Cancer OPTIONS

Cancer Cachexia
Stage-Based Intervention Framework

Exercise · Nutrition · Glutamine Dynamics · Genetics · Clinical Strategy

PATRICIA PEAT

What is cancer cachexia?

50–80%

Cancer patients affected

At some stage during their illness

20–30%

Cancer deaths linked to it

Cachexia directly contributes to mortality

2

Core constituents

ANOREXIA — appetite loss and early satiety
ASTHENIA — physical and mental fatigue

"Cannot be fully reversed by conventional nutritional support alone — functional impairment is progressive."

"Cachexia is not a single state — it is a moving metabolic landscape. The success of any intervention depends entirely on when you use it, and who is standing beside the patient when you do.“

In cachexia, the brain behaves as though the body is experiencing a severe acute infection or injury, even when there is no infection present. This occurs because inflammatory signals released by the tumour and immune system continuously activate pathways in the brain, particularly within the hypothalamus, that normally help us survive short-term illness

Argilés JM, Busquets S, Stemmler B, López-Soriano FJ.
Cancer cachexia: understanding the molecular basis.
Nature Reviews Cancer. 2014;14(11):754-762

— Stage-Based Intervention Framework

The Brain in Cachexia

Fearon et al., Lancet Oncol 2011; Tisdale, Nat Rev Cancer 2002

In **cancer cachexia**, the brain behaves as though the body is experiencing a severe acute infection or injury, even when there is no infection present. This occurs because inflammatory signals released by the tumour and immune system continuously activate pathways in the brain, particularly within the **hypothalamus**, that normally help us survive short-term illness

Hypothalamus

Energy regulation centre

Pro-inflammatory cytokines (IL-1, IL-6, TNF-α) act directly on the hypothalamus. Hunger signals (ghrelin, NPY) are suppressed; satiety signals (leptin, POMC) are amplified. Anorexia is generated neurochemically — independent of actual nutrient status.

Vagus Nerve

Peripheral → brainstem

Inflammatory mediators in peripheral tissues are relayed via afferent vagal fibres directly to the nucleus tractus solitarius. This bypasses higher cortical processing and drives illness behaviour at a reflexive, subcortical level.

HPA Axis

Chronic stress cascade

Chronic cytokine stimulation sustains HPA activation, maintaining elevated cortisol. Hypercortisolaemia accelerates proteolysis and lipolysis — consuming structural muscle tissue even in the presence of caloric intake.

The same neural/hormonal pathways activated in severe sepsis are constitutively active in cachexia — with no physiological off-switch.

Clinical Consequences

Why standard nutritional intervention is insufficient

Argilés et al., J Cachexia Sarcopenia Muscle 2014

Feature	Acute Illness (Adaptive)	Cachexia (Pathological)
Duration of response	Days — resolves with pathogen clearance	**Months to years — no resolution signal**
Appetite suppression	Temporary, proportionate to illness severity	**Persistent; hypothalamic override of nutrient status**
Muscle catabolism	Transient protein mobilisation for immune fuel	**Progressive, irreversible wasting (sarcopenia)**
Fatigue	Adaptive rest to conserve immune resources	**Chronic; profoundly impairs function and QoL**
Response to feeding	Nutritional repletion restores positive balance	**Catabolism continues despite caloric supplementation**

Cachexia affects ~50–80% of cancer patients and is directly responsible for ~20% of cancer-related deaths (Tisdale, 2002).

The Brain Begins Acting as if the Body is Acutely ill

The same pathways activated during severe infection are activated in cachexia.

The brain receives a constant message:

"The body is sick. Conserve energy. Do not seek food."

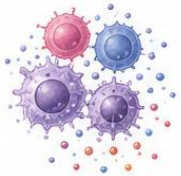
Argilés JM, Busquets S, Stemmler B, López-Soriano FJ.Cancer cachexia: understanding the molecular basis. Nature Reviews Cancer. 2014;14:754–762.

CANCER CACHEXIA: THE VICIOUS CYCLE

TUMOUR AND HOST FACTORS

- Tumour burden
- Treatment toxicity
- Comorbidities
- Ageing

INFLAMMATION



↑ IL-6
TNF-α
IL-1β
MIF
Other cytokines

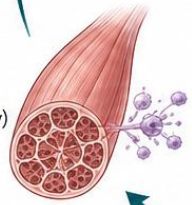
NEUROENDOCRINE DYSREGULATION

↑ HPA axis activation (cortisol)
↑ Insulin resistance
↓ Anabolic hormones (testosterone, IGF-1, GH)
↑ Leptin resistance
↓ Appetite (ghrelin resistance)

ANOREXIA AND ASTHENIA

- Reduced food intake
- Early satiety
- Altered taste
- Profound fatigue
- Loss of motivation

MUSCLE LOSS



↓ Protein synthesis
↑ Proteolysis (ubiquitin-proteasome, autophagy)
↓ Muscle mass (sarcopenia)
↓ Strength and function

REDUCED FUNCTION & QUALITY OF LIFE

↓ Physical function
↓ Treatment tolerance
↓ Quality of life
↑ Complications
↑ Mortality

A SELF-PERPETUATING CYCLE DRIVING DISEASE PROGRESSION

FINAL CONSEQUENCES

- Reduced survival
- Reduced tolerance to anti-cancer therapy
- Increased risk of infections and complications
- Poor quality of life for patient and caregivers

Cancers Most Affected by Cachexia

Fearon et al., Lancet Oncol 2011; Argilés et al., J Cachexia Sarcopenia Muscle 2014

Prevalence by tumour type · Key driving mechanisms

CANCER · PREVALENCE · RELATIVE BURDEN	KEY DRIVING MECHANISMS
Pancreatic 70–84%	Highest cytokine secretion (14 CCTFs) · Warburg metabolic drain · directly disrupts digestion & insulin regulation · surgical resection compounds loss
Gastric / Oesophageal 60–80%	Mechanical obstruction impairs eating & swallowing · high mucosal inflammation · poor nutrient absorption · early satiety
Colorectal 50–60%	CXCL8 overexpression drives systemic wasting · large mucosal surface absorption loss · chronic occult blood loss → anaemia
Lung 45–60%	Systemic IL-6, TNF-α, IL-1β · anorexia & hypermetabolism · EGFR-mutated subtype has lower risk due to slower progression
Head & Neck 40–50%	Structural: tumour physically impairs chewing & swallowing · radiotherapy-induced mucositis severely worsens oral intake

Lowest risk: Breast cancer & melanoma — minimal systemic cytokine burden, no structural barrier to nutrition. Cachexia is directly responsible for ~20% of all cancer deaths (Tisdale, 2002).

Metabolic Effects

of Muscle Breakdown

Skeletal muscle accounts for 40–50% of lean body mass and is the body's primary site of glucose uptake and disposal.

Loss of muscle = loss of metabolic capacity — creating a self-reinforcing cycle of decline.

In Sarcopenia

Insulin Resistance

Less muscle means fewer cells to absorb glucose after meals. Remaining muscle becomes less responsive to insulin, raising blood sugar and increasing type 2 diabetes risk.

Impaired Glucose Disposal

Skeletal muscle normally clears ~80% of dietary glucose. With muscle loss, blood glucose stays elevated longer, driving chronic hyperglycaemia and pancreatic strain.

Fat Accumulation

Insulin resistance triggers increased lipolysis, releasing free fatty acids. These accumulate in muscle and liver (intramuscular fat), worsening metabolic dysfunction.

Vicious Cycle

Insulin resistance itself suppresses muscle protein synthesis (via impaired mTOR signalling), accelerating further muscle loss — which deepens metabolic dysregulation.

Asthenia: the hidden burden

Physical fatigue

Profound exhaustion far beyond tiredness. Generalised weakness and rapid functional decline.

Mental fatigue

Cognitive slowing, poor concentration, brain fog. Impairs decisions and treatment engagement.

Emotional blunting

Reduced motivation, social withdrawal, loss of identity and personal agency.

Mechanism

IL-6 and TNF-α cross the blood-brain barrier → NF-κB activation → neuroinflammation.

HPA axis

Chronically elevated cortisol drives the fatigue–catabolism loop throughout all stages.

Assessment tools

FACIT-Fatigue scale and Brief Fatigue Inventory (BFI). Does not resolve with rest.

"Asthenia is not just 'feeling tired' — it is a neurobiological state driven by systemic inflammation."

The endocrine system in cachexia

Hormonal disruptions

- Insulin resistance → impaired glucose uptake in muscle
- Cortisol (HPA axis) → proteolysis and lipolysis
- Testosterone/oestrogen deficiency → reduced anabolism
- GH resistance and low IGF-1 → accelerated muscle breakdown
- Leptin resistance → disrupted hunger signalling
- Ghrelin dysregulation — compensatory rise, often ineffective
- Low T3 syndrome — peripheral T4→T3 conversion impaired

Cytokine–endocrine crosstalk

- TNF-α ('Cachectin') → insulin resistance and lipolysis
- IL-6 → stimulates HPA axis → excess cortisol production
- IL-1β → suppresses appetite, disrupts hypothalamic hormones
- Adiponectin reduction → worsened systemic inflammation
- Elevated cortisol → muscle proteolysis and fat redistribution
- Inflammatory-endocrine loop self-amplifies over time
- Thyroid dysfunction increases metabolic rate abnormally

GUT BACTERIA

Cancer cachexia is increasingly recognised as a disease of the gut-muscle axis.
depletion of butyrate-producing organisms such as Faecalibacterium prausnitzii (<2–5%) and expansion of inflammatory Proteobacteria (>10–20%):

Driving endotoxin exposure, systemic inflammation, anabolic resistance and progressive muscle loss.
FMT (faecal microbiota transplantation): under active investigation for cachexia

Roy S, Alizadeh Bahmani AH, Davids M, Herrema H, Nieuwdorp M.
Modulating the Gut–Muscle Axis: Increasing SCFA-Producing Gut Microbiota Commensals and Decreasing Endotoxin Production to Mitigate Cancer Cachexia.
Microorganisms. 2025;13(6):1356.

Chemotherapy Effect on Cachexia

↑ Increases	Muscle protein breakdown (proteolysis)	↓ Reduces	Protein & calorie intake
↓ Suppresses	Muscle protein synthesis	↑ Increases	Fatigue, weakness & physical inactivity
↑ Increases	Mitochondrial damage & oxidative stress	↑ Promotes	Insulin resistance & catabolic signalling
↑ Elevates	IL-6, TNF-α & systemic inflammation	↑ Accelerates	Muscle loss & functional decline
↓ Reduces	Nausea, taste changes & appetite	↓ Worsens	Treatment tolerance & survival

↑ Harmful Increase

↓ Harmful Decrease

Genetic polymorphisms (SNPs) associated with cachexia

01 TNF-α rs1800629 (−308G>A) — increased TNF-α production, accelerated muscle breakdown

02 TNF-α rs361525 (−238G>A) — higher inflammation, greater weight loss in cancer cachexia

03 IL-6 rs1800795 (−174G>C) — elevated IL-6, worsened muscle catabolism and appetite suppression

04 IL-1β rs16944 (−511C>T) — higher IL-1β expression and systemic inflammation

05 FOXO3 rs2802292 — muscle atrophy regulation and oxidative stress resistance

06 UCP3 rs1800849 (−55C>T) — mitochondrial efficiency, influences muscle preservation

07 ACTN3 rs1815739 (R577X) — muscle performance and resistance to wasting

08 LEPR rs1137101 (Q223R) — impaired leptin signalling, appetite and energy imbalance

09 MC4R rs17782313 — appetite regulation and energy expenditure disruption

"SNP profiling may enable stratified, genotype-guided interventions in cachexia management."

Key tests and monitoring markers

Inflammation

CRP, IL-6, TNF-α. Correlate directly with muscle wasting severity across all stages.

Nutritional

Serum albumin, pre-albumin, total protein. Sensitive early markers of clinical deterioration.

Hormonal

Cortisol, IGF-1, fasting insulin, testosterone. Define anabolic capacity and resistance.

Thyroid

T3, T4, TSH. Low T3 syndrome is common and worsens energy and muscle metabolism.

Appetite hormones

Leptin and ghrelin. Dysregulation personalises appetite and energy strategy.

Body composition

DEXA scan is the gold standard for lean mass and fat mass quantification over time.

Cachexia as a glutamine redistribution syndrome

Tumour uptake

ASCT2 and SLC1A5 transporters upregulated. Tumour demand for glutamine rises relentlessly.

Muscle mass

Ubiquitin–proteasome system activated. Autophagy accelerates. Muscle becomes a substrate donor.

Net redistribution

Glutamine synthetase shifts away from muscle. The more muscle is lost, the less it can compete.

"Tisdale (Physiol Rev, 2009) · Argilés et al. (Nat Rev Cancer, 2014)"

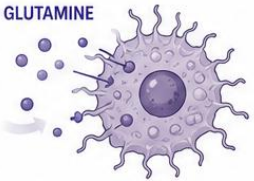
GLUTAMINE VS EXERCISE

IN CANCER CACHEXIA: COMPETITION FOR FUEL

GLUTAMINE

Cancer cells use glutamine as a **key fuel** to grow and survive.

GLUTAMINE



Feeds cancer cell metabolism, supporting tumour growth and worsening cachexia.

RESULT

Increased muscle wasting
Reduced strength and function
Poorer outcomes

COMPETE FOR THE SAME FUEL

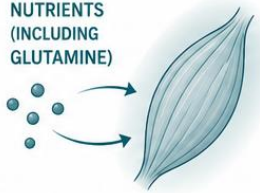
TIMING MATTERS: EXERCISE SOON AFTER EATING

Directs nutrients (including glutamine) to your muscles instead of cancer cells.

EXERCISE

When performed **soon after eating**, exercise helps your muscles compete for nutrients.

NUTRIENTS (INCLUDING GLUTAMINE)



Nutrients are taken up by muscle cells for repair and growth instead of fueling cancer cells.

RESULT

Preserved muscle mass
Improved strength and function
Better outcomes

THE TAKEHOME

Eat protein and then **exercise soon after.**
This helps your muscles compete with cancer cells for glutamine and other nutrients—helping break the cycle of cachexia.

Post-meal muscle activation — the metabolic competition model

30–60

Minutes post-meal

Optimal window to exercise after protein intake. Maximises muscle amino acid transporter activity.

2–3×

Amino acid uptake ↑

Exercise raises muscle amino acid uptake 2–3 fold. Biolo et al. (Am J Physiol, 1995).

5–15

Minutes sufficient

Short, consistent stimulation is enough. Sit-to-stand, bands, steps, isometrics.

"Not 'starving the tumour' — strengthening the host's metabolic authority over circulating glutamine."

The destruction of the patient's relationship with food

Failure at mealtimes

Early satiety creates repeated 'failure experiences'. Every meal becomes a confrontation.

Early satiety

What looks manageable as an amount to eat can become too much quickly. Often perceived as “not trying or giving up”

Dysgeusia

Altered taste and smell make familiar, loved foods suddenly aversive or repellent.

Anticipatory avoidance

Fear of nausea or discomfort causes patients to avoid eating before it even begins.

Identity loss

Food is culture, pleasure and connection. Losing appetite strips away social identity.

Medicalised mealtimes

Meals become clinical events rather than relational moments — damaging relationships. Overload of supplements and medications adds to this

"The erosion of eating as a normal human experience is one of cachexia's most underrecognised harms."

EARLY STAGE

Stage 1: Early cachexia (Pre-cachexia / risk phase)

Biggest window of opportunity — act now

Early stage

Early stage — biological changes

Inflammatory and hormonal

- Mild ↑ IL-6 and TNF-α — inflammation beginning
- Early insulin resistance emerging
- Cortisol beginning to rise subtly
- IGF-1 starting to decline
- Appetite changes — early satiety appearing

Metabolic terrain

- Muscle mass still largely intact
- Mitochondrial function relatively preserved
- Nutrient competition still winnable
- Muscle and immune system outcompete tumour for glutamine
- Exercise amplifies this advantage significantly

Early stage

Early stage — exercise strategy (critical)

Resistance training

The anchor intervention. Even light resistance significantly benefits amino acid uptake.

2–3× amino acid uptake

Post-exercise muscle amino acid uptake rises 2–3 fold. (Biolo et al., Am J Physiol, 1995)

mTOR activation

↑ mTOR signalling → muscle protein synthesis. ↓ proteolysis throughout the day.

Post-meal timing

Light resistance within 30–60 min after protein intake. 5–15 min is sufficient.

Frequency

3–5 sessions per week adapted to tolerance. Sit-to-stand, bands, step-ups, wall push-ups.

Metabolic competition

Reduces net amino acid availability for tumour uptake. Improves insulin sensitivity.

"Exercise is not optional here — it is metabolic protection. (Phillips et al., J Physiol, 2016)"

Early stage — nutrition strategy

01 Protein: 1.2–2.0 g/kg/day — prioritise whey, lean meats, fish, eggs

02 BCAAs (especially leucine) to stimulate mTOR and muscle protein synthesis

03 Omega-3 EPA/DHA: anti-inflammatory, supports muscle maintenance

04 HMB (β-hydroxy β-methylbutyrate): anti-catabolic — prevents breakdown

05 Moderate carbohydrate restriction + flexible ketogenic approach (if tolerated)

06 Berberine + ALA: improve insulin sensitivity and glucose metabolism

07 CoQ10 + L-Carnitine: mitochondrial support and energy metabolism

08 Glutamine: use strategically — pair with exercise and adequate protein only

Early stage

Early stage — genetic and endocrine considerations

Priority tests

IGF-1
CRP
Vit D

Screen early. Act on results before muscle loss begins.

01 Screen for inflammatory SNPs: TNF-α rs1800629, IL-6 rs1800795

02 ACTN3 R577X — informs muscle training response and wasting risk

03 Fasting insulin, cortisol, testosterone, full T3/T4 thyroid panel

04 Elevated CRP + low albumin = early warning combination

05 Low T3 syndrome may appear even at this stage — investigate

06 Leptin and ghrelin assessment helps personalise appetite strategy

07 Vitamin D: deficiency worsens sarcopenia — test and optimise (Kemp et al., 2017)

08 DHEA + ashwagandha may support anabolic balance and cortisol control

MODERATE STAGE

Stage 2: Moderate cachexia (Established cachexia)

Metabolic shift underway — narrowing window

Moderate stage

Moderate stage — biological changes

Systemic disruption

- Significant systemic inflammation now established
- Insulin resistance fully established
- Cortisol chronically elevated
- IGF-1 continuing to fall
- Low T3 syndrome developing

Metabolic terrain

- Muscle mass actively declining
- Mitochondrial function impaired
- Energy inefficiency increasing significantly
- Glutamine competition becoming uncertain
- Anabolic resistance starting to emerge

Moderate stage

Moderate stage — asthenia management

Cortisol control

Phosphatidylserine, Rhodiola rosea, Magnesium, Vitamin C. Adaptogens reduce catabolism.

Mitochondrial

Vitamin D (Fernandes de Medeiros, 2021), CoQ10, L-Carnitine support energy production.

Hydrogen therapy and HBOT

Inhalation reduces TNF-α, IL-6, NF-κB. Preserves muscle mitochondria. (Zhang et al., 2019)

"Mental fatigue at this stage impairs engagement with all clinical recommendations — treat it directly."

Moderate stage

Moderate stage — adapted exercise strategy

01 Shift from performance → metabolic stimulation

02 Light resistance: bands, assisted sit-to-stand, step-ups, wall push-ups

03 Even minimal muscle contraction preserves metabolic priority

04 Post-meal activation (30–60 min): 5–10 min is sufficient

05 Consistency over load — never push to exhaustion

06 Isometric contractions if fatigue limits range of movement

07 Hyperbaric oxygen therapy: may improve tissue oxygenation and reduce fatigue

08 Goal: maintain metabolic signalling and muscle perfusion — not fitness

"Even minimal contraction preserves metabolic priority over tumour."

Moderate stage

Moderate stage — glutamine: case-by-case

Consider if

- Severe depletion is present
- Significant gut mucosal damage
- AKG as safer precursor alternative
- Always pair with protein intake
- Always pair with some movement
- Monitor tumour markers closely
- Reassess at every clinical review

Avoid if

- Rapid tumour progression occurring
- No exercise capacity whatsoever
- Patient unable to take oral protein
- Albumin critically low
- Rapid clinical deterioration
- No monitoring in place
- Stage has progressed to refractory

Moderate stage

Moderate stage — nutrition strategy

01 Protein: increase to 1.5–2.5 g/kg/day

02 Increase caloric density — intake takes priority over dietary perfection

03 Reintroduce carbohydrates as needed for energy

04 HMB: anti-catabolic — preserves lean mass

05 AKG (alpha-ketoglutarate): nitrogen balance, gut lining integrity (Hou et al., 2016)

06 Reduce inflammation – curcumin, bromelain, boswellia, Cox 2 inhibitors

07 Digestive enzymes (bromelain, papain, trypsin): improve protein absorption

08 ION Gut Health or similar : strengthens gut tight junctions, reduces systemic inflammation

Practitioners Navigating Family Dynamics

THE CORE TENSION

FOOD = LOVE

The emotional meaning of food makes cachexia conversations deeply complex

WHAT PRACTITIONERS FACE

Misunderstood Mechanism

Patients & families don't grasp that cachexia — not appetite — drives weight loss. Eating is a major challenge

Conflicting Family Pressures

Siblings, partners and parents disagree on how hard to push eating. Each acts from love — but pulls in different directions.

Psychology of Eating

Eating becomes an emotional and sensory minefield. Avoidance of cooking smells, anxiety around mealtimes, and guilt compound intake challenges.

Practical Adaptations

Small plates, shot glasses for drinks, grazing patterns, and avoiding large presentations reduce overwhelm and improve intake.

YOUR APPROACH

Where do you position your approach?

Educator

Explain the science of cachexia to reframe expectations

Mediator

Facilitate family conversations; validate all perspectives

Pragmatist

Focus on what is achievable; adapt goals to the patient. Is a strict restrictive approach suitable

LATE / REFRACTORY

Stage 3: Late / refractory cachexia

System overwhelmed — priorities change completely

Late / refractory

Late stage — biological changes

Systemic collapse

- Severe systemic inflammation
- Profound endocrine disruption throughout
- Low T3 syndrome established
- Extreme catabolism — profound muscle loss
- Tumour glutamine dominance likely

Metabolic terrain

- Muscle mass severely depleted
- Mitochondrial failure occurring
- Energy crisis state throughout body
- Anabolic resistance is profound
- Traditional exercise no longer possible

Late / refractory

Late stage — asthenia and cognitive burden

Total exhaustion

Profound exhaustion with minimal exertion. Often constant regardless of activity level.

Cognitive impairment

Confusion, memory loss, inability to communicate needs — deeply distressing for families.

Passive movement

Gentle mobilisation, oscillating platforms, bed-based isometric contractions maintain circulation.

Anti-neuroinflammatory

Omega-3s, curcumin, boswellia (Gupta et al., 2012) reduce cytokine burden in the CNS.

Sleep and pain

Sleep support and pain management are inseparable from fatigue management at this stage.

Presence over function

Goal shifts from function to comfort, dignity and connection with loved ones.

Late / refractory

Late stage — exercise and nutrition

Movement alternatives

- Passive movement and gentle mobilisation
- Oscillating platforms if available
- Bed-based isometric contractions
- Goal: circulation, dignity, presence
- Never push to exhaustion

Nutrition priorities

- Priority = intake, not dietary perfection
- High-calorie, high-protein, easy-to-eat
- Smoothies, eggs, fish, soft proteins
- Carbohydrates now useful and necessary
- Ketogenic diet generally inappropriate

Late / refractory

Late stage — gut, psychosocial and supportive care

01 FMT (faecal microbiota transplantation): under active investigation for cachexia

02 Gut microbiome diversity correlates with better protein metabolism (Smith et al., 2021)

03 Appetite support: small frequent meals, patient-led timing, preferred textures

04 Megestrol acetate / dronabinol: appetite stimulants in selected patients

05 Milk thistle (silymarin): liver protection and detox support in chemotherapy patients

06 CoQ10: mitochondrial support, reduces muscle fatigue

07 Boswellia + curcumin: anti-inflammatory, inhibits TNF-α, IL-6, NF-κB

08 CBT, narrative therapy and meaning-centred interventions for psychological support

Drugs

Steroids used in short doses, limited effect on appetite boost but can impact muscle tone so very limited

Megesterol occasionally used pprogesterone that stimulates appetite centrally; weight gain mainly fat not muscle.

NSAID's Reduce PGE_2 and cytokine burden driving muscle proteolysis and anorexia. **LDN** the most mechanistically underappreciated — the TLR4 antagonism at low dose; the central neuroendocrine reset of endorphin tone directly addresses the anorexia-cachexia overlap.

TOP 10

Supplements for Cachexia

PART 1 OF 2

01 EPA / Omega-3

Strongest RCT evidence

Dose: 2–4g EPA/day

Reduces PIF & ubiquitin-proteasome activity. Suppresses IL-6, TNF-α. Direct anti-catabolic effect on muscle.

02 Creatine monohydrate

Synergistic with exercise

Dose: 3–5g/day

Replenishes phosphocreatine → ATP for muscle contraction & protein synthesis. Reduces myofibrillar breakdown.

03 HMB (β-hydroxy β-methylbutyrate)

Works without exercise

Dose: 3g/day

Leucine metabolite that blocks ubiquitin-proteasome degradation AND activates mTORC1. Preserves lean mass in RCTs.

04 Leucine / BCAAs

Primary mTOR trigger

Dose: 3–4g leucine per meal

Leucine directly activates mTORC1. Reduces central serotonin accumulation driving anorexia. Enriched formulas outperform standard protein.

05 Vitamin D_3

Near-universal deficiency

Dose: 2000–4000 IU/day

VDR in skeletal muscle drives myogenesis. Deficiency upregulates atrogin-1/MuRF1 (atrophy genes). Correct before other anabolics.

TOP 10

Supplements for Cachexia

PART 2 OF 2

★ Best stack: 1+3+4+5

06 Glutamine

Gut & immune support

Dose: 10–30g/day

Conditionally essential in catabolism. Fuels enterocytes → maintains gut barrier → reduces endotoxin translocation driving systemic inflammation.

07 Curcumin

⚠ bioavailability critical

Dose: 500–1000mg (bioavailable form)

NF-κB inhibitor → cuts cytokine-driven proteolysis. Inhibits 26S proteasome. Must use Meriva/BioPerin formulation — plain powder is inactive.

08 Zinc

Corrects dysgeusia

Dose: 25–40mg/day

Deficiency causes taste distortion → poor intake. Cofactor for IGF-1 receptor & thymulin (T-cell maturation). Rapid appetite improvement on correction.

09 Magnesium

Often overlooked

Dose: 300–400mg/day

Cofactor for 300+ enzymes including all ATP reactions. Depletion (common with chemo) causes weakness/cramps mimicking wasting. Reduces CRP.

10 Ashwagandha (KSM-66)

Cortisol ↓ / lean mass ↑

Dose: 300–600mg/day

Withanolides lower cortisol (key catabolic driver in cachexia), activate mTOR/IGF-1, inhibit NF-κB. RCT evidence for lean mass gain.

PART 3

Supplements for Cachexia

CONTINUED

★ Stack: 14 + 15 (LOX+COX)

11 CBD (Cannabidiol)

CB1/CB2 + anti-inflammatory

Dose: 20–150mg/day (sublingual oil)

Non-psychoactive cannabinoid that reduces nausea, stimulates appetite via CB1/CB2 receptors, and suppresses TNF-α / IL-6. Also reduces cancer-related pain and anxiety that suppress intake. Full-spectrum oils superior to isolate.

12 Milk Thistle (Silymarin)

Hepatoprotective / anti-catabolic

Dose: 420–600mg/day (70–80% silymarin)

Silymarin inhibits NF-κB and STAT3 signalling — key drivers of cytokine-mediated muscle wasting. Protects liver function critical for albumin synthesis and drug metabolism. Reduces hepatic inflammation that amplifies the cachectic cytokine load.

13 CoQ10 (Ubiquinol)

Mitochondrial bioenergetics

Dose: 200–400mg/day (ubiquinol form)

Essential cofactor in the mitochondrial electron transport chain (Complex I–III). Cachexia causes mitochondrial dysfunction and reduced ATP production in muscle. Ubiquinol form has 3–4× better absorption than ubiquinone. Also a potent lipid-soluble antioxidant reducing oxidative muscle damage.

14 Boswellia (AKBA)

5-LOX & NF-κB inhibitor

Dose: 300–500mg AKBA-standardised extract, 3×/day

Acetyl-11-keto-β-boswellic acid (AKBA) potently inhibits 5-lipoxygenase (5-LOX) and NF-κB — two key inflammatory cascades driving cachexia. Unlike NSAIDs, does not inhibit COX enzymes so avoids GI side effects. Particularly useful for cancer-related pain and gut inflammation worsening anorexia.

15 Curcumin (bioavailable)

NF-κB + proteasome inhibitor

Dose: 500–1000mg (Meriva/LongVida form)

Blocks NF-κB and inhibits 26S proteasome ubiquitin-mediated muscle proteolysis. Suppresses IL-6, TNF-α and COX-2. MUST use Meriva (phospholipid), LongVida, or BioPerin formulation — plain curcumin has <1% bioavailability. Synergistic with boswellia (dual LOX/COX blockade).

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