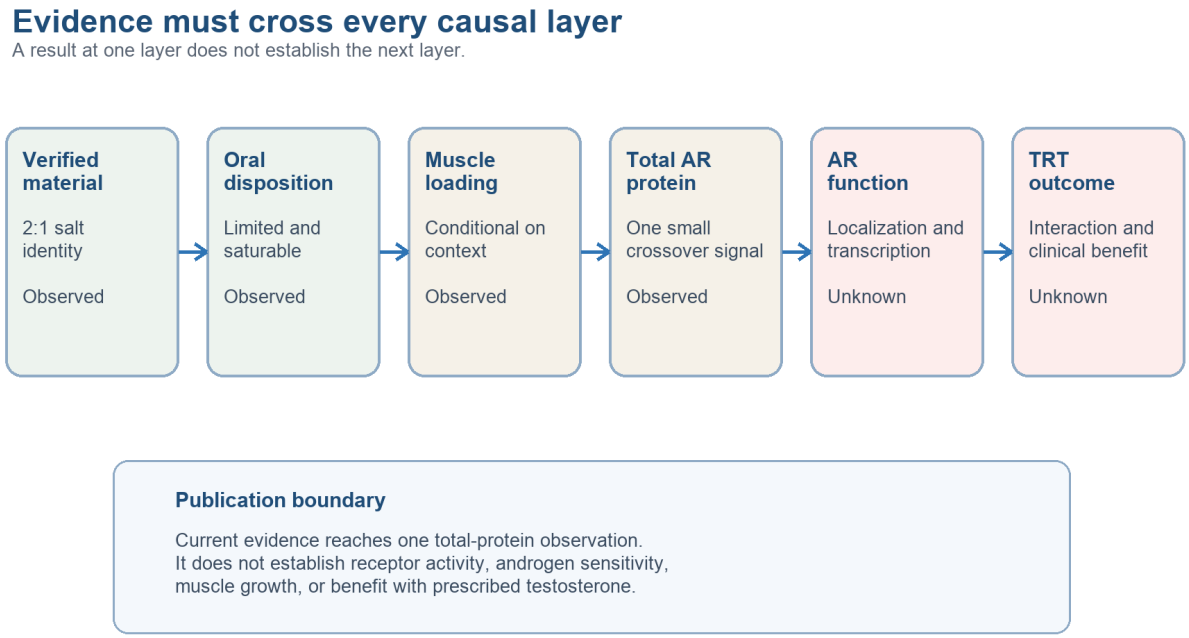

Figure 1. Causal evidence ladder. A result at one layer does not establish the next layer.

Ladder level	Minimum evidence	Current LCLT status
1. Verified material	Lot-specific identity, purity, hydration, stability	Unknown for most published product exposures
2. Dissolved active moiety	Matrix-specific dissociation and levocarnitine-equivalent exposure	Inferred chemically; LCLT-specific PK not established
3. Plasma exposure	Baseline-aware concentration or tracer profile	Observed mainly for free or prescription levocarnitine
4. Tissue exposure	Direct skeletal muscle carnitine and acylcarnitines	Observed under insulin or prolonged coexposure; one LCLT-alone impaired-glucose-tolerance study showed dynamic acetylcarnitine changes but no significant fasting free or acetylcarnitine difference
5. Proximal target state	Replicated total androgen receptor and functional-state measurements	One unreplicated total-protein signal
6. Molecular function	Chromatin binding and target-gene response	Unknown

Ladder level	Minimum evidence	Current LCLT status
7. Tissue function	Protein synthesis, architecture, strength adaptation	Unknown for the androgen receptor pathway
8. Clinical outcome	Prespecified benefit and harm measures	Unknown
9. Testosterone interaction	Controlled factorial contrast	Not identified through the cutoff

Inferred. The evidence ladder prevents mechanistic compression. Evidence at a lower level can justify measuring the next level, but it cannot substitute for it.

5. Methods

5.1 Evidence cutoff and search domains

Observed. Searches were completed through 30 July 2026. The principal domains were PubMed and PubMed Central for biomedical records and full text, Crossref and publisher pages for bibliographic verification, ClinicalTrials.gov for registered interventional studies, PubChem for chemical identity, DailyMed for current prescription levocarnitine labeling, the FDA GRAS inventory for notified food-use conditions, EFSA records and EUR-Lex for European regulatory statements, and indexed correction and retraction notices.

Observed. Search concepts combined material names and identifiers with disposition, transport, skeletal muscle, exercise, androgen receptor, testosterone, safety, and microbial metabolism. Formulation terms included "L-carnitine L-tartrate," "carnitine tartrate," "levocarnitine," "acetyl-L-carnitine," and "propionyl-L-carnitine." The search log is reproduced in Appendix A.

5.2 Source hierarchy

Observed. Evidence was prioritized in the following order:

1. Primary human controlled trials and pharmacokinetic studies.
2. Primary mechanistic human studies.
3. Official chemical registries, drug labels, and regulator records.
4. Primary animal or cell studies used only to define mechanisms or generate hypotheses.
5. Reviews used for orientation when primary sources did not efficiently define a general physiological framework.

Inferred. Reviews, product pages, marketing descriptions, and unsourced summaries were not permitted to carry pivotal quantitative or clinical claims. A regulator's acceptance of a notified food use was not treated as efficacy evidence, and an approved drug label for levocarnitine was not transferred to LCLT.

5.3 Formulation and population separation

Observed. Each extracted record was assigned a material category: analytically described LCLT; product-described LCLT; free levocarnitine; prescription levocarnitine; acetyl-L-carnitine; propionyl-L-carnitine; mixed carnitine product; or unclear formulation. Route, matrix, coexposures, population, health state, age range, sex composition, sample size, and duration were extracted separately.

Inferred. A finding was considered directly informative for LCLT only when the administered material was identified as LCLT. Free levocarnitine pharmacokinetic evidence was used to constrain the behavior of the dissociated active moiety, not to claim LCLT-specific pharmacokinetics. Combination studies were treated as joint interventions.

5.4 Extraction fields

Observed. For each study, the extraction set included:

- publication and registry identifiers;
- study design and allocation;
- material, declared purity or brand, route, and exposure description;
- active-moiety equivalence when calculable;
- participant characteristics and analyzed sample;
- baseline correction and sampling schedule;
- matrix, assay, normalization method, and units;
- prespecified and reported endpoints;
- treatment estimates and uncertainty;
- cointerventions and adherence;
- attrition and adverse-event reporting;
- period, sequence, washout, and carryover handling for crossover studies;
- multiplicity control;
- funding, product supply, employment, and declared conflicts;
- correction, erratum, expression-of-concern, or retraction status.

5.5 Claim-labeling system

Observed. Every substantive proposition in this manuscript uses one of four labels:

- **Observed:** directly measured or officially recorded in the named material, system, population, and endpoint.
- **Inferred:** a bounded interpretation supported by observations but not directly measured as stated.
- **Hypothesized:** a falsifiable causal proposal requiring prospective testing.

- **Unknown:** evidence was insufficient, conflicting, nonidentifiable, or not identified through the evidence cutoff.

Inferred. A label does not grade study quality. An Observed result can still be biased, imprecise, nonreplicated, or clinically uninformative.

5.6 Corrections, errata, and retractions

Observed. The pivotal 2006 androgen receptor article has a one-page corrigendum published in October 2006 [24,25]. The corrigendum was inspected. It changes "fasting" to "fasted" in Experimental Procedures, corrects the free androgen index equation to total testosterone divided by sex hormone-binding globulin, and replaces Figure 2. The corrected Figure 2 caption identifies the values as means ± standard error and includes the corrected immunoblot, bar panel, and significance markers [25].

Observed. Retraction searches identified retracted reproductive-medicine papers involving carnitine formulations. Those reports were excluded from positive evidence synthesis. Their identifiers are recorded in Appendix B to prevent inadvertent reintroduction.

5.7 Limits of the curated approach

Observed. This was not a prospectively registered systematic review. Screening was targeted to the causal chain and the claims contained in the supplied manuscript. A formal dual-reviewer selection process, exhaustive database set, language-complete grey-literature search, and meta-analysis were not performed.

Inferred. The phrase "not identified through the evidence cutoff" therefore means that the described search did not locate a qualifying record. It does not prove that no record exists. Quantitative estimates were not pooled when formulations, baseline handling, units, or models were incompatible.

6. Material identity and conversion

6.1 Chemical identity

Observed. LCLT is a salt composed of two levocarnitine cations for each tartrate dianion. The molecular formula of the anhydrous 2:1 salt is C18H36N2O12 and its formula mass is 472.49 g/mol. Levocarnitine has a formula mass of 161.20 g/mol [1-3]. The pharmacologically relevant carnitine moiety is levocarnitine, the L stereoisomer. A product label that says only "carnitine tartrate" does not by itself establish stereochemical purity, counterion identity, hydration state, or lot composition.

Inferred. Equation 1 applies those registered masses to an idealized anhydrous composition. Its result is a theoretical conversion, not an observed lot property.

EQUATION 1. THEORETICAL LEVOCARNITINE MASS FRACTION

$$w_{LC} = 2\ M_{LC} / M_{LCLT}$$

Units: Dimensionless mass fraction.

Definitions: M_{LC} is the molar mass of levocarnitine, 161.20 g/mol. M_{LCLT} is the molar mass of anhydrous 2:1 LCLT, 472.49 g/mol. w_{LC} is the theoretical mass fraction of levocarnitine in that idealized salt.

Calculation: w_{LC} = (2 x 161.20 g/mol) / 472.49 g/mol = 0.682342, or 68.23% when rounded to two decimal places [1-3].

Assumptions: Correct 2:1 stoichiometry, anhydrous material, specified stereochemistry, no impurities, and exact formula masses.

Identifiability limit: Stoichiometry cannot identify assay content, hydration, residual solvent, degradation, purity, or lot uniformity.

Plain interpretation: The equation converts an ideal chemical formula into a theoretical levocarnitine fraction. It is not a certificate of analysis.

Inferred. Under the ideal assumptions in Equation 1, 2.000 g of LCLT corresponds to 1.365 g of levocarnitine, and 3.000 g corresponds to 2.047 g. These values are arithmetic conversions, not verified delivered amounts [1-3].

Inferred. The ideal 3.000 g example must not be conflated with the pivotal androgen receptor report's historical product description. That report described four capsules totaling 2.944 g of product-described LCLT and a manufacturer-declared 2.000 g levocarnitine equivalent [24]. Equation 1 would yield 2.009 g for 2.944 g of an ideal anhydrous 2:1 salt. The approximately 0.009 g difference is consistent with declaration rounding or a product-specific specification, but its cause cannot be identified from the publication. Neither the ideal calculation nor the rounded historical declaration is a lot assay.

Unknown. No qualifying human evidence was identified through the cutoff showing that the tartrate counterion independently changes levocarnitine bioavailability, skeletal muscle uptake, androgen receptor biology, or response to testosterone. Tartrate should not be assumed to create a material-specific advantage without a direct comparison.

6.2 Identity as an evidentiary gate

Inferred. Material identity is the first causal gate because a biological estimate cannot be attached reliably to an unverified label. At minimum, a mechanistic study intended to support a material-specific claim should document the salt form, stereochemistry, water content, assay, relevant impurities, stability over the study interval, and chain of custody. If the product contains excipients or another active ingredient, the intervention is no longer a clean LCLT perturbation.

Observed. The crystallographic report describes the solution and solid-state structure of a defined LCLT material [1]. It establishes a structural observation for that studied material, not a head-to-head performance comparison with free levocarnitine and not the properties of an untested commercial lot.

Unknown. No qualifying direct formulation-comparison evidence was identified through the cutoff establishing that LCLT has superior stability, crystallinity, storage behavior, processability, or handling performance versus free levocarnitine. Comparative performance would require prespecified analytical tests under matched environmental, packaging, and manufacturing conditions. Generic solid-state description cannot establish lot-specific or comparative superiority.

Table 1. Material identity, active moiety, and conversion boundary

Field	LCLT-specific statement	Evidentiary boundary
Stoichiometry	Two levocarnitine ions to one tartrate ion [1-3]	Applies to the defined 2:1 salt
Formula	C18H36N2O12 [2,3]	Formula alone does not prove lot identity
Formula mass	472.49 g/mol [2,3]	Anhydrous theoretical value
Active moiety	Levocarnitine, L stereoisomer	Does not imply intact-salt transport
Theoretical fraction	68.23% levocarnitine by mass when rounded to two decimal places [1-3]	Not a purity or potency assay
Dissociation	Dissociation into levocarnitine and tartrate species is chemically expected under relevant aqueous conditions	Extent and local speciation depend on formulation, matrix, concentration, pH, and ionic environment
Lot verification	Assay, hydration, purity, impurities, and stability required	Not recoverable from a generic product name
Comparative bioavailability	No human evidence of superior LCLT bioavailability versus free levocarnitine was identified through the cutoff	Comparative superiority is unestablished
Comparative material performance	No direct matched evidence established superior stability, crystallinity, storage behavior, processability, or handling versus free levocarnitine	Generic structural description is not a lot-specific or comparative performance test

7. Regulatory categories and what they do not imply

Observed. Prescription levocarnitine products are approved in the United States for defined primary systemic carnitine deficiency and selected secondary deficiencies associated with inborn errors of metabolism [6]. That drug status concerns levocarnitine products, specified indications, manufacturing controls, and labeled routes. It does not approve LCLT for exercise recovery, androgen receptor modulation, testosterone therapy, or general supplementation.

Observed. FDA GRAS Notice 993 concerns a notifier's intended use of LCLT in cow-milk-based and goat-milk-based term infant formula at a maximum of 0.88 mg LCLT per 100 kcal, corresponding to 0.6 mg levocarnitine per 100 kcal under the notifier's specification [3]. FDA's "no questions" response is limited to

the notified identity and conditions of use. It is not drug approval, a finding of adult efficacy, or a determination about androgen signaling.

Observed. EFSA evaluated LCLT as a source of L-carnitine for particular food uses and addressed safety within the submitted context [4]. Separately, European Commission Regulation (EU) 2021/77 refused authorization of the health claim that L-carnitine contributes to normal lipid metabolism because a cause-and-effect relationship had not been established [5].

Inferred. Regulatory statements must be mapped to their actual object. Chemical-source acceptability, food-use safety under specified conditions, prescription drug approval, and authorization of an efficacy claim are different determinations. None supplies the missing causal bridge from LCLT to functional androgen receptor signaling.

8. Formulation-specific human pharmacokinetics

8.1 Absorption

Observed. Oral availability is low and exposure dependent in small studies. In six healthy adults consuming a low-carnitine diet, absolute bioavailability after oral free levocarnitine was reported as 16% after a 2 g exposure and 5% after a 6 g exposure. Urinary recovery during the first 24 hours was 8% and 4%, respectively [7]. These estimates apply to free levocarnitine under the reported conditions, not LCLT.

Observed. Sahajwalla and colleagues studied multiple-dose pharmacokinetics and bioequivalence of prescription oral levocarnitine formulations in 15 healthy adult male volunteers [51]. A current levocarnitine oral-solution label summarizes baseline-corrected absolute availability as 15.1 ± 5.3% for the marketed tablet and 15.9 ± 4.9% for the oral solution, with a reported maximum concentration time of 3.3 hours [6,51]. These are free prescription levocarnitine formulations, not LCLT.

Observed. In seven healthy adults receiving repeated oral free levocarnitine exposures over seven days, exposure became nonlinear above the lowest tested level, renal clearance increased, and trimethylamine N-oxide, abbreviated TMAO, rose at the highest exposure [10]. A 2025 pair of open-label randomized pharmacokinetic studies in healthy volunteers likewise reported low availability and extensive TMAO formation after free carnitine or acetyl-L-carnitine, with substantial person-level variability [11].

Observed. A 2004 kinetic synthesis described absorption across historical 0.5 g to 6 g supplemental exposures as primarily passive, with carrier-mediated transport contributing more prominently at lower luminal exposure [14]. This is a general levocarnitine framework, not an LCLT-specific estimate and not evidence for a particular exposure schedule.

Inferred. A conceptual model can represent a passive component plus a saturable carrier-associated component, but the available sparse studies cannot uniquely estimate those components for LCLT.

EQUATION 2. CONCEPTUAL DUAL-PATH ORAL ABSORPTION

$$A_{abs}(D) = F_p\, D + A_{max}\, D / (K_D + D)$$
$$\text{subject to } 0 \le F_p \le 1 \text{ and } 0 \le A_{abs}(D) \le D \text{ over the modeled domain}$$

Units: A_{abs} and D are mass or molar amount; F_p is dimensionless; A_{max} has the same amount units as A_{abs}; K_D has the same units as D.

Definitions: D is the administered levocarnitine-equivalent amount. F_p is a conceptual nonsaturable fractional term. A_{max} is the maximum carrier-associated absorbed amount over the modeled interval. K_D is the amount producing half of A_{max}.

Assumptions: The formulation dissolves, the two pathways are additive, all amount parameters are nonnegative, 0 <= F_p <= 1, the parameter set is restricted so total absorbed amount cannot exceed administered amount over the modeled domain, the sampling interval captures relevant absorption, and presystemic microbial loss is represented implicitly rather than mechanistically.

Identifiability limit: F_p, A_{max}, and K_D cannot be estimated uniquely from the cited small studies, and no LCLT-specific parameter set is established.

Plain interpretation: Oral absorption may include both nonsaturable and saturable behavior. The equation is a research model, not a tool for selecting an exposure schedule.

8.2 Plasma disposition

Observed. A study of 12 healthy adults given a liquid free levocarnitine preparation reported a maximum plasma concentration time of 3.4 ± 0.46 hours, a maximum concentration of 84.7 ± 25.2 µmol/L, and an area under the concentration-time curve of 2676.4 ± 708.3 µmol h/L [9]. These quantities are specific to that formulation, population, sampling design, baseline handling, and model.

Observed. The 2009 report listed an elimination half-life of 60.3 ± 15.0 hours, while a 2011 report from an overlapping author group, using the same sample size and the same maximum concentration and area-under-curve values, listed 60.3 ± 15.0 minutes [9,44]. Because the records are incompatible and half-life is model dependent in a compound with endogenous baseline, tissue exchange, and renal reabsorption, no pooled half-life is presented [9,14,44].

Inferred. Plasma concentration is a mixture of absorbed exogenous levocarnitine, endogenous synthesis, dietary baseline, tissue exchange, and renal handling. A baseline-naive one-compartment interpretation is therefore inadequate.

EQUATION 3. BASELINE-AWARE PLASMA AND TISSUE DISPOSITION

$$dX_p/dt = R_{abs}(t) + R_{syn}(t) - J_m(t) - J_v(t) - R_u(t)$$

Units: X_p is amount in the modeled plasma-accessible pool, such as µmol. Each R or J term is amount per time, such as µmol/h.

Definitions: R_{abs} is the appearance rate from the gastrointestinal tract. R_{syn} is endogenous synthesis entering the pool. J_m is net transfer to skeletal muscle. J_v is net transfer to other tissues. R_u is urinary loss.

Assumptions: Each term is defined on the same amount scale and sign convention. Net tissue terms may include bidirectional exchange.

Identifiability limit: Plasma concentration alone does not identify absorption, synthesis, tissue uptake, or urinary loss separately. Direct tracer, urine, and tissue data are needed.

Plain interpretation: A change in blood levocarnitine cannot reveal by itself how much was absorbed or how much reached muscle.

8.3 Tissue distribution and skeletal muscle uptake

Observed. In eight healthy men, experimentally induced hypercarnitinemia increased skeletal muscle total carnitine from 22.0 ± 0.9 to 24.7 ± 1.4 mmol/kg dry muscle only during high-insulin conditions. OCTN2 messenger RNA rose 2.3-fold in that experimental context [15]. The study used intravenous manipulation and cannot be transferred directly to oral LCLT.

Observed. In a 24-week study of 14 healthy men, seven participants assigned LCLT together with a carbohydrate beverage had a 21% rise in skeletal muscle total carnitine, whereas the carbohydrate control group did not [16]. The assigned intervention combined LCLT with 160 g carbohydrate per day. The small sample and substantial coexposure prevent attribution to LCLT alone.

Observed. A later analysis in 12 participants from the same cohort, six per group, reported an approximately 20% rise in muscle total carnitine and a 6% increase in energy expenditure in the combined LCLT-carbohydrate group after 12 weeks [17]. Body mass and fat mass increased in the carbohydrate control group but not in the combined group. This comparison does not establish weight loss, prevention of fat gain under other conditions, or an LCLT-alone body-composition effect.

Observed. In a randomized double-blind placebo-controlled crossover, 11 people with impaired glucose tolerance received a historical 2 g LCLT/day condition for 36 days without protocol-specified carbohydrate coadministration. In the primary report, fasting-biopsy free carnitine and acetylcarnitine did not differ significantly between LCLT and placebo, with reported P values of 0.356 and 0.371, respectively. Magnetic resonance measurements showed enhanced afternoon and exercise-associated acetylcarnitine formation and restored metabolic flexibility, but peripheral insulin sensitivity did not improve [18]. A later report described the underlying muscle total-carnitine values as a numeric increase of approximately 12%, from about 8.5 to 9.5 mmol/kg dry mass [19]. Because the primary report did not establish a statistically significant total-pool treatment effect, this numeric characterization is not presented as a confirmed

increase. The evidence is bounded to a small older population with impaired glucose tolerance, the reported product, the crossover design, and the measured metabolic endpoints; it does not establish uptake in healthy young resistance-trained men or an androgen receptor effect.

Observed. In 14 older men, seven per arm, a prolonged LCLT-containing insulinogenic beverage intervention raised muscle total carnitine by approximately 20% and increased total fat oxidation during moderate exercise by approximately 20%, without improving insulin sensitivity [19]. This result is population and cointervention specific.

Unknown. The pivotal 21-day androgen receptor study did not measure skeletal muscle carnitine. Its total receptor protein result therefore cannot be connected empirically to tissue carnitine accumulation [24].

8.4 Renal handling

Observed. OCTN2, encoded by SLC22A5, is a high-affinity sodium-dependent transporter for levocarnitine. In a heterologous expression system, a Michaelis constant of 4.34 µmol/L was reported [12]. Renal apical OCTN2 participates in tubular reabsorption, with 1:1 sodium coupling described experimentally [13]. These observations concern dissociated levocarnitine transport, not transport of an intact LCLT salt.

Observed. At ordinary plasma concentrations, renal reabsorption has been estimated at approximately 90% to 99%, with low renal clearance around 1 to 3 mL/min in physiological conditions. Reabsorption becomes saturable as concentration rises [14]. These synthesis-level estimates describe general levocarnitine physiology and are not individual predictions.

EQUATION 4. SATURABLE RENAL HANDLING

$$R_{filt}(C_p) = GFR\ C_p$$

$$R_{reabs}(C_p) = \min[R_{filt}(C_p), V_{max,r}\ C_p / (K_{m,r} + C_p)]$$

$$R_u(C_p) = R_{filt}(C_p) - R_{reabs}(C_p) + R_{sec}(C_p)$$

Units: R_u, R_{filt}, R_{reabs}, and R_{sec} are amount per time. GFR is volume per time. C_p and $K_{m,r}$ are concentration. $V_{max,r}$ is amount per time.

Definitions: C_p is unbound plasma levocarnitine concentration. R_{filt} is filtered load. $V_{max,r}$ and $K_{m,r}$ describe the capacity-limited reabsorption term. The minimum operator prevents reabsorption from exceeding filtered availability. R_{sec} is a nonnegative net secretory contribution.

Assumptions: Unbound concentration is the relevant filtered concentration, GFR and all rate parameters are nonnegative, $0 <= R_{reabs}(C_p) <= R_{filt}(C_p)$, $R_{sec}(C_p) >= 0$, reabsorption can be approximated by a saturable term, and all terms refer to the same renal interval.

Identifiability limit: The secretion function and person-specific parameters are not established well enough for individual prediction. Endogenous baseline and changing concentration complicate inference from spot urine.

Plain interpretation: Urinary recovery is the balance of filtration, strong but saturable reabsorption, and possible secretion. It is not equivalent to total absorbed amount.

Inferred. Gastrointestinal nonabsorption, microbial transformation, filtered load, tubular reabsorption, secretion, and measured urinary recovery are distinct quantities. A claim that nearly all absorbed carnitine ultimately appears in urine is not supported by the cited human evidence.

8.5 Host and microbial transformation

Observed. In five adults given a tracer after a 14-day high-carnitine diet with supplemental free levocarnitine, serum tracer peaked between 2.0 and 4.5 hours. TMAO accounted for 8% to 49% of administered tracer, gamma-butyrobetaine for 0.44% to 45%, and urinary total carnitine for 16% to 23%, showing wide person-level variation [8].

Observed. Gut microbial pathways can convert levocarnitine to trimethylamine through enzymes including the CntA/CntB system and can also use a gamma-butyrobetaine route. Host flavin-containing monooxygenases then oxidize trimethylamine to TMAO [31-33]. In a corrected human multi-cohort report, fecal gbu genes, particularly gbuB, were associated with L-carnitine-induced TMAO production across oral carnitine challenge cohorts; the article also included culture and gnotobiotic-model validation [52,53]. The association identifies a candidate microbial biomarker, not a deterministic individual-risk classifier. The relative contribution depends on microbiome composition, dietary context, renal function, and recent exposure.

Observed. Direct LCLT studies in older or postmenopausal women reported marked increases in circulating TMAO over 12 to 24 weeks, while selected inflammatory, oxidative, lipid, or bone endpoints were unchanged within those small studies [34-36]. In a 2026 controlled oral carnitine-challenge experiment, TMAO responses varied strongly between individuals, and the tested pomegranate extract did not reduce overall TMAO area under the curve [37].

Unknown. A higher TMAO concentration after a carnitine exposure is a measured metabolic consequence. Its causal contribution to clinical cardiovascular outcomes at an individual level remains unresolved. Association must not be converted into proven toxicity, and short biomarker studies must not be converted into proof of harmlessness.

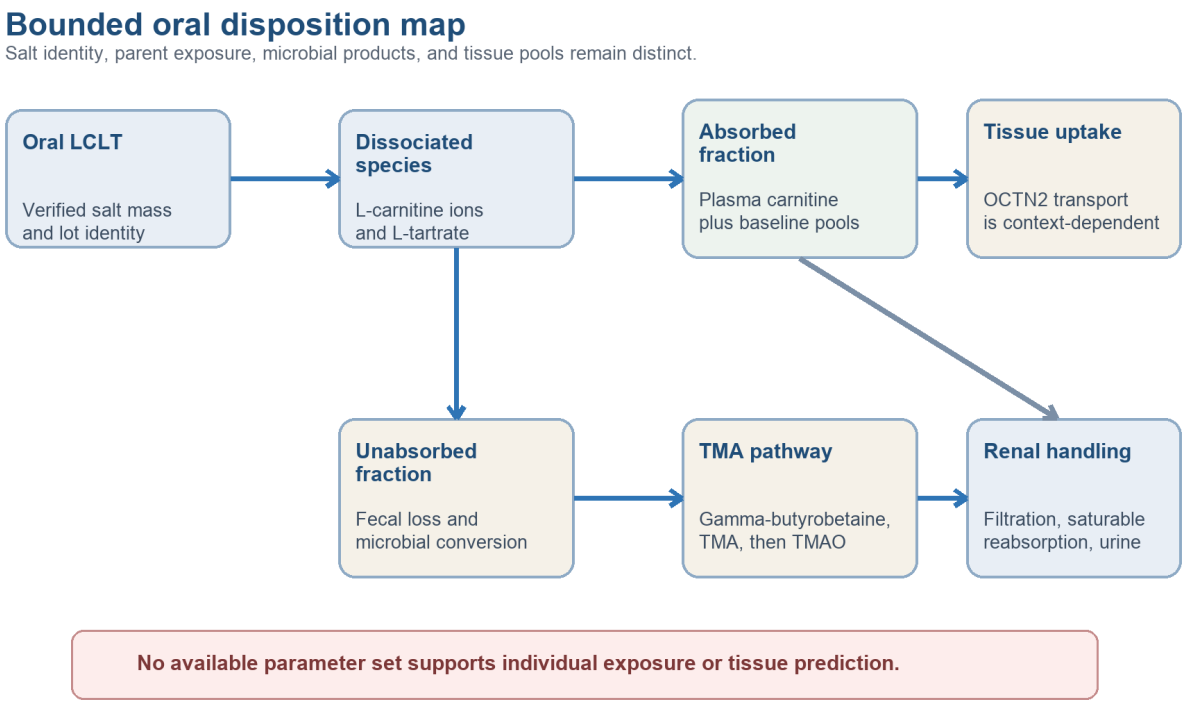

Figure 2. Bounded oral disposition map. Salt, parent exposure, tissue uptake, microbial products, and renal handling are separate objects.

Inferred. Disposition map:

Verified LCLT lot → dissolution and dissociation → unabsorbed intestinal fraction → microbial metabolites
Verified LCLT lot → absorbed levocarnitine → plasma pool → skeletal muscle and other tissues
Plasma pool → glomerular filtration → saturable tubular reabsorption → urinary levocarnitine
Microbial trimethylamine → host oxidation → plasma and urinary TMAO

Inferred. Boundary annotation: Each arrow is material, time, population, and assay dependent. A plasma concentration does not identify muscle uptake. Urinary recovery does not identify absorption without a full mass balance. Microbial metabolite production is heterogeneous. The map is descriptive, not a human-use schedule.

Table 2. Formulation-specific human pharmacokinetic evidence

Study	Material and route	Population	Principal quantitative observation	Boundary
Harper et al. [7]	Oral free levocarnitine	6 healthy adults on a low-carnitine diet	Absolute availability 16% after 2 g and 5% after 6 g; 24-hour urinary recovery 8% and 4%	Not LCLT; small sample; exposure dependent
Sahajwalla et al. [51], summarized in DailyMed [6]	Prescription oral levocarnitine tablet or solution	15 healthy adult men	Availability 15.1 ± 5.3% and 15.9 ± 4.9%; maximum concentration time 3.3 h in the label summary	Drug formulations, not LCLT
Rebouche et al. [8]	Tracer with repeated free levocarnitine context	5 adults	TMAO 8% to 49% and gamma-butyrobetaine 0.44% to 45% of tracer; urinary total carnitine 16% to 23%	Wide variation; complex preexposure
Cao et al. [9,44]	Liquid free levocarnitine, oral	12 healthy adults	Maximum concentration time 3.4 ± 0.46 h; Cmax 84.7 ± 25.2 µmol/L; AUC 2676.4 ± 708.3 µmol h/L	Study-specific model; incompatible hour-versus-minute half-life reports
Bain et al. [10]	Repeated oral free levocarnitine	7 healthy adults	Nonlinearity above the lowest tested exposure; higher renal clearance and TMAO at highest exposure	Not LCLT; small repeated-exposure study
Krims-Davis et al. [11]	Free carnitine or acetyl-L-carnitine, oral	Healthy volunteers in open-label randomized PK studies	Low availability and extensive, variable TMAO formation	Different materials; no LCLT parameterization

9. Established carnitine biology versus supplementation effects

9.1 Carnitine shuttle

Observed. Levocarnitine is a transported substrate in the long-chain fatty-acid shuttle. Carnitine palmitoyltransferase 1, abbreviated CPT1, forms long-chain acylcarnitine on the outer mitochondrial membrane. Carnitine-acylcarnitine translocase exchanges acylcarnitine and carnitine across the inner membrane. Carnitine palmitoyltransferase 2, abbreviated CPT2, regenerates long-chain acyl-CoA on the matrix side [21].

EQUATION 5A. LONG-CHAIN ACYL-GROUP TRANSFER

$$\text{Long-chain acyl-CoA} + \text{carnitine} \rightleftharpoons \text{acylcarnitine} + \text{CoA}$$

Units: Chemical stoichiometry is molar, with one mole of each reactant or product per reaction event.

Definitions: The equation summarizes the reversible acyl transfer catalyzed at the CPT interfaces. The translocase step is required between the CPT1 and CPT2 reactions.

Assumptions: Relevant enzymes, membranes, gradients, and substrates are intact.

Identifiability limit: The reaction establishes physiological capability but does not quantify net in vivo flux or the effect of oral supplementation.

Plain interpretation: Carnitine carries long-chain acyl groups across the mitochondrial inner-membrane system. More circulating carnitine does not guarantee more fat oxidation.

Observed. CPT1 flux is constrained by malonyl-CoA, fatty-acid delivery, acyl-CoA availability, enzyme abundance, mitochondrial demand, redox state, and downstream oxidation capacity [21]. Carnitine is not an enzyme cofactor in the sense of a catalytic prosthetic group. It is transferred between free and esterified pools.

9.2 Acetyl-group buffering

Observed. Carnitine acetyltransferase, abbreviated CrAT, interconverts acetyl-CoA and acetylcarnitine, helping buffer the free CoA and acetyl-CoA relationship in mitochondrial metabolism [20,21].

EQUATION 5B. ACETYL-GROUP BUFFERING

$$\text{Acetyl-CoA} + \text{carnitine} \rightleftharpoons \text{acetylcarnitine} + \text{CoA}$$

Units: Chemical stoichiometry is molar, with one mole of each reactant or product per reaction event.

Definitions: Acetyl-CoA is the activated two-carbon donor, carnitine is the acceptor, acetylcarnitine is the esterified product, and CoA is released.

Assumptions: CrAT is present and the mitochondrial state permits exchange.

Identifiability limit: Pool sizes do not uniquely identify reaction direction or flux. Direct flux measurement or an adequately constrained tracer model is required.

Plain interpretation: Carnitine can temporarily hold acetyl groups and free CoA. The reaction does not prove that an oral LCLT exposure changes exercise performance.

Observed. Proton magnetic resonance spectroscopy in human calf muscle showed that acetylcarnitine increased from 0.5 ± 0.3 to 4.1 ± 1.0 mmol/kg after exercise, illustrating rapid endogenous pool adaptation [20]. This observation demonstrates physiological buffering, not a supplement effect.

9.3 Supplementation boundary

Inferred. A supplement-associated increase in pathway flux requires at least one limiting state to be relieved. If muscle free carnitine is not limiting, if transport is constrained, if malonyl-CoA inhibits CPT1, if substrate delivery is low, or if downstream oxidation capacity is limiting, higher plasma levocarnitine need not increase fat oxidation.

Unknown. No general rule identifies which carnitine-replete individuals have a muscle carnitine or acetyl-buffering limitation that can be changed by LCLT alone. Evidence from insulin-associated uptake or carbohydrate coadministration cannot resolve that question for other contexts.

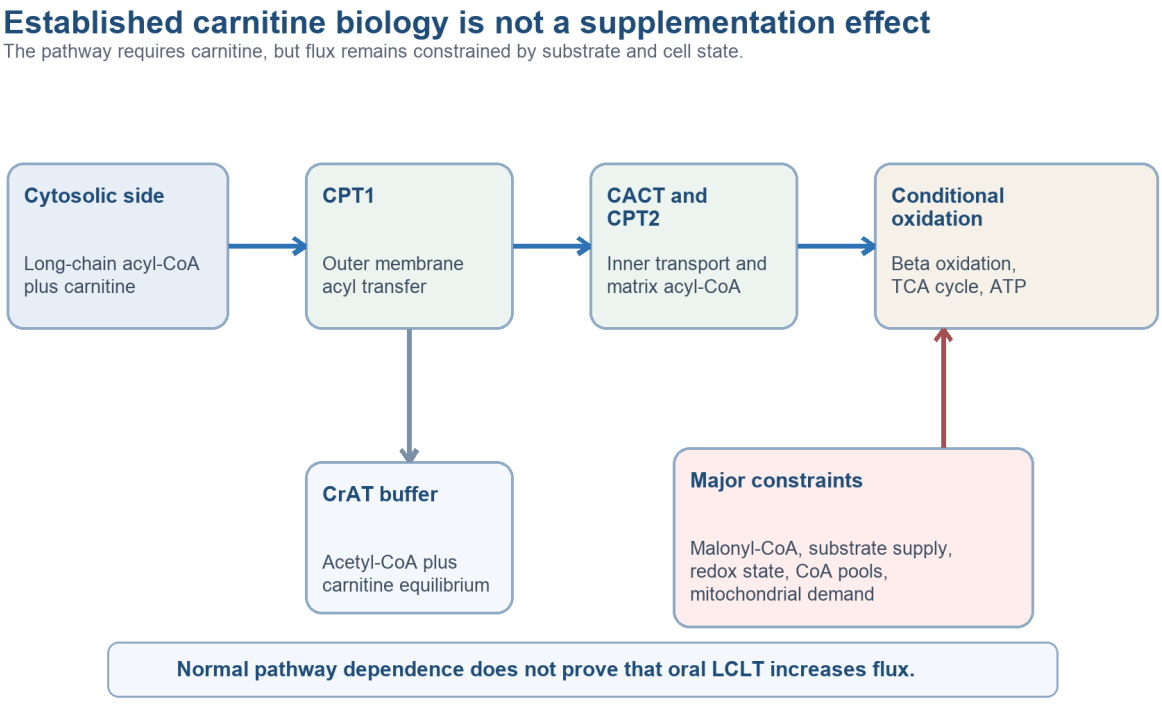

Figure 3. Carnitine-shuttle and acetyl-buffering boundary. Established pathway dependence does not prove a supplement-induced increase in flux.

Observed. Established reactions:

1. Cytosolic long-chain acyl-CoA → CPT1 → long-chain acylcarnitine.
2. Long-chain acylcarnitine → carnitine-acylcarnitine translocase → mitochondrial matrix side.
3. Long-chain acylcarnitine → CPT2 → matrix long-chain acyl-CoA.
4. Acetyl-CoA + carnitine ⇌ CrAT ⇌ acetylcarnitine + CoA.

Inferred. Constraints: muscle uptake, malonyl-CoA, substrate supply, mitochondrial demand, redox state, free CoA availability, enzyme capacity, tissue type, insulin state, training state, and disease state.

Inferred. Supplement boundary: oral LCLT → plasma levocarnitine is not equivalent to muscle accumulation; muscle accumulation is not equivalent to altered shuttle flux; altered flux is not equivalent to a functional or clinical benefit.

10. Human skeletal muscle and exercise evidence

Observed. Human muscle studies separate into at least four evidence classes: acute experimental hypercarnitinemia with insulin manipulation [15], prolonged LCLT with substantial carbohydrate or insulinogenic coexposure [16,17,19], a 36-day LCLT-alone crossover in volunteers with impaired glucose tolerance [18], and shorter LCLT studies that measured recovery markers without measuring muscle carnitine [22-28]. These classes answer different questions.

Table 3. Human muscle-uptake and metabolic studies

Study	Design and analyzed sample	Material and coexposure	Tissue or functional finding	What cannot be inferred
Stephens et al. [15]	Acute human experiment, 8 healthy men	Intravenous hypercarnitinemia with high versus fasting insulin	Muscle total carnitine rose from 22.0 ± 0.9 to 24.7 ± 1.4 mmol/kg dry muscle only with high insulin; OCTN2 mRNA 2.3-fold higher	Oral LCLT-alone uptake; long-term function
Wall et al. [16]	24-week randomized study, 14 men, 7 per arm	LCLT plus 160 g carbohydrate/day versus carbohydrate	Muscle total carnitine increased 21% in combined intervention	LCLT-alone effect; generalizability beyond young men
Stephens et al. [17]	12-week subset analysis, 12 men, 6 per arm	Same combined intervention	Muscle carnitine about 20% higher; energy expenditure 6% higher	Weight-loss effect; independent LCLT contribution
Bruls et al. [18], contextualized by Chee et al. [19]	Randomized double-blind placebo-controlled crossover, 11 people with impaired glucose tolerance, 36 days	Historical 2 g LCLT/day condition without protocol-specified carbohydrate coadministration	No significant fasting-biopsy free or acetylcarnitine difference; enhanced dynamic acetylcarnitine formation and metabolic flexibility; no insulin-sensitivity improvement; later authors described a numeric total-pool increase of about 12%, but primary statistical significance for total carnitine was not established	Confirmed general total-pool increase; healthy young or trained-person uptake; AR mechanism
Chee et al. [19]	25-week randomized study, 14 older men, 7 per arm	LCLT-containing insulinogenic beverage	Muscle carnitine about 20% higher; total fat oxidation during moderate exercise about 20% higher; insulin sensitivity unchanged	LCLT-alone effect; body-composition or TRT effect
Kraemer et al. [24]	21-day crossover condition, 10 young resistance-trained men	Product-described LCLT	Muscle carnitine not measured	Tissue accumulation cannot be assumed
Broad et al. [47]	Randomized double-blind placebo-controlled crossover, 15 trained men, two 4-week conditions	3 g LCLT/day versus placebo	No change in carbohydrate or fat oxidation during 90 minutes of cycling; no LCLT improvement in the subsequent 20 km time trial	Benefit in other populations, exercise modes, or longer exposures
Broad et al. [48]	Randomized pair-matched placebo-controlled parallel study, 20 active nonvegetarian men, 2 weeks	2 g LCLT/day versus placebo	No change in fat, carbohydrate, or protein contribution during prolonged exercise	Longer-term adaptation or effects in women
Abramowicz and Galloway [49]	Randomized double-blind crossover, 12 active adults, 6 men and 6 women	Acute, chronic, and placebo LCLT conditions	No fat-oxidation effect; greater carbohydrate oxidation in men after chronic exposure versus placebo, but not after acute exposure versus placebo	Stable sex interaction, performance benefit, or a general metabolic effect

Study	Design and analyzed sample	Material and coexposure	Tissue or functional finding	What cannot be inferred
Sawicka et al. [50]	Double-blind pilot, 28 enrolled, 22 protocol-compliant completers, homogeneous analysis of 20 older women after two post-completion exclusions, 24 weeks	1.5 g LCLT/day versus isonitrogenous placebo	Plasma free carnitine increased; muscle strength, body composition, and measured circulating markers did not improve	Benefit in older women or inference from plasma to muscle function

Inferred. The prolonged coexposure studies show that skeletal muscle total carnitine can increase under selected conditions [16,17,19]. The smaller LCLT-alone impaired-glucose-tolerance crossover adds direct evidence of altered dynamic acetylcarnitine formation and metabolic flexibility, but not a statistically established fasting free, acetyl, or total-carnitine increase [18,19]. These studies do not show that all oral LCLT exposures produce tissue accumulation, that shorter exposures are ineffective, or that any particular duration is a minimum effective interval. Duration is a study attribute, not an optimized schedule.

Observed. Selected studies reported changes in energy expenditure or exercise fat oxidation only after verified muscle accumulation in a combined intervention [17,19]. These findings do not support a general statement that LCLT increases fat oxidation, causes fat loss, or changes body composition.

Observed. Direct LCLT exercise studies include important null and heterogeneous evidence. In 15 trained men, 3 g/day for four weeks did not change carbohydrate or fat oxidation during prolonged cycling and did not improve the subsequent 20 km time trial [47]. In 20 active men, 2 g/day for two weeks did not change the contribution of fat, carbohydrate, or protein during prolonged exercise [48]. A 12-person crossover study, comprising six men and six women, found no fat-oxidation effect; a greater carbohydrate-oxidation response appeared in the male subgroup after the chronic condition versus placebo but not after the acute condition versus placebo [49]. That sex-specific contrast arises from six men and does not establish a stable sex interaction or a general LCLT effect.

Observed. In a 24-week double-blind pilot, 28 older adults were enrolled, 22 completed while adhering to the protocol, and the homogeneous analysis included 20 older women after exclusion of one male participant and one woman who smoked. The historical 1.5 g LCLT/day condition increased plasma free carnitine but did not improve measured muscle strength, body composition, or circulating markers [50]. The small analyzed sample, post-completion exclusions, older-women population, and absence of a direct muscle-carnitine measurement limit transportability and causal interpretation.

Unknown. Whether the dynamic LCLT-alone tissue response observed in volunteers with impaired glucose tolerance occurs in the population relevant to the androgen receptor hypothesis, includes a reproducible total-pool increase, changes exercise substrate flux or performance, or predicts muscle function remains unestablished [18,19]. The direct null studies constrain positive generalization and prevent either the tissue or coexposure findings from being treated as a universal LCLT effect [17-19,47-50].

11. Exercise-recovery evidence and funding context

11.1 Recovery is not a single endpoint

Observed. Exercise-recovery studies have used heterogeneous outcomes: perceived soreness, perceived recovery, serum creatine kinase, myoglobin, hypoxanthine, xanthine oxidase, malondialdehyde, imaging-

defined disruption, isometric force, jump power, and hormonal responses [22,23,26-28]. These measures differ in biological proximity, precision, temporal behavior, and clinical meaning.

Inferred. A lower serum marker after exercise may reflect altered release, distribution, clearance, or sampling time. It does not by itself demonstrate less histological injury or faster structural repair. A change in soreness need not imply a change in muscle architecture. A preserved laboratory performance measure need not establish injury prevention, hypertrophy, or meaningful long-term adaptation.

11.2 Study-level evidence

Observed. A crossover study in ten resistance-trained men compared three-week LCLT and placebo conditions separated by a one-week washout. The study reported lower postexercise hypoxanthine, xanthine oxidase, myoglobin, creatine kinase, malondialdehyde, soreness, and magnetic-resonance-imaging disruption under the LCLT condition [22]. The endpoints were short-term surrogate or imaging measures in a small, selected sample.

Observed. A related crossover experiment in ten healthy recreationally weight-trained men evaluated anabolic-hormone responses after three weeks per condition. The study did not measure skeletal muscle androgen receptor protein and should not be used as replication of the later receptor result [23].

Observed. In eight men assigned repeated LCLT conditions, a randomized repeated-measures study assessed serum carnitine and selected exercise-recovery biomarkers across product-described exposures [26]. The small sample, multiple endpoints, and repeated-condition design limit stable effect estimation.

Observed. In 18 middle-aged adults, nine men and nine women, a crossover study reported changes in selected biochemical and soreness endpoints after a three-week condition, while strength, power, and a get-up-and-go measure did not improve [27]. Biomarker and symptom signals therefore did not translate uniformly to measured function.

Observed. A 2021 randomized double-blind placebo-controlled trial enrolled 80 adults and reported that 73 completed five weeks. The trial reported group differences in perceived recovery and soreness, serum creatine kinase, and selected strength or power changes after an exercise challenge [28]. Two coauthors were employees of Lonza Consumer Health, and the project was funded by Lonza [28].

Table 4. LCLT exercise and recovery studies

Study	Design and analyzed sample	Main reported domain	Critical boundary	Funding or product context
Volek et al. [22]	Crossover, 10 resistance-trained men, 3 weeks per condition, 1-week washout	Serum markers, soreness, MRI-defined disruption	Surrogates and short follow-up; small selected sample; no histology or hypertrophy	Product-linked research line; disclosure must be read with full article
Kraemer et al. [23]	Balanced crossover, 10 trained men, 3 weeks per condition	Hormonal responses and recovery	Did not measure AR protein or TRT interaction	Same research network as later AR paper
Spiering et al. [26]	Randomized repeated measures, 8 men	Serum carnitine and selected biomarkers or soreness	Very small sample and multiple comparisons	Product-described LCLT
Ho et al. [27]	Crossover, 18 middle-aged adults, 9 men and 9 women	Biochemical markers, soreness, strength, power, mobility	Selected biochemical and soreness changes; no improvement in several functional outcomes	Generalizability limited by sample and duration
Stefan et al. [28]	Randomized double-blind placebo-controlled trial, 80 enrolled, 73 completed, 5 weeks	Perceived recovery, soreness, CK, selected strength and power changes	Multiple outcomes; exercise-challenge context; no tissue-repair or hypertrophy endpoint	Funded by Lonza; two Lonza employee authors

Observed. These positive or mixed recovery reports coexist with direct LCLT counterevidence. Four weeks at 3 g/day in 15 trained men did not improve substrate use or a 20 km cycling time trial [47]. Two weeks at 2 g/day in 20 active men did not change the contribution of fat, carbohydrate, or protein during prolonged exercise [48]. A 12-person crossover found no fat-oxidation effect and only a small male-subgroup carbohydrate-oxidation contrast after the chronic condition [49]. In the homogeneous analysis of 20 older women, 24 weeks at 1.5 g/day increased plasma free carnitine but did not improve muscle strength, body composition, or measured circulating markers [50]. These are historically reported study exposures, not recommendations. Their populations, endpoints, and durations differ, but they prevent selective presentation of marker-positive studies as a consistent functional benefit.

11.3 Sponsorship, clustering, and replication

Observed. Several LCLT exercise and receptor studies arose from overlapping investigator groups, used branded product, or received product-industry support [22-24,28]. Funding or product supply does not invalidate a result, but it is a study characteristic relevant to independence and selective-reporting risk.

Inferred. Repeated findings inside one sponsor-investigator network are not equivalent to independent replication. The evidence base would be stronger with independently supplied material, preregistered outcomes, blinded centralized assays, public protocols, complete adverse-event reporting, and replication by teams without financial or product dependence.

Unknown. No study identified through the cutoff established that an exercise-recovery signal was mediated by androgen receptor signaling. No identified study showed that these short-term markers predict durable tissue repair, hypertrophy, injury reduction, or a better clinical outcome.

12. Critical appraisal of the androgen receptor study

12.1 Design and reported result

Observed. Kraemer and colleagues used a balanced randomized double-blind placebo-controlled crossover design in ten healthy recreationally resistance-trained men, with a mean age of 22 ± 1 years. Each condition lasted 21 days and the conditions were separated by a 7-day washout. Participants underwent two randomized resistance-exercise protocols in each condition, followed by water or a caloric beverage, and provided preexercise and 60-minute postexercise vastus lateralis biopsies for total androgen receptor, abbreviated AR, analysis [24].

Observed. The product was described as L-CARNIPURE LCLT capsules. Four capsules per day were reported, each containing 736 mg LCLT salt declared equivalent to 500 mg levocarnitine plus 236 mg tartrate. The historical study exposure was therefore approximately 2.944 g LCLT salt per day and 2 g declared levocarnitine equivalent per day [24]. This is a study descriptor, not a regimen.

Inferred. Applying Equation 1 to an ideal anhydrous 2:1 salt would make 2.944 g correspond to 2.009 g levocarnitine. The report's 2.000 g declaration is approximately 0.009 g lower and may reflect product specification or rounding, but the publication does not identify the cause. Neither value is an independent lot assay [1-3,24].

Observed. The indexed abstract reports preexercise total androgen receptor protein values of 12.9 ± 5.9 arbitrary units under LCLT and 11.2 ± 4.0 arbitrary units under placebo, $P < 0.05$, without identifying the dispersion statistic [24]. The replacement Figure 2 caption states that the plotted values are means ± standard error [25]. The difference between the reported marginal means is 1.7 arbitrary units.

Observed. The experiment evaluated a broader endpoint family than the preexercise receptor contrast. Within each supplement condition, participants completed randomized resistance-exercise visits followed by water or a mixed meal providing 8 kcal/kg body mass, with serial blood draws and a biopsy 60 minutes after exercise [24]. Reported outcomes included preexercise and postexercise total androgen receptor protein, serum total carnitine, total testosterone, luteinizing hormone, sex hormone-binding globulin, free androgen index, adrenocorticotropic hormone, cortisol, glucose, and lactate across feeding and water conditions [24]. The receptor result must therefore be interpreted within a multi-endpoint, multi-time, feeding-by-exercise analytical family rather than as an isolated confirmatory test.

Observed. The assay used total protein from muscle homogenate, a Bradford protein determination, 150 µg protein per lane, a polyclonal androgen receptor antibody, colorimetric Western blot detection, and densitometry [24]. A modern housekeeping-protein or total-lane normalization procedure was not identified in the inspected method description.

12.2 What the estimate can and cannot provide

Observed. In a complete two-condition crossover, the treatment contrast is based on within-person differences. The published marginal means allow the point difference to be calculated. The indexed abstract does not identify the dispersion statistic paired with its numeric values. The corrected replacement figure identifies its plotted error bars as standard errors, but marginal precision still does not identify the within-person covariance or the variance of paired differences.

EQUATION 6. PAIRED CROSSOVER TREATMENT EFFECT

$$\hat{\tau} = \text{mean}(Y_{LCLT} - Y_{placebo})$$
$$SE(\hat{\tau}) = SD(Y_{LCLT} - Y_{placebo}) / \sqrt{n}$$

Units: $\hat{\tau}$ and its standard error have the outcome units, here arbitrary densitometry units.

Definitions: Y_{LCLT} and $Y_{placebo}$ are the same participant's endpoint under each condition. n is the number of complete paired observations. $SD(Y_{LCLT} - Y_{placebo})$ is the standard deviation of within-person differences.

Assumptions: The paired differences are validly aligned, period and carryover effects are absent or modeled, and the reported endpoint is measured comparably in both conditions.

Identifiability limit: The publication does not provide the within-person difference variance or the cross-condition correlation. Even if the corrected plotted error bars are read as marginal standard errors, they cannot reconstruct a paired standard error, confidence interval, or paired standardized effect.

Plain interpretation: The reported means show a 1.7-arbitrary-unit difference, but the precision of the actual crossover contrast is unavailable.

Unknown. A reanalysis cannot determine how sensitive the reported P value is to participant-level observations, period, sequence, blot batch, normalization choice, or outlier handling without the raw data and analysis code.

12.3 Carryover and period effects

Observed. The washout was 7 days [24]. The paper did not establish that this interval returned muscle androgen receptor protein, carnitine-related pools, training response, or any persistent treatment-associated state to baseline.

EQUATION 7. PERIOD AND CARRYOVER MODEL

$$Y_{pk} = \mu + \tau\, T_{pk} + \pi\, P_k + \kappa\, S_p + \rho\, C_{pk} + b_p + \varepsilon_{pk}$$

Units: All fixed and random terms are expressed on the endpoint scale, such as arbitrary units or a transformed scale.

Definitions: Y_{pk} is participant p's endpoint in period k. mu is the intercept. T_{pk} indicates current treatment. P_k indicates period. S_p identifies assigned treatment sequence. C_{pk} indicates possible carryover from the prior condition. b_p is a participant-specific random intercept. ε_{pk} is residual error.

Assumptions: Treatment, period, sequence, and carryover are encoded correctly; residual structure is appropriate; and there are enough data to estimate the model.

Identifiability limit: In a small two-period two-sequence crossover, first-order carryover is strongly confounded with assigned sequence. Ten participants provide little information for separating treatment, period, sequence, and carryover. The published aggregate data cannot fit this model, so it is a diagnostic specification rather than an estimable reanalysis.

Plain interpretation: A crossover estimate can be distorted if the earlier condition still matters in the later period. A 7-day washout cannot simply be assumed sufficient.

12.4 Multiplicity and selective emphasis

Observed. The experiment combined two supplement conditions, feeding and water comparisons, preexercise and postexercise biopsies, serial hormones, and multiple statistical contrasts [24]. The total androgen receptor result was one result inside a broad analytical set.

Inferred. Without a prospectively registered primary endpoint and multiplicity strategy, a nominal $P < 0.05$ should be interpreted as a hypothesis-generating signal. The concern is not that the result must be false. The concern is that its long-run false-positive probability cannot be read from that isolated P value.

12.5 Transparency, independence, and reporting

Observed. The study predates contemporary routine registration. No prospective trial registration was identified through the cutoff. Product and funding support were provided in part by Lonza, the product manufacturer or supplier connected to L-CARNIPURE [24]. The accessible report did not provide the level of adherence, sequence-specific attrition, adverse-event, raw-blot, and code transparency expected for a current confirmatory trial.

Observed. The corrigendum in the same journal volume was inspected and is linked wherever the original result is interpreted [25]. It replaces Figure 2, corrects the free androgen index equation, and makes one procedural wording correction. The replacement androgen receptor figure retains means ± standard error and significance markers [25]. No independent replication of the preexercise total androgen receptor protein difference was identified through the evidence cutoff.

Table 5. Critical appraisal of the androgen receptor crossover study

Domain	Observed record [24,25]	Adversarial interpretation	Required resolution
Population	10 young resistance-trained men, mean age 22 ± 1 years	Very low precision and narrow external validity	Larger sex-inclusive and age-relevant sample
Design	Balanced randomized double-blind crossover	Efficient for within-person comparison if carryover absent	Sequence disclosure, raw paired data, period model
Condition duration	21 days	A study duration, not an efficacy threshold	Time-course measurement
Washout	7 days	Biological adequacy not demonstrated	Empirical return-to-baseline data or parallel design
Material	Branded LCLT product, declared levocarnitine equivalent	Lot assay and full composition not reported to current standard	Independent identity, purity, and stability certificate
Endpoint	Total AR protein by colorimetric Western blot	Protein abundance is not function; arbitrary units	Orthogonal validated assays and blinded central analysis

Domain	Observed record [24,25]	Adversarial interpretation	Required resolution
Point result	Indexed abstract: 12.9 ± 5.9 versus 11.2 ± 4.0 arbitrary units, P < 0.05, dispersion statistic unnamed; replacement Figure 2 caption states plotted means ± standard error [24,25]	Marginal standard errors, where available from the corrected figure, do not identify within-person covariance or paired precision	Participant-level paired values and prespecified model
Normalization	150 µg total protein loaded; modern lane normalization not identified	Blot loading and batch effects can imitate abundance shifts	Total-protein normalization, calibrator, batch controls
Multiplicity	Multiple hormones, times, feeding states, and comparisons	Nominal significance may be selective	Registered primary endpoint and familywise strategy
Tissue exposure	Muscle carnitine not measured	Mechanistic bridge from LCLT exposure is absent	Plasma tracer plus muscle carnitine and acylcarnitines
Functional AR	Not measured	No evidence of localization, occupancy, transcription, or sensitivity	Nuclear fraction, occupancy, coregulators, chromatin, RNA
Functional muscle outcome	No protein-synthesis or hypertrophy endpoint	Clinical meaning unresolved	Integrated synthesis, architecture, strength, symptoms
Testosterone interaction	No exogenous testosterone condition	No adjunct or synergy evidence	Factorial controlled interaction study
Independence	Product and funding support in part from Lonza	Sponsorship and investigator clustering warrant independent replication	Independently funded multicenter confirmation
Corrections	Inspected corrigendum replaces Figure 2, corrects the free androgen index equation, and changes "fasting" to "fasted" [25]	Corrected Figure 2, caption, and significance markers govern interpretation	Preserve and cite the corrected record

13. Why receptor abundance is not receptor function

13.1 Functional-state decomposition

Observed. The androgen receptor is a ligand-regulated transcription factor. A functional response depends on more than total protein. Relevant states include ligand availability, receptor conformation, cytoplasmic and nuclear localization, phosphorylation and other modifications, chaperone interactions, dimerization, coregulator recruitment, chromatin occupancy, and target-gene context [43].

EQUATION 8. ANDROGEN RECEPTOR FUNCTIONAL-STATE FACTORIZATION

$$R_{active}(t) = R_{total}(t)\, f_N(t)\, f_{L|N}(t)\, f_{C|N,L}(t)$$

Units: R_{active} and R_{total} may be expressed as normalized receptor amount or activity units. Each conditional f term is a dimensionless fraction between 0 and 1 in this conceptual representation.

Definitions: R_{total} is total receptor protein. f_N is the fraction in the relevant nuclear state. $f_{L|N}$ is the ligand-competent or ligand-occupied fraction conditional on nuclear state. $f_{C|N,L}$ is the transcriptionally competent coregulator and chromatin fraction conditional on both nuclear and ligand state.

Assumptions: The factors are sequential conditional fractions measured on compatible time and tissue scales. This avoids treating interacting marginal fractions as statistically independent.

Identifiability limit: The conditional state fractions remain schematic and may require a richer state-transition model. A total-protein immunoblot measures at most R_{total} and cannot identify the other terms.

Plain interpretation: More receptor protein can fail to produce more receptor activity if the receptor is in the wrong compartment, lacks ligand, or cannot engage the transcriptional machinery.

Inferred. Even if the reported total-protein difference is analytically valid, the active fraction could remain unchanged, increase, or decrease. A change in total protein can reflect synthesis, degradation, cell-type composition, fluid shifts, sampling heterogeneity, or assay normalization rather than a change in androgen responsiveness.

13.2 Missing measurements

Observed. The pivotal study did not measure androgen receptor messenger RNA, receptor synthesis or turnover, isoform composition, phosphorylation, nuclear translocation, ligand binding or occupancy, chaperone release, dimerization, coregulator recruitment, androgen-response-element occupancy, target-gene transcription, single-cell localization, or cell-type composition [24].

Observed. It also did not measure integrated muscle protein synthesis, myofibrillar protein synthesis, satellite-cell behavior, fiber cross-sectional area, lean-tissue accretion, strength adaptation, symptoms relevant to testosterone deficiency, or adverse androgen-sensitive outcomes [24].

Unknown. The direction and magnitude of any functional androgen receptor effect therefore remain unidentifiable.

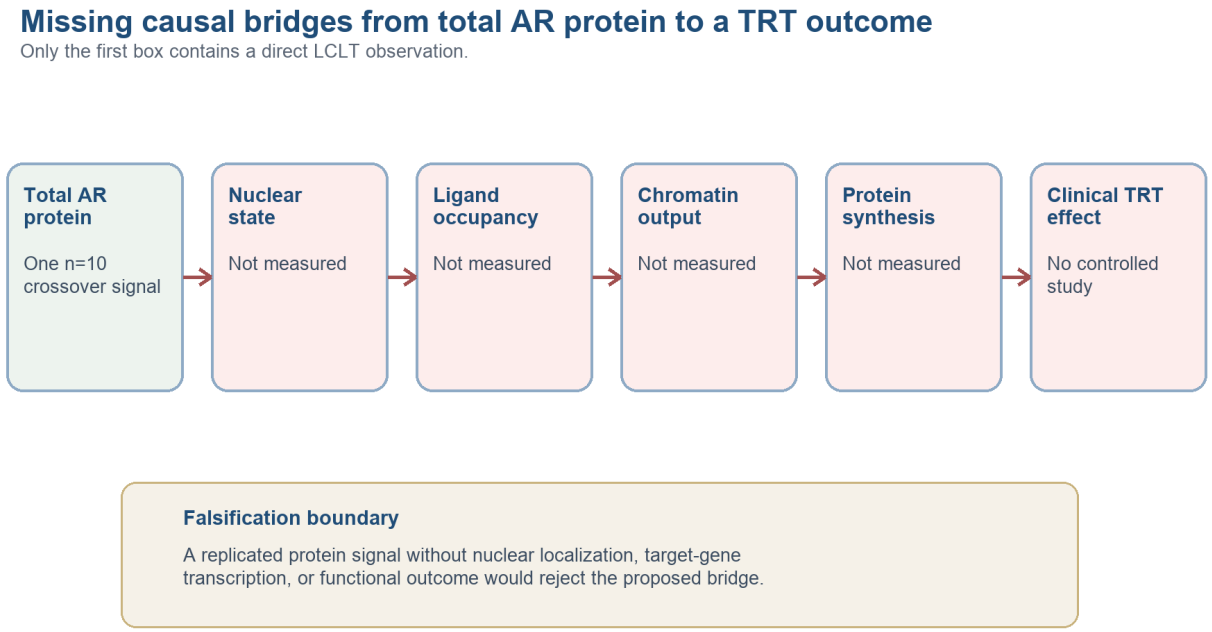

Figure 4. Missing causal bridges from total androgen receptor protein to a clinical testosterone-therapy outcome.

Verified LCLT material

→ measured levocarnitine exposure
→ measured skeletal muscle carnitine state
→ reproducible total AR protein change
→ nuclear and ligand-competent AR state
→ coregulator recruitment and chromatin binding
→ target-gene transcription
→ protein synthesis and tissue adaptation
→ patient-relevant benefit or harm
→ differential response under prescribed testosterone

Inferred. Status: Chemical identity is definable. General levocarnitine disposition is partially observed. Muscle accumulation is observed only in selected contexts. The single total-AR signal is observed but unreplicated. All downstream LCLT-specific bridges are Unknown. The final testosterone interaction is Hypothesized and not estimated.

14. Causal-edge map from exposure to a clinical outcome

Table 6. Causal edges, status, missing tests, and falsifiers

Causal edge	Status	Missing test	Example falsifier
Product label → verified LCLT lot	Unknown in many trials	Independent analytical release testing	Material fails stoichiometry, stereochemistry, or assay specification
LCLT lot → plasma levocarnitine exposure	Partially inferred	LCLT-specific tracer PK with baseline and mass balance	No exposure difference from control despite verified administration

Causal edge	Status	Missing test	Example falsifier
Plasma exposure → muscle carnitine	Observed only in selected contexts	Direct serial muscle sampling or validated spectroscopy	Plasma rises but muscle pools do not change
Muscle carnitine → metabolic flux	Context-specific	Stable-isotope flux and acylcarnitine profiling	Pool changes without flux or CoA-state change
LCLT → total AR protein	Observed once, unreplicated	Preregistered blinded independent replication	Confirmatory estimate centered near zero with adequate precision
Total AR → active nuclear AR	Unknown	Fractionation, imaging, ligand occupancy, phosphorylation	Total AR rises while active nuclear fraction does not
Active AR → transcription	Unknown	Chromatin occupancy and target-gene RNA	Nuclear AR changes without coherent androgen-response program
Transcription → protein synthesis	Unknown	Integrated or myofibrillar synthesis measurement	Transcription changes without synthesis change
Protein synthesis → tissue adaptation	Unknown	Longitudinal imaging, fiber, strength, and function	Acute synthesis signal without durable adaptation
LCLT → testosterone response	Hypothesized	Factorial controlled experiment	Interaction contrast compatible with zero or opposite direction
Biomarker recovery → clinical recovery	Inferred at most	Validated patient-relevant or functional endpoint	Biomarker shifts without functional improvement
TMAO rise → clinical harm	Unknown	Long-duration causal outcome design	Metabolite change without predicted intermediate or clinical effect

15. Testosterone-therapy relevance as an unresolved hypothesis

15.1 Evidence located

Observed. No controlled study testing LCLT and testosterone together was identified through the evidence cutoff. No identified trial estimated whether LCLT modifies the effect of prescribed testosterone on skeletal muscle androgen receptor function, protein synthesis, body composition, strength, symptoms, erythrocytosis, prostate-related measures, fertility, cardiovascular outcomes, or another patient-relevant endpoint.

Observed. A randomized study in 120 older men compared testosterone undecanoate with a combination of propionyl-L-carnitine and acetyl-L-carnitine and with placebo [39]. It was a comparison between interventions, not an LCLT adjunct trial. The carnitine formulations were not LCLT, and the study did not estimate an LCLT-by-testosterone interaction.

Observed. Male-fertility trials have evaluated acetyl-L-carnitine, free L-carnitine, or combinations, with mixed findings, including a small null randomized study [40,45,46]. No LCLT-specific male-fertility randomized trial was identified through the evidence cutoff. These records cannot be used to infer that LCLT enhances, preserves, or impairs fertility during testosterone therapy.

15.2 Interaction is an estimand, not a narrative

EQUATION 9. ADDITIVE-SCALE LCLT-BY-TESTOSTERONE INTERACTION

$$\Delta_{int} = (\mu_{TL} - \mu_{T0}) - (\mu_{0L} - \mu_{00})$$

Units: The units of the prespecified outcome, such as percent change, kg, N m, transcript units, or a transformed scale.

Definitions: μ_{TL} is the mean under testosterone plus LCLT. μ_{T0} is the mean under testosterone without LCLT. μ_{0L} is the mean under LCLT without testosterone. μ_{00} is the mean under neither exposure.

Assumptions: A factorial design or equivalent identification strategy, randomized treatment assignment, a prespecified outcome and scale, adequate adherence, and no uncontrolled post-randomization bias.

Identifiability limit: Existing studies do not contain all four cells. The interaction is therefore not estimable from the current literature.

Plain interpretation: The equation asks whether the combined effect differs from the sum of the two separate effects on one chosen scale. It is not a universal synergy coefficient.

Inferred. An interaction depends on endpoint, time, exposure, population, baseline androgen state, and scale. A positive interaction on a molecular marker could coexist with no interaction on strength and an adverse interaction on another outcome. The word "synergy" is therefore scientifically incomplete without a prespecified null model and endpoint.

15.3 Competing hypotheses

Hypothesized. Enhancement model: Verified LCLT exposure increases a functional receptor state, producing a larger downstream response at the same controlled testosterone exposure.

Hypothesized. Null model: LCLT changes neither functional receptor state nor the response to testosterone. The reported total-protein signal is nonreplicable, analytically nonfunctional, or irrelevant to the tested endpoint.

Hypothesized. Ceiling model: Testosterone exposure already saturates a downstream step, so a receptor-protein change does not alter function.

Hypothesized. State-dependent model: An interaction occurs only in a subgroup defined by tissue carnitine, insulin sensitivity, training state, androgen status, age, sex, microbiome, renal function, or another prespecified modifier.

Hypothesized. Adverse-interaction model: A molecular or metabolic change amplifies an undesirable androgen-sensitive endpoint without improving the intended outcome.

Unknown. Current evidence cannot rank these models reliably.

16. Timing, washout, and state dependence

Inferred. Cross-source evidence indicates that plasma levocarnitine, urinary excretion, microbial metabolites, skeletal muscle carnitine pools, total receptor protein, receptor-state changes, transcription, protein synthesis, and structural adaptation operate on different time scales [7-20,24,31-37,52,53]. A single sampling time can therefore miss or misclassify an effect.

Inferred. The 21-day condition in the pivotal receptor study is not a minimum effective duration. The 7-day washout is not proof of biological reset. The 12-week to 25-week muscle-accumulation studies are not optimized schedules [16,17,19,24]. They are observation windows chosen by investigators.

Hypothesized. A valid temporal study would first establish the return-to-baseline behavior of plasma levocarnitine, muscle carnitine pools, microbial metabolites, and receptor-state endpoints. Sampling windows would then be selected from those empirical time courses, not from convenience or retrospective significance.

EQUATION 10. LONGITUDINAL FUNCTIONAL OUTCOME MODEL

$$g(E[Y_{it} \mid b_i]) = \alpha + f_T(E_{Ti,t}) + f_L(E_{Li,t}) + f_{TL}(E_{Ti,E}_Li,t) + b_i$$

Units: Y_{it} has the endpoint's natural units before transformation by link g. E_{Ti} and E_{Li} are participant-specific testosterone and levocarnitine exposure metrics, with concentration or area-under-curve units. Model terms are on the link scale.

Definitions: Y_{it} is participant i's outcome at time t. b_i is the participant-specific random effect. alpha is the conditional intercept. f_T is the testosterone exposure-time function. f_L is the LCLT-derived levocarnitine exposure-time function. f_{TL} is their interaction over time.

Assumptions: Exposure metrics are measured with adequate accuracy, time functions are prespecified or regularized, missingness is handled defensibly, and the outcome distribution matches the link.

Identifiability limit: Sparse sampling, correlated exposures, post-randomization adherence, and flexible functions can make f_{TL} nonidentifiable. Existing studies do not supply the required joint data.

Plain interpretation: A credible interaction study must follow both exposures and the outcome through time. One preexercise blot cannot establish a durable combined effect.

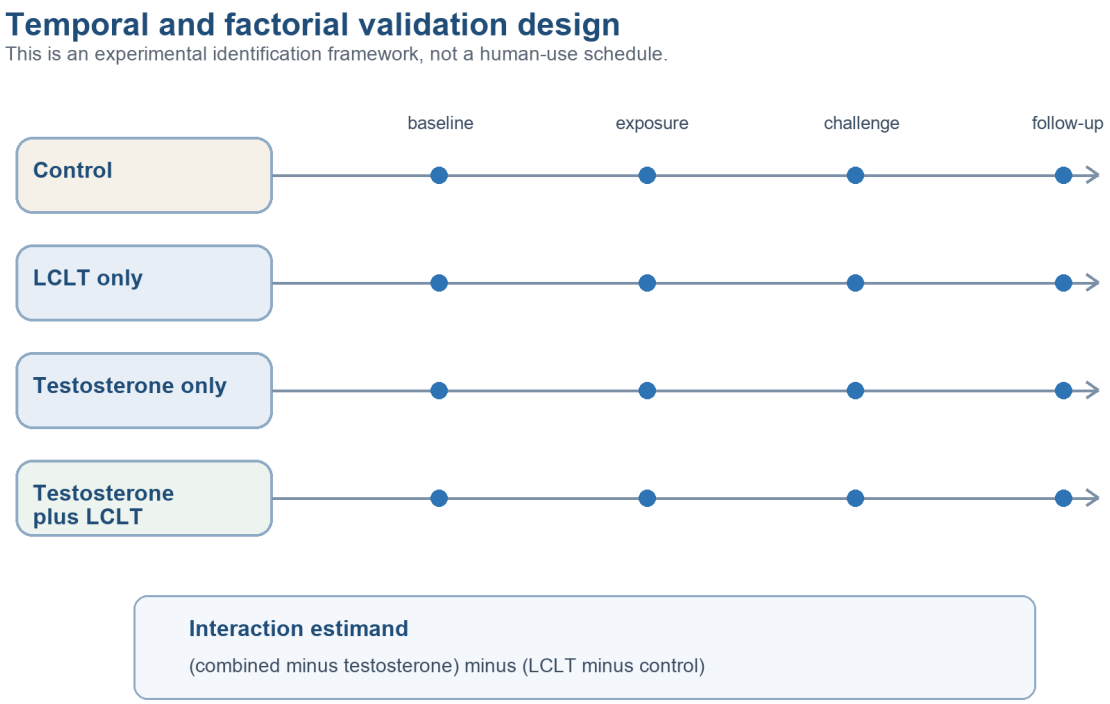

Figure 5. Temporal factorial validation framework. The four arms and repeated measurements identify an additive-scale LCLT-by-testosterone interaction.

Hypothesized. Design concept, not a dosing schedule:

Screen and characterize → verify material and baseline state → randomize factorial conditions → measure both exposures → sample proximal receptor states → sample transcription and tissue function → follow prespecified benefit and harm endpoints → complete return-to-baseline or post-intervention observation

The factorial conditions are:

- neither experimental exposure;
- LCLT condition only;
- controlled testosterone condition only;
- combined condition.

Inferred. Required temporal layers: early disposition, intermediate tissue state, receptor function, downstream transcription, protein synthesis, structural adaptation, and safety. Exact exposures and timing require a separately justified protocol, regulatory review, and clinical oversight. This figure must not be read as a treatment or self-experimentation schedule.

17. Quantitative models and estimands

17.1 Purpose and limits

Inferred. Equations 1 through 10 formalize where a claim becomes identifiable. They are not a mechanistic simulation validated for individual prediction. Their primary value is to expose missing measurements and prevent a numerical result at one level from being propagated into an unsupported downstream claim.

Observed. Equation 1 is fully determined only under ideal chemical assumptions. Equations 2 through 4 require formulation-specific absorption, tracer, tissue, and renal data. Equations 5a and 5b describe established chemistry but not net flux. Equations 6 and 7 define the missing paired and carryover information. Equation 8 shows why total protein is insufficient. Equations 9 and 10 define the unmeasured testosterone interaction.

17.2 Minimum reporting for a quantitative claim

Inferred. A defensible quantitative estimate should report:

- material identity and active-moiety basis;
- route and coexposures;
- population and analyzed sample;
- baseline definition and correction;
- sampling and assay units;
- prespecified estimand and analysis scale;
- point estimate, standard error or interval, and raw denominators;
- missingness and attrition;
- multiplicity handling;
- period, sequence, and carryover where applicable;
- model diagnostics and sensitivity analyses;
- data and code access sufficient for reconstruction.

Inferred. A P value without an estimand and uncertainty interval is not an adequate effect description. A percent change without a denominator and scale is not transportable. A pharmacokinetic parameter without formulation, route, baseline, sampling, and model is not generalizable.

18. Safety, interactions, and vulnerable contexts

18.1 Formulation boundary

Observed. The most detailed current adverse-effect language comes from prescription levocarnitine labeling, not LCLT trials. That label records nausea, vomiting, abdominal cramps, diarrhea, body odor, seizures in people with or without prior seizure activity, hypersensitivity including rash, urticaria, and facial edema, serious hypersensitivity reactions with intravenous use, and reports of increased international normalized ratio in people receiving warfarin [6].

Inferred. These label observations identify signals and vulnerable contexts for levocarnitine exposure. They do not supply incidence estimates for LCLT in healthy adults. Conversely, the absence of a signal in a small LCLT trial does not exclude an uncommon or delayed event.

18.2 Renal impairment and microbial metabolites

Observed. The prescription label warns that chronic oral levocarnitine in severe renal impairment or end-stage renal disease can lead to accumulation of trimethylamine and TMAO because renal clearance is impaired [6]. Direct LCLT studies show that circulating TMAO can rise substantially in some populations [34-37].

Unknown. The clinical consequence of a given TMAO response depends on causal biology that remains contested and on renal, microbial, dietary, and cardiovascular context. No threshold from the reviewed LCLT studies can classify an individual's risk.

18.3 Cardiometabolic uncertainty

Observed. In a randomized trial of 157 adults with metabolic syndrome and carotid plaque, six months of free L-carnitine did not improve the primary total plaque-volume endpoint. A secondary percent-stenosis endpoint was 9.3% higher and total and low-density-lipoprotein cholesterol were higher in the intervention group [38]. The formulation was not established as LCLT in the report used here.

Inferred. The null primary endpoint prevents an efficacy claim, while the secondary findings prevent an unqualified safety assurance. The secondary stenosis result is not proof that LCLT causes atherosclerosis. It is a reason to prespecify cardiovascular safety measures in longer studies.

18.4 Thyroid and medication context

Observed. In 50 women receiving suppressive levothyroxine therapy, free L-carnitine antagonized selected peripheral thyroid-hormone effects [41]. This is a context-specific pharmacodynamic observation, not a universal contraindication.

Observed. Pivalate-containing drugs can cause urinary loss of pivaloylcarnitine and deplete carnitine in susceptible contexts [42]. A concurrent-medication inventory is therefore relevant to studies of carnitine status.

Observed. Reports of increased international normalized ratio with warfarin are included in prescription levocarnitine labeling [6]. Prospective studies involving anticoagulated participants would require prespecified international-normalized-ratio event collection and medical governance.

18.5 Limited LCLT safety observations

Observed. In ten healthy men studied for three weeks, product-described LCLT was not associated with differences in the reported complete blood count or clinical chemistry measures [29]. This is limited short-duration reassurance in a very small selected sample.

Observed. In an exercise study of 18 participants assigned 4 g per day of free L-carnitine, five participants withdrew because of nausea or diarrhea [30]. This was free L-carnitine, not LCLT, but it demonstrates that gastrointestinal intolerance can be operationally important.

Unknown. Long-term LCLT safety has not been characterized adequately across renal impairment, seizure disorders, anticoagulant use, thyroid-hormone treatment, pregnancy, lactation, adolescence, advanced age, diverse microbiomes, or concurrent testosterone therapy.

Table 7. Safety, interaction, regulatory, and uncertainty matrix

Domain	Observed evidence	Formulation or population boundary	Defensible conclusion
Gastrointestinal effects	Nausea, vomiting, cramps, diarrhea in prescription label; withdrawals in a free-carnitine trial [6,30]	No LCLT incidence estimate exists	Prospective LCLT studies should collect gastrointestinal events systematically
Body odor	Listed for prescription levocarnitine [6]	Frequency for LCLT unknown	Prospective LCLT studies should collect the event without assigning a rate in advance
Seizures	Reported with or without prior seizure activity [6]	Causality and LCLT-specific incidence uncertain	Seizure history is a vulnerable context
Hypersensitivity	Rash, urticaria, facial edema; serious reactions noted for intravenous product [6]	Route and formulation matter	Do not transfer IV incidence to oral LCLT
Warfarin	Increased INR reports [6]	Evidence is postmarketing and levocarnitine-specific	Potential interaction requires clinical governance
Renal impairment	TMA and TMAO accumulation warning [6]	Severe impairment and ESRD especially relevant	Healthy-volunteer reassurance is not transportable
Microbial TMAO	Variable and sometimes marked increases [8,10,11,31-37]	Strong diet, microbiome, and renal dependence	Metabolic effect observed; clinical meaning unresolved
Cardiometabolic outcomes	Null primary plaque outcome with concerning secondary findings in free-carnitine trial [38]	Not established as LCLT	Neither safety nor harm is proven
Thyroid context	Antagonism of peripheral thyroid-hormone action in treated women [41]	Free L-carnitine and suppressive therapy	Context-specific interaction signal
Pivalate drugs	Urinary pivaloylcarnitine loss [42]	Medication-specific	Medication inventory is required
Short LCLT laboratory safety	No CBC or chemistry differences in 10 men over 3 weeks [29]	Very small, short, selected sample	Cannot establish broad or long-term safety
FDA drug status	Levocarnitine approved for specified deficiencies [6]	Not LCLT and not AR or TRT	No transfer of indication

Domain	Observed evidence	Formulation or population boundary	Defensible conclusion
FDA GRAS notice	No-questions response for specified infant-formula use [3]	Narrow notified conditions	Not adult efficacy, safety generalization, or drug approval
European efficacy claim	Lipid-metabolism health claim not authorized [5]	Regulatory claim standard	General fat-metabolism claim not established

Inferred. The appropriate global safety statement is uncertainty, not "low risk" and not "proven dangerous." Any benefit-risk assessment must be endpoint, population, formulation, duration, and comparator specific.

19. Falsification-ready validation program

19.1 Stage 0: material and assay qualification

Inferred. Before biological testing, the LCLT lot should undergo independent identity, stereochemistry, assay, hydration, impurity, dissolution, and stability evaluation. Levocarnitine and tartrate should be quantified independently where feasible. Blinding should include indistinguishable packaging and documented code custody.

Inferred. Falsifier: Failure of material identity or stability invalidates downstream material-specific interpretation.

Inferred. Androgen receptor assays should be qualified using orthogonal platforms, prespecified normalization, calibrators across batches, blinded replicate samples, and performance thresholds. Total receptor protein, nuclear fraction, phosphorylation, ligand occupancy or a validated proxy, and functional transcription should be distinguished.

Inferred. Falsifier: A signal confined to one antibody, one normalization method, or one blot batch is not a robust receptor effect.

19.2 Stage 1: formulation-specific disposition

Hypothesized. Verified LCLT produces a measurable levocarnitine exposure and a time-resolved metabolite profile distinguishable from baseline.

Inferred. Minimum measurements: baseline diet and carnitine status, plasma levocarnitine, acylcarnitines, tartrate where analytically useful, urine mass balance, TMA, TMAO, gamma-butyrobetaine, renal function, and microbiome features. A stable-isotope strategy is preferable for separating exogenous from endogenous carnitine.

Inferred. Falsifier: The verified intervention fails to produce the prespecified exposure contrast or exposure is too variable to support the next stage.

19.3 Stage 2: tissue uptake and metabolic state

Hypothesized. The exposure contrast changes skeletal muscle total carnitine, free carnitine, and selected acylcarnitine pools.

Inferred. Minimum measurements: paired tissue sampling or a validated noninvasive method, dry-mass or wet-mass basis stated explicitly, free and esterified pools, muscle fiber and cell composition, insulin and substrate state, and tracer-derived flux where possible.

Inferred. Falsifier: Plasma exposure rises but the prespecified muscle pool or flux endpoint remains unchanged with an interval excluding the minimum biologically relevant effect.

19.4 Stage 3: independent receptor replication

Hypothesized. LCLT changes preexercise skeletal muscle total androgen receptor protein.

Inferred. Minimum design: independently funded, preregistered, adequately powered, randomized, blinded study with a parallel design or empirically justified crossover washout. The primary endpoint, tissue, time, assay, normalization, estimand, and multiplicity family must be fixed before unblinding.

Inferred. Falsifier: The confirmatory estimate is compatible with no relevant effect, is assay dependent, or reverses direction across qualified platforms.

19.5 Stage 4: receptor function

Hypothesized. Any replicated total-protein change increases the ligand-responsive nuclear receptor state and a coherent androgen-regulated transcriptional program.

Inferred. Minimum measurements: nuclear and cytoplasmic receptor, receptor modification state, ligand exposure, coregulator engagement, chromatin occupancy, target-gene RNA, cell-type-resolved analysis, and negative-control transcriptional programs.

Inferred. Falsifier: Total protein changes without nuclear localization, occupancy, chromatin engagement, or a prespecified target-gene response.

19.6 Stage 5: tissue function

Hypothesized. A functional receptor-state change alters a prespecified skeletal muscle function.

Inferred. Minimum measurements: integrated or myofibrillar protein synthesis, proteolysis, muscle architecture, fiber cross-sectional area, strength, power, fatigue, and validated patient-relevant outcomes, with adequate duration and blinded analysis.

Inferred. Falsifier: Molecular changes occur without the prespecified functional effect or are accompanied by an adverse effect that defeats the proposed benefit.

19.7 Stage 6: factorial testosterone interaction

Hypothesized. The LCLT effect differs under controlled testosterone exposure.

Inferred. Minimum design: a clinically governed factorial trial with all four cells required by Equation 9, measured testosterone exposure, clinically appropriate eligibility, fertility and safety boundaries, prespecified interaction scale, adequate power for interaction rather than main effects, and independent monitoring.

Inferred. Falsifier: The interaction estimate is centered near zero with a confidence interval excluding the minimum relevant interaction, reverses across functional endpoints, or improves a surrogate while worsening a prespecified safety outcome.

Table 8. Minimum validation measurements and estimands

Layer	Minimum measurement	Primary estimand	Essential sensitivity analysis
Material	Identity, assay, stereochemistry, hydration, impurities, stability	Proportion of lots meeting specification	Reanalysis excluding any excursion
Exposure	Baseline-aware plasma tracer profile and metabolite mass balance	Difference in exposure AUC	Diet, renal function, microbiome adjustment
Tissue uptake	Muscle free, total, and acylcarnitine	Between-group change in prespecified muscle pool	Wet versus dry mass; fiber composition
Metabolic function	Stable-isotope flux and CoA-state measures	Difference in prespecified flux	Insulin and substrate-state interaction
Total AR	Orthogonal normalized protein assays	Between-group or paired treatment contrast	Batch, antibody, outlier, period, carryover
Active AR	Nuclear fraction, occupancy, modification, coregulator state	Difference in active receptor fraction	Cell-type composition and ligand exposure
Transcription	Chromatin occupancy and target-gene RNA	Prespecified pathway score	Negative-control genes and multiplicity
Muscle function	Protein synthesis, architecture, strength, symptoms	Difference in selected functional endpoint	Missingness, adherence, baseline training
Testosterone interaction	Four-cell factorial outcome	Δ_{int} on prespecified scale	Exposure-response, sex, age, baseline status
Safety	GI, seizures, hypersensitivity, INR, renal, thyroid, TMAO, cardiometabolic measures	Risk difference or longitudinal change	Vulnerable-subgroup and competing-risk analysis

Inferred. Progression between stages should depend on predefined evidence thresholds. A positive exploratory signal should trigger replication, not immediate clinical translation.

20. Discussion

20.1 What survives adversarial review

Observed. Four observations remain defensible after formulation separation and claim-level audit. First, registry and structural records define LCLT as a 2:1 levocarnitine-tartrate salt [1-3]. Second, levocarnitine has established physiological roles in acyl-group transport and acetyl-group buffering [20,21]. Third, skeletal muscle total carnitine can increase in humans under selected insulin-associated or prolonged coexposure conditions [15-17,19]. A 36-day LCLT-alone crossover in volunteers with impaired glucose tolerance showed enhanced dynamic acetylcarnitine formation and metabolic flexibility, but no significant fasting free or acetylcarnitine difference; a later numeric description of an approximately 12% total-pool increase was not established as statistically significant in the primary report [18,19]. Fourth, one small crossover study reported higher preexercise total skeletal muscle androgen receptor protein after an LCLT condition than after placebo in a corrected replacement figure [24,25].

Inferred. Applying the registry molecular masses to the ideal anhydrous 2:1 composition gives a theoretical levocarnitine mass fraction of 68.23% when rounded to two decimal places [1-3]. It is not a lot assay.

Inferred. None of those propositions establishes the next proposition in the chain. Chemical content does not establish systemic availability. Physiological necessity does not establish supplement responsiveness. Muscle accumulation in one population, formulation, or coexposure setting does not establish accumulation in another. Total receptor protein does not establish receptor function. A molecular signal does not establish improved recovery, hypertrophy, or response to testosterone.

20.2 Why the original translational argument fails

Observed. The pivotal receptor study did not include a testosterone intervention, did not measure muscle carnitine, and did not measure functional receptor states or downstream adaptation [24]. No controlled LCLT-by-testosterone study was identified through the evidence cutoff.

Inferred. An adjunct-to-testosterone argument derived from that study commits several inferential substitutions:

1. It substitutes a declared product exposure for verified tissue exposure.
2. It substitutes total receptor protein for ligand-responsive receptor function.
3. It substitutes a preexercise molecular signal for an exercise-recovery mechanism.
4. It substitutes a young resistance-trained sample for people receiving testosterone therapy.

5. It substitutes a main-effect comparison for an interaction estimate.
6. It substitutes an exploratory P value for replicated magnitude and uncertainty.

Each substitution can change the answer. The chain is therefore not merely incomplete. It is nonidentifiable from the current data.

20.3 The correct role of mechanistic theory

Hypothesized. Mechanistic theory is useful when it specifies observations that would distinguish competing causal models. For LCLT and androgen signaling, useful hypotheses include tissue-uptake dependence, receptor-localization dependence, ligand-state dependence, transcriptional competence, ceiling effects under testosterone exposure, and subgroup modification by baseline metabolic state.

Inferred. Mechanistic language becomes misleading when it is used to fill missing edges. A plausible pathway is not evidence that the pathway operated in the studied participant. A pathway diagram must display negative controls, alternative paths, missing measurements, and falsifiers, not only arrows that support a desired conclusion.

20.4 Recovery signals do not rescue the receptor hypothesis

Observed. Several LCLT studies reported changes in soreness, serum markers, imaging disruption, perceived recovery, or selected performance outcomes after exercise [22,26-28]. Other functional measures were unchanged in at least one crossover study [27]. The research line includes small samples, multiple endpoints, overlapping investigators, branded material, and industry funding or employment in selected reports [22-24,28].

Observed. Direct LCLT studies also reported no improvement in substrate use or cycling time-trial performance after four weeks in 15 trained men, no change in fat, carbohydrate, or protein contribution after two weeks in 20 active men, and no fat-oxidation effect in a 12-person crossover [47-49]. In a 24-week pilot whose homogeneous analysis included 20 older women, plasma free carnitine increased but muscle strength, body composition, and measured circulating markers did not improve [50]. One sex-specific carbohydrate-oxidation contrast in six men does not offset the broader null pattern or establish an interaction [49].

Unknown. It is not known whether any recovery signal is mediated by muscle carnitine accumulation, altered oxidative metabolism, androgen receptor signaling, a non-AR pathway, altered marker kinetics, or chance. The studies do not establish a common mechanism.

20.5 Pharmacokinetic heterogeneity is part of the mechanism

Observed. Oral availability, renal handling, and TMAO formation vary with exposure, formulation, baseline, microbiome, and renal function [6-14,31-37]. Direct muscle uptake is context dependent [15-19].

Inferred. This heterogeneity should not be hidden by a single "bioavailability" percentage or a universal time-to-peak statement. It is a source of potentially informative effect modification. A definitive study would measure the exposure chain and test whether tissue and receptor responses occur only above a prespecified exposure or in a prespecified phenotype.

20.6 Clinical and regulatory discipline

Observed. Prescription levocarnitine approval, a narrowly scoped GRAS notice for an infant-formula use, an EFSA source opinion, and refusal of a lipid-metabolism health claim are distinct regulatory records [3-6]. None authorizes an LCLT-androgen or LCLT-testosterone claim.

Inferred. A publication can discuss an unresolved translational hypothesis without turning it into treatment guidance. The necessary discipline is to state the estimand, preserve material distinctions, describe known adverse-effect signals, make uncertainty visible, and specify what outcome would refute the hypothesis.

21. Limitations

Observed. This manuscript is a curated critical narrative review, not a prospectively registered systematic review. Database coverage, language coverage, grey-literature retrieval, duplicate screening, and risk-of-bias adjudication were not exhaustive. The search was designed around a defined causal chain and the claims in the source manuscript.

Observed. Several pivotal studies were small and reported incomplete participant-level information. The androgen receptor crossover study did not provide the paired difference variance, raw values, period-specific estimates, or a contemporary preregistration [24]. Its corrigendum was inspected and incorporated, including the replacement androgen receptor figure and corrected free androgen index equation [25].

Observed. LCLT-specific pharmacokinetics are not established. Much disposition evidence comes from free levocarnitine, prescription formulations, or other carnitine compounds [6-11,51]. Human muscle evidence includes insulin manipulation, substantial coexposures, and one small 36-day LCLT-alone crossover in volunteers with impaired glucose tolerance that showed dynamic acetylcarnitine effects but no significant fasting free or acetylcarnitine difference [15-19].

Observed. The evidence base contains heterogeneous endpoints, sampling times, analytical methods, cointerventions, and funding contexts. Those differences prevented meta-analysis and make a single pooled effect scientifically inappropriate.

Unknown. Unpublished studies, nonindexed records, or inaccessible data may alter the map. "Not identified through the evidence cutoff" is not proof of absence.

Inferred. The equations are conceptual identification frameworks. Except for the chemical conversion, they are not validated population models and must not be used for individual prediction or exposure selection.

Inferred. The claim-labeling system distinguishes evidentiary status but does not replace a formal certainty-of-evidence framework. An Observed result may still have high risk of bias, weak precision, or poor transportability.

22. Bounded conclusions

1. **Observed.** Registry and structural records define LCLT as a stereochemically specified 2:1 levocarnitine-tartrate salt [1-3]. A registry identity does not verify the material in a tested lot.
2. **Inferred.** Applying the registry molecular masses to the ideal anhydrous 2:1 composition gives a theoretical levocarnitine mass fraction of 68.23% when rounded to two decimal places. Corresponding mass equivalents are theoretical calculations, not observed lot potency or delivered content [1-3].
3. **Observed.** Oral levocarnitine availability is low and exposure dependent in small supplemental studies, with values spanning approximately 5% to 16% in the directly cited free or prescription formulations [6,7,51]. No superior human bioavailability of LCLT versus free levocarnitine was identified through the cutoff.
4. **Observed.** Plasma exposure does not establish skeletal muscle uptake. Human muscle accumulation has been shown in selected insulin-associated and prolonged coexposure settings [15-17,19]. In one 36-day LCLT-alone crossover in 11 volunteers with impaired glucose tolerance, fasting free and acetylcarnitine did not differ significantly, while dynamic acetylcarnitine formation and metabolic flexibility improved [18]. A later numeric description of an approximately 12% total-pool increase was not established as statistically significant in the primary report [18,19]. These findings do not establish uptake in the androgen receptor study population.
5. **Observed.** Carnitine is a transported substrate in the long-chain acyl shuttle and acetyl-buffering system. Established physiology does not prove that LCLT increases pathway flux in carnitine-replete people [20,21].
6. **Observed.** One crossover study in ten young resistance-trained men reported a 1.7-arbitrary-unit difference in preexercise total androgen receptor protein after LCLT versus placebo [24,25]. The indexed abstract does not identify the dispersion statistic for its numeric values; the corrected figure identifies plotted values as means ± standard error. The paired uncertainty is not recoverable because the within-person covariance and paired-difference variance were not reported.
7. **Observed.** That study did not measure muscle carnitine, receptor function, transcription, protein synthesis, hypertrophy, or testosterone response [24].
8. **Unknown.** Independent replication of the total receptor protein signal was not identified through the evidence cutoff.
9. **Unknown.** No controlled LCLT-by-testosterone study was identified through the evidence cutoff. Synergy, improved androgen sensitivity, and benefit during testosterone therapy are unestablished.

10. **Observed.** LCLT exercise studies report selected recovery-marker, symptom, imaging, or performance signals, but direct counterevidence includes no substrate-use or endurance benefit in 15 trained men, no change in fat, carbohydrate, or protein contribution in 20 active men, and no fat-oxidation effect in a 12-person crossover [22,26-28,47-49]. A carbohydrate-oxidation contrast observed in the six-man subgroup of the crossover is exploratory and does not establish a stable sex interaction [49].
11. **Observed.** In a 24-week pilot whose homogeneous analysis included 20 older women, the historical 1.5 g LCLT/day condition increased plasma free carnitine but did not improve muscle strength, body composition, or measured circulating markers [50]. The small sample and post-completion exclusions limit generalizability.
12. **Unknown.** Long-term safety and clinical consequences of person-variable microbial TMAO production remain incompletely characterized [31-38,52,53].
13. **Inferred.** The next defensible step is staged falsification: verify material, quantify exposure, demonstrate tissue uptake, replicate total receptor protein, measure receptor function, establish tissue function, and only then estimate a prespecified testosterone interaction.
14. **Inferred.** Current evidence supports a research program, not a clinical regimen or adjunct recommendation.

23. Claim-level evidence register

Generated view of the canonical claim register

Observed. This section is a generated human-readable view of the canonical 12-field machine-readable register. It reproduces all 32 stable claim identifiers and the exact proposition, label, primary-source description, authoritative identifier, key limitation, permitted wording, and falsifier or required test. Evidence grade, directness, population or system, and material or formulation remain explicit in the canonical CSV and are omitted from this view only to preserve readable page geometry.

Appendix table. Canonical claim register

Claim ID	Proposition	Label	Primary source and identifier	Key limitation and required test	Permitted wording
LCLT-R1-C001	Levocarnitine tartrate is registered as a 2:1 salt or solvate of stereochemically defined levocarnitine and L-tartrate, with formula C18H36N2O12 and molecular mass about 472.5 g/mol; FDA GSRS identifies levocarnitine as the active moiety.	Observed	PubChem CID 57349413; FDA GSRS record 4D8F2Q45LQ https://pubchem.ncbi.nlm.nih.gov/compound/57349413 | https://precision.fda.gov/ginas/app/ui/substances/91fd162a-a5e6-43c2-b1fa-fb31a0f7ba08	A registry identity does not verify hydration state, purity, counterion content, or composition of a tested lot. Required test: Orthogonal structure confirmation and a lot-specific certificate of analysis would be required to establish the identity of material actually tested.	The registered anhydrous 2:1 chemical identity has levocarnitine as its active moiety.
LCLT-R1-C002	Using registry molecular masses, the theoretical levocarnitine mass fraction of anhydrous 2:1 levocarnitine tartrate is approximately 68.23%.	Inferred	Calculation from PubChem and FDA GSRS registry identities: 2 x 161.20 / 472.5 https://pubchem.ncbi.nlm.nih.gov/compound/57349413 | https://precision.fda.gov/uniisearch/srs/unii/0G389FZZ9M	The value is theoretical and changes if the material contains water, impurities, a different salt ratio, or assay deviation. Required test: A validated lot assay that materially disagrees with the theoretical fraction would supersede the calculation for that lot.	Anhydrous 2:1 levocarnitine tartrate is approximately 68.23% levocarnitine by theoretical mass.
LCLT-R1-C003	The identity, purity, hydration state, stereochemical purity, and assayed levocarnitine content of the material discussed in the submitted source are not established by a lot-specific analytical record.	Unknown	Submitted source file SHA-256 d5a50bd7aa227e3f521a02abf200b93425faaa4438c0628daaea371d1fa7f55f; FDA GSRS identity boundary https://precision.fda.gov/ginas/app/ui/substances/91fd162a-a5e6-43c2-b1fa-fb31a0f7ba08	A generic ingredient name or registry entry cannot substitute for a certificate of analysis tied to the tested lot. Required test: A traceable certificate of analysis plus validated identity, purity, water, counterion, stereochemistry, and quantitative assay results would resolve the uncertainty.	Lot-specific composition is unknown in the source manuscript.

Claim ID	Proposition	Label	Primary source and identifier	Key limitation and required test	Permitted wording
LCLT-R1-C004	In six healthy participants receiving free L-carnitine, estimated oral bioavailability was 16% after 2 g and 5% after 6 g, with 24-hour urinary recovery of 8% and 4%, respectively.	Observed	Harper P, Elwin CE, Cederblad G. Eur J Clin Pharmacol. 1988;35:69-75. PMID:3220097. https://doi.org/10.1007/BF00555510	The study was very small, used free L-carnitine rather than LCLT, and does not establish a schedule or population-wide parameter. Required test: A replicated, adequately sampled, baseline-corrected LCLT mass-balance study could establish formulation-specific bioavailability.	Small free L-carnitine studies reported dose-dependent oral bioavailability spanning approximately 5% to 16%.
LCLT-R1-C005	In 15 healthy adult men at steady state, three prescription free-levocarnitine oral formulations were bioequivalent and had baseline-corrected absolute bioavailability near 15%.	Observed	Sahajwalla CG, Helton ED, Purich ED, Hoppel CL, Cabana BE. J Pharm Sci. 1995;84:627-633. https://doi.org/10.1002/jps.2600840520	The formulations were not LCLT; multiple dosing, baseline correction, and sponsor involvement constrain transfer to other products. Required test: A direct crossover comparison using analytically verified LCLT and the reference formulations would be required to claim equivalence.	Prescription oral free-levocarnitine formulations showed approximately 15% bioavailability in one small study.
LCLT-R1-C006	Two overlapping reports of a single 2 g liquid free-L-carnitine exposure in 12 healthy participants reported the same Tmax, Cmax, and AUC values but incompatible terminal half-life units: 60.3 ± 15.0 hours in 2009 and 60.3 ± 15.0 minutes in 2011.	Observed	Cao Y, Wang YX, Liu CJ, Wang LX, Han ZW, Wang CB. Clin Invest Med. 2009;32:E13-E19. PMID:19178874; Cao Y, Qu HJ, Li P, Wang CB, Wang LX, Han ZW. Tohoku J Exp Med. 2011;224:209-213. PMID:21701126. https://doi.org/10.25011/cim.v32i1.5082 | https://doi.org/10.1620/tjem.224.209	The reports concern free L-carnitine, overlap in investigators and quantitative data, and contain an unresolved hour-versus-minute unit conflict; neither value is a defensible LCLT parameter. Required test: A publisher correction or access to the underlying analysis plus a prespecified, baseline-aware, densely sampled LCLT pharmacokinetic study would resolve the unit conflict and test formulation transfer.	One small liquid free-L-carnitine study reported a Tmax of 3.4 ± 0.46 hours; its terminal half-life is unresolved because overlapping reports give incompatible units.

Claim ID	Proposition	Label	Primary source and identifier	Key limitation and required test	Permitted wording
LCLT-R1-C007	After brief intravenous free L-carnitine infusion in ten healthy participants, baseline-corrected data fit a three-compartment model with central volume 0.11 to 0.20 L/kg and terminal half-life 10 to 23 hours.	Observed	Uematsu T, Itaya T, Nishimoto M, et al. Eur J Clin Pharmacol. 1988;34:213-216. https://doi.org/10.1007/BF00614562	Intravenous disposition cannot be pooled with oral LCLT disposition, and the old small study does not support route escalation. Required test: A route-matched, formulation-specific study is required before comparing terminal phases across oral LCLT and intravenous levocarnitine.	Intravenous free L-carnitine displayed multicompartment disposition in a small healthy-volunteer study.
LCLT-R1-C008	Repeated oral free L-carnitine in seven healthy participants produced a plasma plateau above the lowest tested exposure and increased renal clearance, consistent with saturable tubular reabsorption.	Observed	Bain MA, Milne RW, Evans AM. J Clin Pharmacol. 2006;46:1163-1170. https://doi.org/10.1177/0091270006292851	The sample was very small, tested free L-carnitine, and cannot identify individual renal parameters or an optimal exposure. Required test: A baseline-corrected LCLT study with measured filtration, urinary recovery, secretion, and tubular reabsorption would be needed for quantitative prediction.	Renal handling of free L-carnitine is saturable, and higher oral exposure did not proportionally increase mean plasma concentration in this study.
LCLT-R1-C009	Human OCTN2, encoded by SLC22A5, is a sodium-dependent high-affinity carnitine transporter; kidney studies localize it to the apical tubular membrane and structural work confirms a carnitine and sodium transport mechanism.	Observed	Tamai I, China K, Sai Y, et al. Biochim Biophys Acta. 2001;1512:273-284; Davies JS, Zeng YC, Briot C, et al. Nat Commun. 2025;17:181. https://doi.org/10.1016/S0005-2736(01)00328-5 | https://doi.org/10.1038/s41467-025-66867-6	Transporter function does not establish tissue loading, pathway flux, or clinical benefit after oral LCLT. Required test: Direct tissue exposure, transporter dependency, and functional endpoints are required to connect oral LCLT to an outcome.	OCTN2 is an established high-affinity human carnitine transporter.
LCLT-R1-C010	The 2006 LCLT androgen-receptor study did not measure skeletal-muscle carnitine, so its plasma or nominal exposure cannot be treated as evidence of muscle loading.	Observed	Kraemer WJ, Spiering BA, Volek JS, et al. Med Sci Sports Exerc. 2006;38:1288-1296. https://doi.org/10.1249/01.mss.0000227314.85728.35	Absence of a tissue measurement does not prove that loading did not occur; it makes the link unobserved. Required test: A replicated trial with paired plasma and muscle free, total, and acylcarnitine measurements would test the missing link.	Skeletal-muscle carnitine was not measured in the pivotal androgen-receptor study.

Claim ID	Proposition	Label	Primary source and identifier	Key limitation and required test	Permitted wording
LCLT-R1-C011	During five hours of intravenous hypercarnitinemia in eight healthy men, high insulin was associated with increased skeletal-muscle total carnitine, whereas fasting insulin was not.	Observed	Stephens FB, Constantin-Teodosiu D, Laithwaite D, Simpson EJ, Greenhaff PL. FASEB J. 2006;20:377-379. https://doi.org/10.1096/fj.05-4985fje	This was an acute clamp-like intravenous context, not ordinary oral LCLT exposure, and it does not establish clinical benefit. Required test: An oral LCLT trial that measures insulin, plasma exposure, muscle carnitine, and transporter dependence would be required for transfer.	Human muscle carnitine uptake can be insulin-dependent under experimentally induced hypercarnitinemia.
LCLT-R1-C012	In 14 healthy men, skeletal-muscle total carnitine increased by 21% after 24 weeks of LCLT plus substantial carbohydrate. In an 11-person impaired-glucose-tolerance crossover, the primary Bruls report found no significant fasting-biopsy difference in free carnitine or acetylcarnitine, with p = 0.356 and p = 0.371, while magnetic resonance measurements showed enhanced afternoon and exercise-associated acetylcarnitine formation and metabolic flexibility. Chee et al. later characterized the Bruls total-pool values as a numeric increase of about 12%, from approximately 8.5 to 9.5 mmol/kg dry mass, but the primary report did not establish a statistically significant total-carnitine treatment effect.	Observed	Wall BT, Stephens FB, Constantin-Teodosiu D, et al. J Physiol. 2011;589:963-973. PMID:21224234; Bruls YMH, de Ligt M, Lindeboom L, et al. EBioMedicine. 2019;49:318-330. PMID:31676389; Chee C, Shannon CE, Burns A, et al. Aging Cell. 2021;20:e13303. PMID:33464721. https://doi.org/10.1113/jphysiol.2010.201343 | https://doi.org/10.1016/j.ebiom.2019.10.017 | https://doi.org/10.1111/acel.13303	Both studies were small and population specific. Wall included a substantial carbohydrate coexposure. Bruls involved impaired glucose tolerance, found no significant fasting-biopsy free-carnitine or acetylcarnitine difference, and did not establish a statistically significant total-carnitine effect in the primary report. The approximate 12% total-pool change is a later numeric characterization and must not be presented as a confirmed LCLT-alone loading effect. Required test: Independent formulation-verified trials with a prespecified direct total-muscle-carnitine endpoint in the target population, plus a factorial design where carbohydrate is a coexposure, would test reproducibility and the independent LCLT contribution.	Muscle total carnitine loading was demonstrated under a prolonged LCLT-plus-carbohydrate cointervention. An LCLT-alone crossover in impaired glucose tolerance altered time-dependent and exercise-associated acetylcarnitine formation and metabolic flexibility, but did not establish a statistically significant total-muscle-carnitine treatment effect.

Claim ID	Proposition	Label	Primary source and identifier	Key limitation and required test	Permitted wording
LCLT-R1-C013	Three months of high oral free L-carnitine in eight healthy men did not significantly increase skeletal-muscle carnitine or physical performance.	Observed	Wachter S, Vogt M, Kreis R, et al. Clin Chim Acta. 2002;318:51-61. https://doi.org/10.1016/S0009-8981(01)00804-X	The study was small and did not test LCLT or insulin-stimulating coexposure; a null result does not establish universal nonresponse. Required test: A larger randomized formulation-specific study with tissue assay precision sufficient to detect a prespecified change could test the result.	Oral free L-carnitine did not increase muscle carnitine in one small three-month study of healthy men.
LCLT-R1-C014	Three controlled LCLT studies provide direct counterbalancing exercise evidence: two trials in active or trained men found no improvement in exercise substrate contribution or endurance performance after two or four weeks, and a 12-person crossover found no fat-oxidation effect while a chronic-condition increase in carbohydrate oxidation appeared only in the six-man subgroup.	Observed	Broad EM, Maughan RJ, Galloway SDR. Int J Sport Nutr Exerc Metab. 2005;15:665-679. PMID:16521850; Broad EM, Maughan RJ, Galloway SDR. Int J Sport Nutr Exerc Metab. 2008;18:567-584. PMID:19164828; Abramowicz WN, Galloway SDR. Int J Sport Nutr Exerc Metab. 2005;15:386-400. PMID:16286670. https://doi.org/10.1123/ijsnem.15.6.665 | https://doi.org/10.1123/ijsnem.18.6.567 | https://doi.org/10.1123/ijsnem.15.4.386	The trials were small and context specific. The Abramowicz male-subgroup contrast involved six men and does not establish a stable sex interaction, performance benefit, or general metabolic effect. Required test: Independent, adequately powered trials with verified material, tissue exposure, prespecified performance endpoints, a formal sex-interaction test, and multiplicity control would be required to support a performance claim.	Short controlled LCLT trials show null or mixed exercise-metabolism results and do not support a general increase in fat oxidation or endurance performance.
LCLT-R1-C015	Several controlled LCLT studies reported changes in post-exercise soreness, creatine kinase, magnetic-resonance disruption area, or strength and power recovery after a standardized challenge.	Observed	Volek JS, Kraemer WJ, Rubin MR, et al. Am J Physiol Endocrinol Metab. 2002;282:E474-E482; Ho JY, Kraemer WJ, Volek JS, et al. Metabolism. 2010;59:1190-1199; Stefan M, Sharp M, Gheith R, et al. Nutrients. 2021;13:3432. https://doi.org/10.1152/ajpendo.00277.2001 | https://doi.org/10.1016/j.metabol.2009.11.012 | https://doi.org/10.3390/nu13103432	Endpoints, exercise challenges, populations, washouts, and analyses differ; biomarker changes are not proof of faster tissue repair or clinical recovery. Required test: Independent replication with preregistered functional endpoints, adequate washout, blinded analysis, and direct tissue measures could strengthen or refute the signal.	Some LCLT trials reported favorable recovery-related biomarkers or performance retention under specific exercise-challenge conditions.

Claim ID	Proposition	Label	Primary source and identifier	Key limitation and required test	Permitted wording
LCLT-R1-C016	Positive LCLT recovery evidence is partly concentrated in overlapping investigator networks, and the 2021 trial was funded by Lonza with two Lonza employees as authors.	Observed	Volek et al. 2002; Ho et al. 2010; Stefan et al. 2021 conflict-of-interest statement https://doi.org/10.1152/ajpendo.00277.2001 | https://doi.org/10.1016/j.metabol.2009.11.012 | https://doi.org/10.3390/nu13103432	Investigator or sponsor clustering does not invalidate a result; it changes the confidence assigned before independent replication. Required test: Independent multisite replication with sponsor-independent analysis and complete protocol, data, and adverse-event reporting would reduce this uncertainty.	The positive recovery literature includes overlapping research groups and disclosed commercial involvement.
LCLT-R1-C017	In a 24-week double-blind pilot, 28 older adults were enrolled, 22 protocol-compliant participants completed, and the homogeneous analysis included 20 older women; LCLT increased plasma free carnitine but did not materially change body composition, muscle strength, or the reported circulating markers.	Observed	Sawicka AK, Hartmane D, Lipinska P, et al. Nutrients. 2018;10:255. PMID:29473908. https://doi.org/10.3390/nu10020255	The pilot was small and population specific, and the homogeneous analysis followed two post-completion exclusions, so it cannot establish absence of effect in other populations. Required test: A larger preregistered trial with validated composition and strength endpoints, prespecified analysis populations, and complete attrition handling could test whether a clinically meaningful effect was missed.	A small 24-week LCLT pilot did not demonstrate improved body composition or muscle strength in the analyzed older-women group.

Claim ID	Proposition	Label	Primary source and identifier	Key limitation and required test	Permitted wording
LCLT-R1-C018	In a randomized crossover study of ten young resistance-trained men, 21 days of LCLT was associated with higher preexercise skeletal-muscle total androgen-receptor protein than placebo, reported as 12.9 ± 5.9 versus 11.2 ± 4.0 arbitrary units. The indexed abstract gives these endpoint values without naming their dispersion measure. The corrigendum replaces Figure 2, whose corrected caption explicitly describes plotted values as means ± SE.	Observed	Kraemer WJ, Spiering BA, Volek JS, et al. Med Sci Sports Exerc. 2006;38:1288-1296. PMID:16826026; Corrigendum. Med Sci Sports Exerc. 2006;38(10):1861. DOI:10.1249/01.mss.0000240847.43553.73. https://doi.org/10.1249/01.mss.0000227314.85728.35 | https://doi.org/10.1249/01.mss.0000240847.43553.73 | https://pubmed.ncbi.nlm.nih.gov/16826026/	The study was small and unreplicated, used a seven-day washout, and reported arbitrary-unit total protein. The corrected Figure 2 values are marginal means ± SE, but within-person covariance and paired-difference variance are unavailable, so the paired standard error and confidence interval cannot be reconstructed. Required test: Independent replication with adequate washout, prespecified primary analysis, participant-level paired data, paired effect uncertainty, assay validation, and full reporting could confirm or refute the signal.	One small crossover study reported a higher total androgen-receptor protein signal during LCLT than placebo; the corrected marginal SEs do not identify paired uncertainty.
LCLT-R1-C019	Total androgen-receptor protein abundance is not equivalent to ligand occupancy, nuclear localization, DNA binding, co-regulator recruitment, target-gene transcription, muscle protein synthesis, or hypertrophy.	Observed	Kraemer et al. 2006; Bergamasco JGA, Scarpelli MC, Godwin JS, et al. Med Sci Sports Exerc. 2024;56:2146-2155. https://doi.org/10.1249/01.mss.0000227314.85728.35 | https://doi.org/10.1249/MSS.0000000000003509	Later exercise studies do not directly test LCLT, but they demonstrate that receptor compartments, DNA binding, and hypertrophy are separable endpoints. Required test: A mechanistic trial measuring receptor localization, ligand occupancy, chromatin binding, target transcription, protein synthesis, and hypertrophy with dependency tests would bridge the claim.	The LCLT study measured total androgen-receptor protein only, not receptor function or muscle growth.

Claim ID	Proposition	Label	Primary source and identifier	Key limitation and required test	Permitted wording
LCLT-R1-C020	No controlled study directly testing an LCLT-by-prescribed-testosterone interaction was identified through 30 July 2026.	Unknown	Curated PubMed and ClinicalTrials.gov searches through the evidence cutoff https://pubmed.ncbi.nlm.nih.gov/?term=%28L-carnitine+L-tartrate+OR+LCLT%29+AND+%28testosterone+therapy+OR+testosterone+replacement%29 | https://clinicaltrials.gov/search?term=%22L-carnitine%20L-tartrate%22%20testosterone	Failure to identify a study is not proof that none exists, and related carnitine formulations or comparator trials do not answer the interaction question. Required test: A registered, adequately powered 2 x 2 factorial trial using verified LCLT and prescribed testosterone would resolve the direct evidence gap.	A controlled LCLT-by-testosterone interaction study was not identified through the evidence cutoff.
LCLT-R1-C021	Published carnitine-and-testosterone studies located in the search used carnitine formulations as comparators to testosterone or combined free L-carnitine with tadalafil; they did not test LCLT as an adjunct to testosterone.	Observed	Cavallini G, Caracciolo S, Vitali G, Modenini F, Biagiotti G. Urology. 2004;63:641-646; Zhang et al. Zhonghua Nan Ke Xue. 2014;20:95-99. https://doi.org/10.1016/j.urology.2003.11.009 | https://pubmed.ncbi.nlm.nih.gov/24520664/	Different formulations, endpoints, and comparator structures cannot establish adjunct efficacy or synergy. Required test: Only a direct factorial adjunct trial with clinically relevant endpoints can estimate the interaction.	Related trials are comparator evidence, not evidence that LCLT augments testosterone therapy.
LCLT-R1-C022	For a prespecified endpoint on an additive scale, a possible LCLT-by-testosterone interaction can be defined by the four-cell contrast in Equation 9; the existing evidence does not estimate this contrast.	Hypothesized	VanderWeele TJ, Knol MJ. Epidemiol Methods. 2014;3:33-72; current evidence map gap analysis https://doi.org/10.1515/em-2013-0005	Interaction depends on endpoint, time, population, exposure, and effect scale; the contrast is not a universal synergy coefficient. Required test: Estimate all four randomized cell means with prespecified timing, exposure confirmation, confidence intervals, multiplicity control, and a functional endpoint.	Testosterone relevance is an unresolved factorial research hypothesis, not demonstrated synergy.
LCLT-R1-C023	Repeated oral free L-carnitine increased plasma trimethylamine and, at the highest tested exposure, markedly increased mean plasma TMAO with substantial between-person variability in seven healthy participants.	Observed	Bain MA, Milne RW, Evans AM. J Clin Pharmacol. 2006;46:1163-1170. https://doi.org/10.1177/0091270006292851	This was a very small free-L-carnitine study; TMAO elevation alone does not establish cardiovascular benefit or harm. Required test: A larger LCLT mass-balance study with microbiome, isotope tracing, kidney function, diet control, and clinical follow-up would quantify the pathway.	Oral carnitine can increase TMA and TMAO, with large person-to-person variability.

Claim ID	Proposition	Label	Primary source and identifier	Key limitation and required test	Permitted wording
LCLT-R1-C024	Human TMAO production from carnitine is microbiome-dependent and heterogeneous; recent human challenge work associates the microbial gbu gene cluster with high-producer status.	Observed	Koeth RA, Wang Z, Levison BS, et al. Nat Med. 2013;19:576-585; Wu WK, Lo YL, Chiu JY, et al. Gut Microbes. 2025;17:2446374, with correction. https://doi.org/10.1038/nm.3145 | https://doi.org/10.1080/19490976.2024.2446374 | https://doi.org/10.1080/19490976.2025.2457204	Associations between producer phenotype and genes do not prove that LCLT causes cardiovascular events, and kidney function strongly affects circulating TMAO. Required test: Prospective LCLT studies with metagenomics, isotope tracing, measured GFR, standardized diet, and adjudicated outcomes would test clinical relevance.	Carnitine-derived TMAO production varies materially with host microbiome and renal context.
LCLT-R1-C025	In 157 participants with metabolic syndrome, six months of free L-carnitine did not change the primary carotid total-plaque-volume outcome versus placebo, while a greater stenosis increase was reported as a secondary finding.	Observed	Johri AM, Hetu MF, Heyland DK, et al. Nutr Metab (Lond). 2022;19:26. https://doi.org/10.1186/s12986-022-00661-9	The primary endpoint was null, the stenosis result was secondary, and the formulation and population differ from healthy LCLT studies; neither proof of safety nor proof of harm follows. Required test: Replication with prespecified vascular endpoints, verified formulation, TMAO phenotyping, renal stratification, and longer follow-up is required.	A randomized trial found no difference in its primary plaque-volume outcome and reported a concerning secondary stenosis signal.
LCLT-R1-C026	A three-week crossover study in ten healthy active men found no statistically significant LCLT-versus-placebo differences in the measured hematology and clinical chemistry panel.	Observed	Rubin MR, Volek JS, Gomez AL, et al. J Strength Cond Res. 2001;15:486-490. https://doi.org/10.1519/1533-4287(2001)015%3C0486:SMOLCL%3E2.0.CO;2	The study was small, short, and limited to selected laboratory variables; it cannot establish long-term safety, rare events, or safety in vulnerable populations. Required test: Longer independent studies with prospective adverse-event capture, vulnerable-population exclusions, and prespecified renal, neurologic, immune, and cardiovascular measures are required.	No differences were detected in selected short-term laboratory safety measures in one small healthy-male LCLT study.

Claim ID	Proposition	Label	Primary source and identifier	Key limitation and required test	Permitted wording
LCLT-R1-C027	Current prescription levocarnitine labeling reports gastrointestinal complaints, body odor, seizures, and hypersensitivity reactions from clinical or postmarketing experience.	Observed	DailyMed levocarnitine oral solution label, Rising Pharma, revised July 2025 https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=ada35959-e317-4161-ae79-3475096c679f	Voluntary reports cannot establish incidence or causality, route matters for serious hypersensitivity reports, and direct transfer from prescription levocarnitine to LCLT is uncertain. Required test: Formulation-specific prospective LCLT safety surveillance with denominator data and event adjudication would quantify incidence and causality.	Levocarnitine labeling identifies gastrointestinal, odor, seizure, and hypersensitivity safety signals that should not be omitted from a bounded safety discussion.
LCLT-R1-C028	Prescription levocarnitine labeling states that oral safety and efficacy have not been evaluated in renal insufficiency and warns that chronic high exposure in severe renal impairment or dialysis may accumulate TMA and TMAO.	Observed	DailyMed levocarnitine oral solution label, Rising Pharma, revised July 2025, Precautions https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=ada35959-e317-4161-ae79-3475096c679f	The label warning does not quantify LCLT risk and should not be converted into a universal contraindication or an individualized prediction. Required test: A dedicated LCLT pharmacokinetic and safety study stratified by measured GFR, with TMA and TMAO endpoints, would resolve formulation-specific risk.	Renal impairment is a material uncertainty because carnitine-derived metabolites are renally cleared.
LCLT-R1-C029	Prescription levocarnitine labeling records reports of increased INR with warfarin and calls for clinical monitoring when levocarnitine is initiated or changed.	Observed	DailyMed levocarnitine oral solution label, Rising Pharma, revised July 2025, Drug Interactions https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=ada35959-e317-4161-ae79-3475096c679f	The report does not establish incidence, mechanism, or direct LCLT equivalence; this publication provides no patient-specific instruction. Required test: A controlled interaction study or robust pharmacovigilance analysis with formulation identity and confounder control would quantify the association.	Warfarin-associated INR elevation is a labeled levocarnitine interaction signal and a relevant uncertainty for LCLT translation.

Claim ID	Proposition	Label	Primary source and identifier	Key limitation and required test	Permitted wording
LCLT-R1-C030	FDA-regulated prescription levocarnitine oral solution is indicated for primary systemic carnitine deficiency and certain secondary deficiencies caused by inborn errors of metabolism.	Observed	DailyMed levocarnitine oral solution label, Rising Pharma, revised July 2025, Indications and Usage https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=ada35959-e317-4161-ae79-3475096c679f	Drug approval for defined deficiencies does not establish that LCLT treats healthy adults, improves exercise outcomes, or augments testosterone therapy. Required test: Any new therapeutic claim requires direct evidence and the applicable regulatory authorization for that product, population, and indication.	Prescription levocarnitine has specific deficiency indications that are separate from LCLT supplement claims.
LCLT-R1-C031	FDA's no-questions response to GRAS Notice 993 concerns a notified LCLT use in specified term-infant formula at the stated maximum level; it is not drug approval or an efficacy determination.	Observed	FDA GRAS Notice 993 inventory and response letter https://hfpappexternal.fda.gov/scripts/fdcc/index.cfm?id=993&set=GRASNotices	GRAS conclusions are condition-specific and do not establish safety for unrelated adult exposures, therapeutic use, or clinical efficacy. Required test: A claim outside the notified conditions requires its own applicable safety, efficacy, and regulatory basis.	GRN 993 is a narrow food-ingredient review under its notified conditions, not evidence of adult therapeutic efficacy.
LCLT-R1-C032	Three retracted L-carnitine reproductive studies were excluded from positive evidence; their original DOIs are 10.1016/j.ejogrb.2014.06.008, 10.1002/ijgo.12902, and 10.1080/09513590.2019.1576622.	Observed	Publisher retraction records linked to the three original articles. https://doi.org/10.1016/j.ejogrb.2023.09.028 | https://doi.org/10.1002/ijgo.14995 | https://doi.org/10.1080/09513590.2024.2419767	Retraction exclusion does not imply that all reproductive evidence is invalid; it prevents withdrawn findings from supporting this publication. Required test: Future revisions must repeat PubMed and publisher correction-status checks before any excluded record can be reconsidered.	Three retracted reproductive studies were excluded from positive evidence.

24. References

1. Schmidbaur H, Schier A, Bayler A. The solution and solid state structure of L-carnitine L-tartrate. Z Naturforsch B. 1998;53(8):788-791. doi:10.1515/znb-1998-0802.

2. National Center for Biotechnology Information. PubChem Compound Summary for CID 57349413, L-carnitine tartrate. National Library of Medicine. Accessed 30 July 2026. https://pubchem.ncbi.nlm.nih.gov/compound/57349413.

3. US Food and Drug Administration. GRAS Notice No. 993: L-carnitine L-tartrate. FDA GRAS Notice Inventory. 2021. Accessed 30 July 2026. https://hfpappexternal.fda.gov/scripts/fdcc/index.cfm?id=993&set=GRASNotices.

4. European Food Safety Authority. Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food on L-carnitine L-tartrate for use in foods for particular nutritional uses. EFSA Journal. 2003;1(12):19. doi:10.2903/j.efsa.2003.19.

5. European Commission. Commission Regulation (EU) 2021/77 of 27 January 2021 refusing to authorise certain health claims made on foods. Official Journal of the European Union. 2021. https://eur-lex.europa.eu/eli/reg/2021/77/oj/eng.

6. DailyMed. Levocarnitine oral solution: prescribing information. US National Library of Medicine. Updated 17 July 2025. Accessed 30 July 2026. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=ada35959-e317-4161-ae79-3475096c679f.

7. Harper P, Elwin CE, Cederblad G. Pharmacokinetics of bolus intravenous and oral doses of L-carnitine in healthy subjects. Eur J Clin Pharmacol. 1988;35(1):69-75. PMID:3220097. doi:10.1007/BF00555510.

8. Rebouche CJ. Quantitative estimation of absorption and degradation of a carnitine supplement by human adults. Metabolism. 1991;40(12):1305-1310. PMID:1961125. doi:10.1016/0026-0495(91)90033-S.

9. Cao Y, Wang YX, Liu CJ, Wang LX, Han ZW, Wang CB. Comparison of pharmacokinetics of L-carnitine, acetyl-L-carnitine and propionyl-L-carnitine after single oral administration of L-carnitine in healthy volunteers. Clin Invest Med. 2009;32(1):E13-E19. PMID:19178874. doi:10.25011/cim.v32i1.5082.

10. Bain MA, Milne RW, Evans AM. Disposition and metabolite kinetics of oral L-carnitine in humans. J Clin Pharmacol. 2006;46(10):1163-1170. PMID:16988205. doi:10.1177/00912700006292851.

11. Krims-Davis K, Ozola M, Razzivina V, Gukalova B, Konrade I, Dambrova M, Liepinsh E. Low bioavailability and high TMAO production: novel insights into acetylcarnitine and carnitine metabolism. Mol Nutr Food Res. 2025;69(24):e70316. PMID:41243468. doi:10.1002/mnfr.70316.

12. Tamai I, Ohashi R, Nezu J, et al. Molecular and functional identification of sodium ion-dependent, high affinity human carnitine transporter OCTN2. J Biol Chem. 1998;273(32):20378-20382. PMID:9685390. doi:10.1074/jbc.273.32.20378.

13. Tamai I, China K, Sai Y, Kobayashi D, Nezu J, Kawahara E, Tsuji A. Na(+)-coupled transport of L-carnitine via high-affinity carnitine transporter OCTN2 and its subcellular localization in kidney. Biochim Biophys Acta. 2001;1512(2):273-284. PMID:11406104. doi:10.1016/S0005-2736(01)00328-5.

14. Rebouche CJ. Kinetics, pharmacokinetics, and regulation of L-carnitine and acetyl-L-carnitine metabolism. Ann N Y Acad Sci. 2004;1033:30-41. PMID:15591001. doi:10.1196/annals.1320.003.

15. Stephens FB, Constantin-Teodosiu D, Laithwaite D, Simpson EJ, Greenhaff PL. Insulin stimulates L-carnitine accumulation in human skeletal muscle. FASEB J. 2006;20(2):377-379. PMID:16368715. doi:10.1096/fj.05-4985fje.

16. Wall BT, Stephens FB, Constantin-Teodosiu D, Marimuthu K, Macdonald IA, Greenhaff PL. Chronic oral ingestion of L-carnitine and carbohydrate increases muscle carnitine content and alters muscle fuel metabolism during exercise in humans. J Physiol. 2011;589(Pt 4):963-973. PMID:21224234. doi:10.1113/jphysiol.2010.201343.

17. Stephens FB, Wall BT, Marimuthu K, et al. Skeletal muscle carnitine loading increases energy expenditure, modulates fuel metabolism gene networks and prevents body fat accumulation in humans. J Physiol. 2013;591(18):4655-4666. PMID:23818692. doi:10.1113/jphysiol.2013.255364.

18. Bruls YMH, de Ligt M, Lindeboom L, et al. Carnitine supplementation improves metabolic flexibility and skeletal muscle acetylcarnitine formation in volunteers with impaired glucose tolerance: a randomised controlled trial. EBioMedicine. 2019;49:318-330. PMID:31676389. doi:10.1016/j.ebiom.2019.10.017.

19. Chee C, Shannon CE, Burns A, et al. Increasing skeletal muscle carnitine content in older individuals increases whole-body fat oxidation during moderate-intensity exercise. Aging Cell. 2021;20(2):e13303. PMID:33464721. doi:10.1111/acel.13303.

20. Ren J, Lakoski S, Haller RG, Sherry AD, Malloy CR. Dynamic monitoring of carnitine and acetylcarnitine in the trimethylamine signal after exercise in human skeletal muscle by 7T proton magnetic resonance spectroscopy. Magn Reson Med. 2013;69(1):7-17. PMID:22473634. doi:10.1002/mrm.24249.

21. Houten SM, Violante S, Ventura FV, Wanders RJA. The biochemistry and physiology of mitochondrial fatty acid beta-oxidation and its genetic disorders. Annu Rev Physiol. 2016;78:23-44. PMID:26828774. doi:10.1146/annurev-physiol-021115-105045.

22. Volek JS, Kraemer WJ, Rubin MR, Gomez AL, Ratamess NA, Gaynor P. L-carnitine L-tartrate supplementation favorably affects markers of recovery from exercise stress. Am J Physiol Endocrinol Metab. 2002;282(2):E474-E482. PMID:11788381. doi:10.1152/ajpendo.00277.2001.

23. Kraemer WJ, Volek JS, French DN, et al. The effects of L-carnitine L-tartrate supplementation on hormonal responses to resistance exercise and recovery. J Strength Cond Res. 2003;17(3):455-462. PMID:12930169. https://pubmed.ncbi.nlm.nih.gov/12930169/.

24. Kraemer WJ, Spiering BA, Volek JS, et al. Androgenic responses to resistance exercise: effects of feeding and L-carnitine. Med Sci Sports Exerc. 2006;38(7):1288-1296. PMID:16826026. doi:10.1249/01.mss.0000227314.85728.35.

25. Corrigendum. Med Sci Sports Exerc. 2006;38(10):1861. doi:10.1249/01.mss.0000240847.43553.73. Correction to: Kraemer WJ, et al. Androgenic responses to resistance exercise: effects of feeding and L-carnitine [24].

26. Spiering BA, Kraemer WJ, Vingren JL, et al. Responses of criterion variables to different supplemental doses of L-carnitine L-tartrate. J Strength Cond Res. 2007;21(1):259-264. PMID:17313301. doi:10.1519/00124278-200702000-00046.

27. Ho JY, Kraemer WJ, Volek JS, et al. L-carnitine L-tartrate supplementation favorably affects biochemical markers of recovery from physical exertion in middle-aged men and women. Metabolism. 2010;59(8):1190-1199. PMID:20045157. doi:10.1016/j.metabol.2009.11.012.

28. Stefan M, Sharp M, Gheith R, et al. L-carnitine tartrate supplementation for 5 weeks improves exercise recovery in men and women: a randomized, double-blind, placebo-controlled trial. Nutrients. 2021;13(10):3432. PMID:34684429. doi:10.3390/nu13103432.

29. Rubin MR, Volek JS, Gomez AL, Ratamess NA, French DN, Sharman MJ, Kraemer WJ. Safety measures of L-carnitine L-tartrate supplementation in healthy men. J Strength Cond Res. 2001;15(4):486-490. PMID:11726261. https://pubmed.ncbi.nlm.nih.gov/11726261/.

30. Villani RG, Gannon J, Self M, Rich PA. L-carnitine supplementation combined with aerobic training does not promote weight loss in moderately obese women. Int J Sport Nutr Exerc Metab. 2000;10(2):199-207. PMID:10861338. doi:10.1123/ijsnem.10.2.199.

31. Koeth RA, Wang Z, Levison BS, et al. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. Nat Med. 2013;19(5):576-585. PMID:23563705. doi:10.1038/nm.3145.

32. Zhu Y, Jameson E, Crosatti M, et al. Carnitine metabolism to trimethylamine by an unusual Rieske-type oxygenase from human microbiota. Proc Natl Acad Sci U S A. 2014;111(11):4268-4273. PMID:24591617. doi:10.1073/pnas.1316569111.

33. Koeth RA, Levison BS, Culley MK, et al. Gamma-butyrobetaine is a proatherogenic intermediate in gut microbial metabolism of L-carnitine to TMAO. Cell Metab. 2014;20(5):799-812. PMID:25440057. doi:10.1016/j.cmet.2014.10.006.

34. Samulak JJ, Sawicka AK, Hartmane D, et al. L-carnitine supplementation increases trimethylamine-N-oxide but not markers of atherosclerosis in healthy aged women. Ann Nutr Metab. 2019;74(1):11-17. PMID:30485835. doi:10.1159/000495037.

35. Olek RA, Samulak JJ, Sawicka AK, et al. Increased trimethylamine N-oxide is not associated with oxidative stress markers in healthy aged women. Oxid Med Cell Longev. 2019;2019:6247169. PMID:31636806. doi:10.1155/2019/6247169.

36. Olek RA, Samborowska E, Wisniewski P, Wojtkiewicz P, Wochna K, Zielinski J. Effect of a 3-month L-carnitine supplementation and resistance training program on circulating markers and bone mineral density in postmenopausal women: a randomized controlled trial. Nutr Metab (Lond). 2023;20(1):32. PMID:37533033. doi:10.1186/s12986-023-00752-1.

37. Haarhuis JE, Ahn-Jarvis J, Savva GM, et al. Effect of a polyphenol-rich pomegranate extract on plasma trimethylamine N-oxide levels following an oral carnitine challenge: a randomized controlled crossover trial in healthy adults. Front Nutr. 2026;13:1822840. PMID:42293209. doi:10.3389/fnut.2026.1822840.

38. Johri AM, Hetu MF, Heyland DK, et al. Progression of atherosclerosis with carnitine supplementation: a randomized controlled trial in the metabolic syndrome. Nutr Metab. 2022;19(1):26. PMID:35366920. doi:10.1186/s12986-022-00661-9.

39. Cavallini G, Caracciolo S, Vitali G, Modenini F, Biagiotti G. Carnitine versus androgen administration in the treatment of sexual dysfunction, depressed mood, and fatigue associated with male aging. Urology. 2004;63(4):641-646. PMID:15072869. doi:10.1016/j.urology.2003.11.009.

40. Sigman M, Glass S, Campagnone J, Pryor JL. Carnitine for the treatment of idiopathic asthenospermia: a randomized, double-blind, placebo-controlled trial. Fertil Steril. 2006;85(5):1409-1414. PMID:16600222. doi:10.1016/j.fertnstert.2005.10.055.

41. Benvenga S, Ruggeri RM, Russo A, Lapa D, Campenni A, Trimarchi F. Usefulness of L-carnitine, a naturally occurring peripheral antagonist of thyroid hormone action, in iatrogenic hyperthyroidism: a randomized, double-blind, placebo-controlled clinical trial. J Clin Endocrinol Metab. 2001;86(8):3579-3594. PMID:11502782. doi:10.1210/jcem.86.8.7747.

42. Melegh B, Kerner J, Bieber LL. Pivampicillin-promoted excretion of pivaloylcarnitine in humans. Biochem Pharmacol. 1987;36(20):3405-3409. PMID:3675603. doi:10.1016/0006-2952(87)90318-2.

43. Davey RA, Grossmann M. Androgen receptor structure, function and biology: from bench to bedside. Clin Biochem Rev. 2016;37(1):3-15. PMID:27057074. https://pubmed.ncbi.nlm.nih.gov/27057074/.

44. Cao Y, Qu HJ, Li P, Wang CB, Wang LX, Han ZW. Single dose administration of L-carnitine improves antioxidant activities in healthy subjects. Tohoku J Exp Med. 2011;224(3):209-213. PMID:21701126. doi:10.1620/tjem.224.209.

45. Balercia G, Regoli F, Armeni T, et al. Placebo-controlled double-blind randomized trial on the use of L-carnitine, L-acetylcarnitine, or combined L-carnitine and L-acetylcarnitine in men with idiopathic asthenozoospermia. Fertil Steril. 2005;84(3):662-671. PMID:16169400. doi:10.1016/j.fertnstert.2005.03.064.

46. Lenzi A, Sgro P, Salacone P, et al. A placebo-controlled double-blind randomized trial of the use of combined L-carnitine and L-acetylcarnitine treatment in men with asthenozoospermia. Fertil Steril. 2004;81(6):1578-1584. PMID:15193480. doi:10.1016/j.fertnstert.2003.10.034.

47. Broad EM, Maughan RJ, Galloway SDR. Effects of four weeks L-carnitine L-tartrate ingestion on substrate utilization during prolonged exercise. Int J Sport Nutr Exerc Metab. 2005;15(6):665-679. PMID:16521850. doi:10.1123/ijsnem.15.6.665.

48. Broad EM, Maughan RJ, Galloway SDR. Carbohydrate, protein, and fat metabolism during exercise after oral carnitine supplementation in humans. Int J Sport Nutr Exerc Metab. 2008;18(6):567-584. PMID:19164828. doi:10.1123/ijsnem.18.6.567.

49. Abramowicz WN, Galloway SDR. Effects of acute versus chronic L-carnitine L-tartrate supplementation on metabolic responses to steady state exercise in males and females. Int J Sport Nutr Exerc Metab. 2005;15(4):386-400. PMID:16286670. doi:10.1123/ijsnem.15.4.386.

50. Sawicka AK, Hartmane D, Lipinska P, et al. L-carnitine supplementation in older women: a pilot study on aging skeletal muscle mass and function. Nutrients. 2018;10(2):255. PMID:29473908. doi:10.3390/nu10020255.

51. Sahajwalla CG, Helton ED, Purich ED, Hoppel CL, Cabana BE. Multiple-dose pharmacokinetics and bioequivalence of L-carnitine 330-mg tablet versus 1-g chewable tablet versus enteral solution in healthy adult male volunteers. J Pharm Sci. 1995;84(5):627-633. PMID:7658356. doi:10.1002/jps.2600840520.

52. Wu WK, Lo YL, Chiu JY, et al. Gut microbes with the gbu genes determine TMAO production from L-carnitine intake and serve as a biomarker for precision nutrition. Gut Microbes. 2025;17(1):2446374. PMID:39722590. doi:10.1080/19490976.2024.2446374.

53. Correction. Gut Microbes. 2025;17(1):2457204. doi:10.1080/19490976.2025.2457204. Correction to: Wu WK, et al. Gut microbes with the gbu genes determine TMAO production from L-carnitine intake and serve as a biomarker for precision nutrition [52].

25. Appendices

Appendix A. Search log

Search completion date: 30 July 2026

Databases and official sources searched:

- PubMed and PubMed Central;
- publisher pages and Crossref;
- ClinicalTrials.gov;
- PubChem;
- DailyMed;
- FDA GRAS Notice Inventory;
- EFSA records;
- EUR-Lex;
- PubMed correction and retraction links;
- DOI and title searches for errata, expressions of concern, and retractions.

Core material queries:

- "L-carnitine L-tartrate" OR "carnitine tartrate";
- "levocarnitine" AND pharmacokinetics;
- "L-carnitine" AND bioavailability AND human;
- "L-carnitine L-tartrate" AND muscle carnitine;
- "L-carnitine L-tartrate" AND substrate utilization;
- "L-carnitine L-tartrate" AND carbohydrate AND protein AND fat metabolism;
- "L-carnitine L-tartrate" AND older women AND muscle strength;
- "L-carnitine L-tartrate" AND bioavailability AND comparator;
- "L-carnitine L-tartrate" AND tartrate AND androgen receptor;
- "L-carnitine L-tartrate" AND androgen receptor;
- "carnitine" AND OCTN2 AND renal;
- "L-carnitine" AND TMAO AND trial;
- "gbu" AND "oral carnitine challenge" AND TMAO;
- "L-carnitine" AND bioavailability AND "15 healthy volunteers";
- "L-carnitine L-tartrate" AND safety;
- "L-carnitine L-tartrate" AND testosterone;
- "L-carnitine L-tartrate" AND testosterone therapy;
- "L-carnitine L-tartrate" AND fertility;
- "Androgenic responses to resistance exercise" AND erratum;
- "10.1249/01.mss.0000240847.43553.73";
- "10.1080/19490976.2024.2446374" AND correction.

Formulation expansion queries:

- "acetyl-L-carnitine" AND testosterone;
- "propionyl-L-carnitine" AND testosterone;
- "carnitine" AND idiopathic asthenospermia AND randomized;
- "levocarnitine" AND warfarin;
- "levocarnitine" AND seizure;
- "levocarnitine" AND renal impairment AND TMAO;
- "L-carnitine" AND thyroid hormone antagonist;
- "pivaloylcarnitine" AND human.

Eligibility logic:

- Human primary studies were prioritized for exposure, tissue, exercise, receptor, safety, and clinical claims.
- Official records were used for identity, approved indications, labeling, notified uses, and regulatory claim status.
- Animal and cell studies were used only to define a mechanism or falsifier and were not used to claim human efficacy.
- Free levocarnitine, prescription products, ALCAR, PLCAR, and mixed products were retained only with explicit formulation labels.
- Combination interventions were not attributed to LCLT alone.
- Retracted records were excluded from positive synthesis.
- Duplicate or near-duplicate pharmacokinetic reports were not counted as independent evidence.

Negative search results stated with bounded language:

- No controlled LCLT-by-testosterone study was identified through the evidence cutoff.
- No independent replication of the pivotal preexercise skeletal muscle total androgen receptor protein result was identified through the evidence cutoff.
- No LCLT-specific randomized male-fertility trial was identified through the evidence cutoff.
- No human study demonstrating superior oral bioavailability of LCLT versus free levocarnitine was identified through the evidence cutoff.

Search limitation: This was a targeted curated search, not an exhaustive systematic review. An exhaustive systematic-review design would require prospective protocol registration, broader database and regional coverage, trial-registry mirrors, conference proceedings, regulatory submissions, and dual-reviewer screening.

Appendix B. Source correction and exclusion log

Appendix table. Source correction log

Source-manuscript proposition or risk	Revision 1 correction
Title implied an established pharmacological chain and practical testosterone relevance	Replaced with a critical evidence-map title and an explicitly unresolved hypothesis
LCLT content treated as a simple product potency	Recalculated ideal anhydrous fraction as 0.682342, or 68.23% at two decimals, and separated it from lot assay
Product identity inferred from label	Added stereochemistry, stoichiometry, hydration, purity, impurity, stability, and chain-of-custody requirements
Superior stability, crystallinity, and handling versus free levocarnitine asserted from generic material description	Removed as an established comparative claim; a solid-state description was separated from lot-specific stability and from direct matched tests of storage, processability, or handling performance
LCLT assumed to have superior bioavailability	Removed; no qualifying human superiority study was identified
Free levocarnitine PK generalized to LCLT	All PK records labeled by formulation and route
Narrow universal bioavailability percentage	Replaced with formulation-specific values and study descriptors
Approximate 3.4-hour peak treated as general	Restricted to one 12-person liquid free-levocarnitine study [9]
Half-life values combined	Not pooled because the records and models are incompatible
More than 95% of absorbed carnitine claimed to appear in urine	Removed; filtration, reabsorption, secretion, urinary recovery, nonabsorption, and microbial loss separated
OCTN1 treated as primary high-affinity transporter	Corrected to OCTN2/SLC22A5 for high-affinity levocarnitine transport [12,13]
Carnitine called an enzyme cofactor	Corrected to transported substrate and acyl-group acceptor
Established physiology converted into supplement efficacy	Added muscle uptake, flux, malonyl-CoA, redox, substrate, and tissue-state gates
Muscle carnitine assumed to rise in the AR study	Corrected: muscle carnitine was not measured [24]
Carbohydrate coadministration evidence attributed to LCLT alone	Reclassified as a joint intervention [16,17]
Direct LCLT muscle evidence described as either absent or conclusively positive	Corrected: the 36-day impaired-glucose-tolerance crossover showed no significant fasting free or acetylcarnitine difference but did show enhanced dynamic acetylcarnitine formation; a later numeric approximately 12% total-pool description was not statistically established in the primary report [18,19]
AR abundance represented as receptor activity	Added functional-state decomposition and missing measurements
Dispersion statistic assigned to the indexed AR abstract or marginal values used as paired uncertainty	Corrected: the abstract leaves dispersion unnamed, the replacement Figure 2 caption states means ± standard error, and within-person covariance and paired-difference variance remain unavailable [24,25]

Source-manuscript proposition or risk	Revision 1 correction
Seven-day washout assumed adequate	Reclassified as Unknown and modeled as possible carryover
Nominal P value treated as confirmatory	Reclassified as one unreplicated, multiplicity-exposed signal
Corrigendum omitted	Inspected and incorporated all three corrections: "fasting" to "fasted," free androgen index corrected to total testosterone divided by sex hormone-binding globulin, and Figure 2 replaced with corrected means ± standard error caption, immunoblot, bar panel, and significance markers [25]
Recovery markers represented as tissue repair	Restricted to measured biomarkers, symptoms, imaging, or functional endpoints
Marker-positive LCLT studies presented without direct counterevidence	Added null or heterogeneous substrate-use, endurance, and older-women functional studies with analyzed samples and design limits [47-50]
Sponsor-linked studies treated as independent replication	Funding, product, investigator overlap, and need for independent replication made explicit
Testosterone adjunct benefit asserted	Removed; no controlled LCLT-by-testosterone study identified
Synergy asserted without a null model	Replaced with an unestimated additive-scale interaction
Other carnitine formulations transferred to LCLT	ALCAR, PLCAR, free levocarnitine, and mixed products separated
Fertility benefit generalized	No LCLT-specific male-fertility RCT identified; mixed other-formulation evidence not transferred
TMAO called either proven toxicity or harmless	Both claims rejected; production is observed and clinical meaning remains unresolved
Human microbial gene evidence omitted	Added the corrected multi-cohort gbu report and bounded gbuB as a candidate response biomarker rather than a deterministic individual-risk classifier [52,53]
Small short safety study used for a broad low-risk claim	Reframed as limited short-term laboratory observation
Prescription approval transferred to LCLT	Drug indication and LCLT supplement or food status separated
GRAS response represented as efficacy or broad safety approval	Restricted to the notifier's infant-formula conditions
European status implied a lipid-metabolism claim	Added the 2021 refusal of that health claim [5]
Practical exposure, timing, or route language	Removed from all interpretive sections
Retracted reproductive papers available for inadvertent reuse	Excluded original doi:10.1016/j.ejogrb.2014.06.008 with retraction doi:10.1016/j.ejogrb.2023.09.028; original doi:10.1002/ijgo.12902 with retraction doi:10.1002/ijgo.14995; and original doi:10.1080/09513590.2019.1576622 with retraction doi:10.1080/09513590.2024.2419767

Appendix C. Publication disclosures

Authorship: Kamil Khoury, Researcher, Author, Architect.

Author responsibility: The author is responsible for the scientific claims, interpretation, final wording, and decision to release this preprint.

Funding: Not declared for preparation of this manuscript.

Competing interests: Not declared for preparation of this manuscript.

Automated assistance: Automated tools were used under author direction for evidence retrieval, claim checking, quantitative formalization, consistency checking, and document preparation. Automated assistance does not constitute authorship and does not transfer responsibility for the manuscript.

Peer review: This is a preprint and has not been peer reviewed.

Clinical boundary: This manuscript is a research evidence map. It is not a clinical protocol, compounding record, prescribing document, safety determination, or instruction for human use.

Data availability: No new participant-level data were generated. Extracted claims derive from the cited public records. This release package includes the finalized evidence registry, search log, correction log, and machine-readable claim register.

Revision provenance: Revision 1 replaces the supplied pre-release version 1.1 as the first publication-ready critical evidence-map release. It constitutes a new independent Research Library record, not a revision of another publication.