# Rapamycin vs Diet + Lifestyle

*mTOR inhibition, upstream signaling, pharmacology, risk-tier allocation, and future strategy*

| Clinical briefing | Prepared for McCoy \| 11 July 2026 |
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## Executive determination

**Diet and lifestyle can reproduce the direction of rapamycin biology, but not its pharmacological magnitude, duration, tissue penetration, or independence from upstream signals.**

The most defensible longevity objective is not maximum mTOR inhibition. It is metabolic oscillation:

- Low mTORC1 activity during fasting, energy deficit and aerobic energy stress.
- Preserved local mTORC1 activation after resistance exercise and adequate protein.
- Avoidance of chronically elevated insulin, amino-acid availability and adiposity.

Rapamycin directly imposes mTORC1 inhibition. Lifestyle creates periods in which the organism reduces mTORC1 because insulin, IGF-1, amino acids or cellular energy are low. These are analogous states, but not equivalent interventions.

- Low-risk appetite: diet, exercise, sleep and adiposity control dominate.
- Medium-risk appetite: lifestyle plus treatment of actual metabolic pathology; rapamycin preferably deferred pending stronger human evidence.
- High-risk appetite: participation in a controlled rapalog trial is the rational route. Unsupervised off-label use or multi-drug mTOR stacks has a poor uncertainty-to-benefit ratio.

## I. Biomolecular audit

### 1. The mTOR architecture

#### mTORC1

mTOR complex 1 integrates:

- Insulin/IGF-1: IRS -> PI3K -> AKT -> TSC1/2 -> Rheb.
- Amino acids: Rag GTPases and lysosomal recruitment, with leucine, arginine and methionine/S-adenosylmethionine sensing.
- Cellular energy: AMP/ATP ratio through AMPK.
- Mechanical tension: especially in skeletal muscle.
- Oxygen, inflammation and cellular stress.

Its major downstream outputs include:

- S6K1 and ribosomal protein S6 activation.
- 4E-BP1 phosphorylation and cap-dependent translation.
- Lipid and nucleotide synthesis.
- Inhibition of ULK1-mediated autophagy.
- Cellular growth and proliferation.

#### mTORC2

mTORC2 regulates AKT Ser473, glucose homeostasis and insulin signaling, cytoskeletal organization, and cell survival.

Rapamycin-FKBP12 acutely inhibits mTORC1 by interfering with substrate access to mTOR. Prolonged or sufficiently intensive exposure can disrupt mTORC2 assembly in some tissues, one proposed mechanism for metabolic toxicity. [1]

### 2. Why upstream suppression is not identical to rapamycin

mTORC1 functions approximately as a multi-input coincidence detector. Growth-factor signaling activates Rheb; amino acids recruit mTORC1 to the lysosome. Weakening one input reduces activation probability, but alternative inputs and tissue-specific signals remain operational.

**Lifestyle removes activation signals; rapamycin pharmacologically blocks the signaling node.**

This distinction explains why lowering insulin, IGF-1 or leucine does not produce a predictable rapamycin-equivalent dose.

# II. Rapamycin versus diet and lifestyle

| Intervention | mTOR effect | Temporal pattern | Major advantage | Principal liability |
|---|---|---|---|---|
| Sirolimus / rapamycin | Direct, potent mTORC1 inhibition; possible mTORC2 effects with sustained exposure | Multi-day exposure because of long half-life | Reliable target engagement independent of feeding state | Drug interactions, stomatitis, dyslipidemia, glucose effects, infection and wound-healing concerns |
| Calorie restriction / weight loss | Indirect: lower insulin, nutrient flux and adipose inflammatory signaling | Continuous but physiologically regulated | Broad cardiometabolic benefit | Lean-mass and bone loss if excessive |
| Prolonged fasting | Reduces insulin/amino acids and measurable muscle mTOR signaling | Strong but temporary | Autophagy-compatible low-nutrient state | Catabolism and muscle amino-acid release |
| Protein / BCAA moderation | Reduces lysosomal amino-acid signaling and may lower IGF-1 | Mainly postprandial | Targets a major mTORC1 input | Sarcopenia risk, especially in older adults |
| Refined-carbohydrate reduction | Reduces insulin signaling when it improves glycemia and energy balance | Meal-dependent | Low risk; improves metabolic control | Weak effect in already insulin-sensitive people |
| Aerobic exercise | AMPK activation and improved insulin sensitivity; tissue- and time-dependent modulation | Pulsatile | Improves mitochondrial and cardiometabolic function | Excess endurance plus energy deficit can become catabolic |
| Resistance exercise | Activates muscle mTORC1 locally | Brief post-exercise anabolic pulse | Preserves strength, muscle and bone | Not an mTOR-suppressive intervention - and should not be |
| Sleep / circadian optimization | Indirect through insulin sensitivity, cortisol and appetite control | Daily circadian modulation | Very low risk | Not a demonstrated direct mTOR inhibitor |

## Critical analogy

Both rapamycin and nutrient scarcity can produce lower S6K/4E-BP1 signaling, reduced protein synthesis, increased autophagy permissiveness, reduced growth-oriented metabolism, and attenuation of some senescence-associated processes.

## Critical differences

### Selectivity

Lifestyle is organism-regulated and tissue-specific. During resistance training, muscle mTORC1 should activate even when whole-body insulin exposure is generally low. Rapamycin is pharmacologically imposed and may inhibit tissues in which anabolic signaling is temporarily desirable.

### Duration

A fast or low-insulin meal pattern generates hours of suppression. Sirolimus has an approximately 62 +/- 16-hour terminal half-life, so even intermittent administration creates multi-day exposure. [2]

### Evidence

Lifestyle interventions have strong human evidence for reducing cardiometabolic morbidity, although proof that these benefits are specifically mediated by mTOR is incomplete.

Rapamycin has exceptionally strong lifespan evidence in multiple animal models, but no human trial has shown extension of lifespan or reduction of all-cause mortality.

The 2025 PEARL trial randomized healthy adults aged 50-85 to placebo, compounded rapamycin 5 mg weekly or 10 mg weekly for 48 weeks. Its primary endpoint - visceral adiposity - was negative. Some secondary sex-specific and self-reported outcomes improved, while adverse-event counts were similar. However, only 114 participants completed the study; the compounded formulation produced approximately one-third of the 24-hour blood concentration of commercial rapamycin, and the small subgroup findings require replication. [3]

Earlier low-dose rapalog trials in older adults showed improved influenza-vaccine responses and, in another study, reductions in infection-related outcomes. These are important human target-validation signals, but they remain immune-function endpoints rather than proof of longevity. [4]

# III. Can upstream signals reproduce rapamycin's effect?

## 1. Insulin and glucose

Insulin activates the insulin receptor -> IRS -> PI3K -> AKT pathway. AKT inhibits TSC2, increasing Rheb-GTP and activating mTORC1.

Reducing refined carbohydrate and excess energy intake can lower fasting and postprandial insulin, AKT-TSC-Rheb signaling, hepatic nutrient flux, and adiposity-associated mTOR activation.

But reducing sugar does not necessarily suppress mTOR if total calories remain excessive, amino-acid availability remains high, the person is already insulin-sensitive, or mechanical and inflammatory pathways continue to activate mTOR.

CALERIE demonstrated that sustained moderate calorie restriction improved numerous cardiometabolic variables and reduced some circulating senescence-associated biomarkers. Yet human calorie restriction did not consistently reduce IGF-1, emphasizing that the human response differs from the classic rodent model. [5]

## 2. IGF-1

IGF-1 uses much of the same PI3K-AKT-TSC2 pathway. However, circulating IGF-1 is not simply a bad longevity molecule. It also supports muscle maintenance, bone remodeling, tissue repair, and neurovascular function.

In a small human experiment, lowering protein intake from approximately 1.67 to 0.95 g/kg/day for three weeks reduced serum IGF-1 from approximately 194 to 152 ng/mL. Long-term calorie restriction without protein restriction did not produce the same effect. [6]

This demonstrates biological leverage - but not that intentionally driving IGF-1 downward is beneficial for every age group. Observational human data suggest that associations between low protein, IGF-1 and outcomes vary substantially with age, with the putative advantage of low protein not extending clearly into older populations. [7]

## 3. Leucine and other BCAAs

Leucine is a powerful amino-acid signal for mTORC1, particularly in muscle. Leucine-enriched essential amino acids combined with carbohydrate and resistance exercise produce marked activation of AKT-mTOR-S6K signaling and muscle protein synthesis. [8]

- Eliminating unnecessary BCAA supplements can reduce gratuitous mTOR stimulation.
- Continuous high-protein grazing creates more anabolic signaling time than discrete meals.
- Strategically placing adequate protein near resistance training preserves muscle while leaving longer low-amino-acid intervals.

Aggressive leucine suppression is a poor longevity strategy in older or sarcopenic individuals. ESPEN recommends at least approximately 1.0 g/kg/day protein in older adults, individually adjusted for nutritional status, activity and disease. [9]

## 4. Fasting

A human 72-hour fasting study demonstrated reduced skeletal-muscle mTOR phosphorylation, reduced downstream signaling, increased net phenylalanine release from muscle, and evidence of a more catabolic state. Thus, prolonged fasting clearly can inhibit mTOR - but the price is increased muscle amino-acid release. [10]

A 12-14-hour overnight fast is metabolically lower-risk, but its quantitative mTOR effect is likely much weaker and has not been shown to equal rapamycin.

## 5. Exercise

Exercise does not produce a single global mTOR state. Aerobic energy stress increases AMPK activity and improves insulin sensitivity. Resistance exercise activates muscle mTORC1 and muscle protein synthesis. Nutrient timing modifies the amplitude of the post-exercise response.

This compartmentalization is desirable. Suppressing muscle mTOR after resistance exercise would undermine preservation of lean mass. Human muscle-biopsy studies demonstrate distinct mTOR and autophagy responses after aerobic versus resistance exercise. [11]

# IV. Pharmacological matrix

## 1. Sirolimus - direct intervention

### Pharmacokinetics

- Absorption: variable; oral-solution systemic availability approximately 14%; tablet exposure higher than solution.
- Tmax: approximately one hour in healthy subjects.

- Distribution: very large apparent distribution volume, approximately 12 L/kg; approximately 92% protein bound; extensive partitioning into blood cells.
- Metabolism: intestinal and hepatic CYP3A4; substrate of P-glycoprotein.
- Excretion: approximately 91% in feces and 2.2% in urine after radiolabeled dosing.
- Terminal half-life: approximately 62 +/- 16 hours. [2]

**Interaction matrix**

Exposure can rise markedly with clarithromycin and other macrolides, azole antifungals, ritonavir-containing antiviral regimens, diltiazem or verapamil, cyclosporine, grapefruit, and cannabidiol in some circumstances.

Exposure can fall with rifampin/rifapentine, carbamazepine, phenytoin, phenobarbital, and St John's wort. The FDA label recommends avoiding strong CYP3A4/P-gp inhibitors and inducers. [2]

**Main toxicological liabilities**

The approved-dose experience identifies stomatitis, hypertriglyceridemia and hypercholesterolemia, cytopenias, impaired wound healing, edema, proteinuria, glucose intolerance/new-onset diabetes, infection and noninfectious pneumonitis, and reproductive effects. The magnitude of these risks at intermittent geroscience exposure is likely lower than at transplant dosing, but it is not zero and long-term incidence remains insufficiently characterized. [2]

## 2. Everolimus - another direct rapalog

Everolimus directly inhibits mTORC1 and has a shorter mean elimination half-life of approximately 30 hours. It remains a CYP3A4 and P-gp substrate, with substantial interaction exposure to azoles, macrolides, protease inhibitors, verapamil, diltiazem, rifampin and related agents. Approximately 80% of radiolabeled material is recovered in feces and 5% in urine. It is not established as safer or more effective than sirolimus for human longevity. [12]

## 3. Metformin - indirect upstream modulation

Metformin can reduce hepatic glucose production, lower insulin exposure and activate AMPK-related signaling. Its mTOR effects are indirect and context-dependent, not equivalent to rapamycin.

- Oral bioavailability approximately 50-60%.
- Negligible plasma-protein binding.
- Not materially metabolized.
- Eliminated unchanged by renal filtration and tubular secretion.
- Plasma half-life approximately 6.2 hours; whole-blood half-life approximately 17.6 hours.

There is no important CYP450 metabolism. Interaction risk instead concentrates on renal function and OCT/MATE transport inhibitors. Accumulation during renal failure, hypoxia, sepsis or major acute illness increases lactic-acidosis risk. [13]

Assessment: reasonable when diabetes, prediabetes or another accepted indication exists. Weak justification solely as an mTOR-lowering longevity drug in a metabolically healthy person.

## 4. Acarbose - postprandial upstream modulation

Acarbose delays intestinal carbohydrate digestion, reducing postprandial glucose and insulin peaks. It is primarily active within the gastrointestinal tract and has very low systemic exposure; the plasma half-life of absorbed active material is approximately two hours. [14]

Assessment: potentially useful for clinically relevant postprandial hyperglycemia, but not a direct mTOR inhibitor. Its main adverse effects are flatulence, abdominal discomfort and diarrhea; hepatic enzymes require consideration at pharmacological doses.

## 5. Supplements

No supplement or supplement combination currently has all four of the following:

**1.** Reproducible human bioavailability.

**2.** Demonstrated suppression of mTORC1 in relevant human tissues.

**3.** A validated exposure-response relationship.

**4.** Prospective human healthspan or longevity benefit.

Some compounds activate AMPK, mitophagy or autophagy-related pathways in cells or animals, but that does not establish rapamycin-equivalent mTOR inhibition. High-dose spermidine supplementation, for example, increased plasma spermine rather than spermidine itself in a human study, illustrating the disconnect between oral intake and target exposure. [15]

**A supplement mTOR stack is not presently pharmacologically calibratable. It adds variability rather than reliably reproducing rapamycin.**

# V. Risk-appetite allocation

| Population tier | Preferred strategy | Rapamycin position | Net assessment |
|---|---|---|---|
| A. Low risk appetite | Lifestyle-mediated mTOR oscillation; metabolic risk correction; strength preservation | Avoid for longevity outside a trial | Lifestyle overwhelmingly preferred |
| B. Medium risk appetite | Lifestyle plus evidence-based treatment of insulin resistance, diabetes, obesity or dyslipidemia | Reassess as larger trials mature; trial participation reasonable | Lifestyle remains base; drugs only for established indications |
| C. High risk appetite | Optimized lifestyle plus controlled experimental intervention | Rapalog trial preferred; specialist-supervised off-label exposure is a second-best option | Possible biological upside, but human longevity benefit remains unproven |

## A. Low risk appetite

Best expected-value configuration:

- No rapamycin.
- Normal adiposity and waist circumference.
- Refined-carbohydrate control.
- No BCAA supplementation.
- Overnight fasting without prolonged starvation.
- Aerobic and resistance training.
- Adequate age-adjusted protein.
- Treatment of hypertension, ApoB elevation and diabetes using interventions with proven clinical outcomes.

This captures much of the upstream biology without adding immunological, metabolic or CYP3A4 uncertainty.

## B. Medium risk appetite

Add pharmacology only when a clinical phenotype justifies it:

- Metformin for diabetes or selected prediabetes.
- Acarbose for significant postprandial dysglycemia.
- Obesity pharmacotherapy when adiposity is the dominant mTOR/insulin driver.
- Lipid-lowering treatment based on cardiovascular risk.

Using these agents solely to lower mTOR is not supported by current evidence.

## C. High risk appetite

The cleanest high-risk approach is enrollment in a structured rapalog PK/PD trial. NIA-funded studies are examining rapamycin and everolimus pharmacology, daily versus intermittent schedules, immune and metabolic endpoints, and dosing in older adults precisely because the optimal human exposure remains unknown. [16]

High risk appetite should not mean:

- Combining rapamycin, metformin, acarbose and multiple supplements.
- Manipulating sirolimus exposure with grapefruit or CYP3A4 inhibitors.
- Using transplant trough concentrations as longevity targets.
- Continuing around surgery, major infection or impaired wound healing without specialist direction.

That converts informed experimentation into uncontrolled polypharmacy.

# VI. Pragmatic protocol

## Lifestyle-based mTOR modulation

### Energy balance

- In overweight or insulin-resistant individuals: a sustainable approximately 10-15% energy deficit until metabolic and waist targets improve.
- In lean older individuals: avoid chronic energy deficit unless clinically indicated.
- Avoid repeated weight cycling.

CALERIE showed broad metabolic benefit from sustained moderate restriction but also documented reductions in lean mass and bone density, illustrating why more restriction is not automatically better. [5]

### Meal architecture

- Create a consistent 12-14-hour overnight noncaloric interval.
- Avoid continuous caloric grazing.
- Eliminate or sharply reduce sugar-sweetened beverages and isolated refined carbohydrates.
- Use fibre-rich carbohydrates and predominantly minimally processed food.
- Do not interpret fasting as permission for chronic protein inadequacy.

### Protein and amino-acid control

- Avoid isolated BCAA/leucine supplementation unless there is a specific sports or clinical rationale.
- Do not pursue low-leucine or very-low-protein diets in frailty, sarcopenia, illness or advanced age.
- For older adults, maintain at least approximately 1.0 g/kg/day, commonly 1.0-1.2 g/kg/day depending on training, health status and renal function. [9]
- Concentrate meaningful protein intake in discrete meals and around resistance training rather than maintaining a continuous amino-acid-fed state.

### Exercise

- Aerobic: 150-300 minutes/week moderate intensity or equivalent.
- Resistance: all major muscle groups at least twice weekly.
- Add balance and power work in older adults.
- Do not attempt to suppress the post-resistance-exercise muscle mTOR pulse; that pulse protects structural reserve. [17]

### Sleep and circadian timing

- Maintain approximately 7-8 hours of good-quality sleep.
- Keep wake time and meal timing reasonably consistent.
- Minimize substantial late-night caloric intake.

Sleep is not a direct rapamycin analogue, but it protects insulin sensitivity and appetite regulation. [18]

## VII. Monitoring architecture

### Lifestyle arm

Every 3-6 months during active optimization:

- Body weight and waist circumference.
- Blood pressure.
- Fasting glucose and insulin.
- HbA1c.
- Triglycerides and HDL-C.
- ApoB / LDL-C.
- hs-CRP.
- Liver enzymes.
- Creatinine / eGFR.
- IGF-1 when protein restriction is being considered.
- Grip strength or major-lift performance.
- Lean mass by DXA or validated bioimpedance when available.

**Serum insulin and IGF-1 are upstream markers, not direct measures of tissue mTOR activity. Routine blood testing cannot prove that lifestyle has reproduced rapamycin-level mTORC1 inhibition.**

### Rapamycin arm

Baseline and repeated surveillance ordinarily requires:

- CBC with differential and platelets.
- Creatinine / eGFR.
- AST, ALT and bilirubin.

- Fasting glucose and HbA1c.
- Fasting lipid panel and ApoB.
- Urinalysis and urine albumin / creatinine ratio.
- Blood pressure.
- Oral examination for stomatitis.
- Infection surveillance.
- Review of surgery, dental procedures and wound healing.
- Complete CYP3A4 / P-gp drug, food and supplement audit.

Sirolimus blood concentrations may document exposure, but there is no validated longevity trough target. Transplant targets should not be imported into geroscience practice.

## VIII. Final decision under rapid AI-driven medical development

AI will probably accelerate:

- Discovery of mTORC1-selective agents that spare mTORC2.
- Prediction of tissue-specific exposure.
- Identification of responders and toxicity phenotypes.
- Biomarker development.
- Adaptive trial design.
- Combination optimization.

That strengthens the argument for preserving optionality, not for taking rapamycin prematurely.

### Present optimal allocation

#### Low and medium risk appetite

**Diet and lifestyle now; preserve muscle and metabolic reserve; wait for superior human evidence.**

This strategy produces proven cardiovascular and metabolic benefit independently of mTOR, carries little irreversible downside, does not interfere with later adoption of a better mTORC1-selective drug, and allows current PK/PD studies to resolve dose, schedule and responder questions.

#### High risk appetite

**Controlled rapamycin experimentation is scientifically defensible only as a deliberate geroscience experiment - not as established preventive medicine.**

The hierarchy should be:

**1.** Optimized lifestyle.
**2.** Clinical-trial participation.
**3.** Specialist-supervised off-label rapamycin after formal interaction and laboratory screening.
**4.** Never an uncontrolled rapamycin-plus-supplement stack.

### Bottom line

Lifestyle cannot reproduce the pharmacological force of rapamycin. It can, however, reproduce a substantial part of the physiological state that makes mTOR inhibition beneficial, while preserving adaptive anabolic signaling.

**Engineer low basal nutrient signaling, periodic fasting physiology, high insulin sensitivity and preserved resistance-training anabolism - then reserve rapamycin for trials or genuinely high-risk experimental preferences.**

## References

**[1]** Lamming DW et al. Rapamycin-induced insulin resistance and mTORC2 disruption. Source
**[2]** U.S. FDA. Rapamune (sirolimus) prescribing information. Source
**[3]** PEARL Trial report. Aging-US, 2025. Source
**[4]** Mannick JB et al. mTOR inhibition improves immune function in the elderly. Source

**[5]** CALERIE randomized calorie-restriction trial. Source
**[6]** Fontana L et al. Long-term effects of calorie or protein restriction on IGF-1. Source
**[7]** Levine ME et al. Low protein intake, IGF-1 and mortality by age. Source
**[8]** Human leucine-enriched amino acid / resistance exercise signaling study. Source
**[9]** ESPEN practical guideline: clinical nutrition and hydration in geriatrics. Source
**[10]** Human 72-hour fasting study of skeletal-muscle mTOR signaling. Source
**[11]** Human exercise, mTOR and autophagy muscle-biopsy study. Source
**[12]** U.S. FDA. Afinitor (everolimus) prescribing information. Source
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**[14]** U.S. FDA. Precose (acarbose) prescribing information. Source
**[15]** Human spermidine supplementation pharmacokinetic study. Source
**[16]** ClinicalTrials.gov. Rapamycin / everolimus pharmacology in older adults, NCT05949658. Source
**[17]** U.S. Physical Activity Guidelines for Americans, executive summary. Source
**[18]** U.S. CDC. About sleep. Source

**Scope note:** This document reproduces the preceding analytical response in a publication-ready format. It is an evidence synthesis rather than a personalized prescription; any rapalog use requires clinician-led risk assessment, interaction review and monitoring.