

A natural lifter's guide to insulin sensitivity

Muscle, Not Fat

How natural lifters use insulin sensitivity to build a leaner physique

About this guide

Endo & Iron publishes evidence-based guides on hormones, metabolism and training.

These guides grew out of the research reading behind a master's degree in endocrinology and metabolism, in France. Every claim is checked against published, peer-reviewed studies, and every study is listed with a link to the original paper or its official abstract.

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Why your surplus turns into fat

Two natural lifters eat the same 300-calorie surplus for six months. One adds lean mass and stays sharp. The other gains a few pounds of muscle buried under a soft layer of fat. Training, genetics and protein explain part of the gap. Much of the rest comes down to one variable most lifters never measure: how well their muscle responds to insulin.

Insulin is the hormone that decides where incoming fuel goes. When skeletal muscle is sensitive to it, glucose and amino acids are pulled into muscle at low insulin levels, and fat tissue gets less of the share. When muscle becomes resistant, the pancreas has to release more insulin to clear the same meal. Chronically higher insulin keeps fat storage switched on and fat burning switched off. That is the core idea behind “nutrient partitioning”, and it is the idea this guide is built on.

This guide is written for natural lifters. Everything in it relies on training, nutrition, sleep, environment and evidence-based supplements. It contains no drug protocols, and nothing in it replaces medical care. If you have diabetes, prediabetes or take glucose-lowering medication, talk to your doctor before changing anything, because several strategies here lower blood glucose.

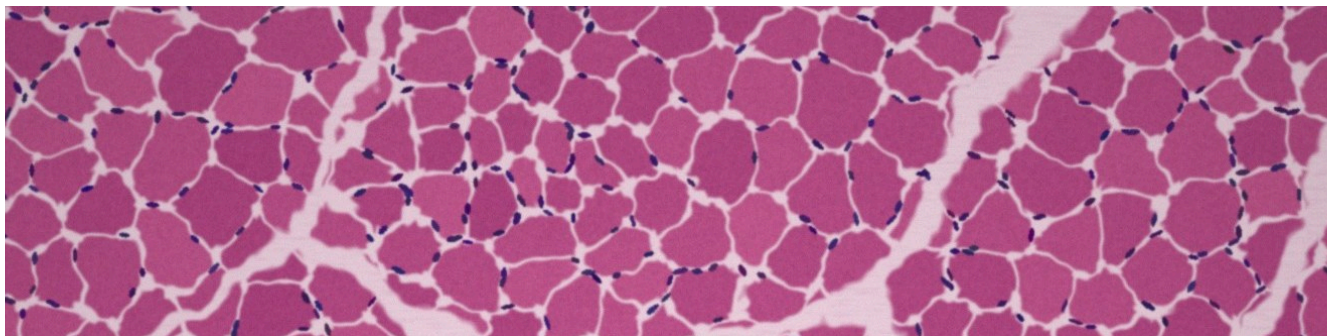
How to read this guide

Each chapter has two layers:

- **The Science:** the mechanisms, with references to the studies behind them. This is the part you will rarely find explained properly online.
- **In Plain English:** a short box that tells you what it means for you, ending with a one-line **Do this** action. If you just want the practical side, read these boxes, then go straight to the protocols in Chapter 6. Any unfamiliar word is explained in the glossary at the end of the guide, with a simple image to remember it.

Chapter 1 builds the foundation: what insulin does, how muscle loses sensitivity, and how you can measure where you stand. Chapters 2 to 5 cover the levers you control: training, nutrition, supplements, then sleep, stress, alcohol and cold. Chapter 6 turns everything into a day-by-day plan.

Units. Like the research it is based on, this guide uses metric units. 1 kg = 2.2 lb, so 2 g of protein per kg of body weight is about 0.9 g per pound. Blood values are given in US units (mg/dL), with mmol/L where useful.



Chapter 1

The Science of Insulin Sensitivity

1.1 What insulin actually does: one hormone, three tissues

Insulin sends one message, “fuel is coming in, store it”, but each tissue answers it differently. Who answers loudest decides whether a surplus builds muscle or fat.

THE SCIENCE

Skeletal muscle is the main destination. Under insulin clamp conditions, the gold-standard lab test of insulin action, roughly 80 to 90% of infused glucose is taken up by skeletal muscle (DeFronzo & Tripathy, 2009). In muscle, insulin does three things:

1. Moves glucose transporters (GLUT4) to the cell surface, so glucose can enter.
2. Activates glycogen synthase, so that glucose is stored as muscle glycogen, the fuel of hard sets.
3. Suppresses muscle protein breakdown.

The third point is the one most lifters get wrong. In a classic dose-response study in young men, amino acids alone doubled muscle protein synthesis at fasting insulin levels (about 5 $\mu\text{U/mL}$). Raising insulin to about 30 $\mu\text{U/mL}$ cut leg protein breakdown roughly in half. Pushing insulin to 72 and 167 $\mu\text{U/mL}$ added nothing further, to either synthesis or breakdown (Greenhaff et al., 2008). A normal mixed meal already pushes insulin past 30 $\mu\text{U/mL}$.

In other words, muscle needs only a modest rise in insulin to get its full anti-catabolic effect. Big, repeated insulin spikes bring no extra muscle. What they do bring is more storage signaling in the other two tissues.

Fat tissue. Adipose tissue is extremely sensitive to the anti-lipolytic effect of insulin: small rises are enough to switch off fat release. Insulin also activates lipoprotein lipase in fat tissue, which pulls fatty acids out of the blood for storage. As long as insulin stays elevated, fat cells store and do not release.

The liver. Insulin tells the liver to stop producing glucose and to store glycogen. When the liver is full and insulin stays high, the liver turns surplus carbohydrate into fat (de novo lipogenesis).

Nutrient partitioning is the result of these three responses. When muscle is highly sensitive, it clears a meal fast, insulin returns to baseline quickly, and fat tissue gets back to releasing fat between meals. When muscle is resistant, insulin stays high for longer after every meal, and the fat cells spend more of the day in storage mode.

In Plain English

Your muscles only need a small insulin “nudge” to stop breaking down.

More insulin does not build more muscle; it mainly tells your fat cells to store. The goal of this guide is not to spike insulin, but to make your muscles respond so well that a small amount does the job.

Do this: Stop chasing insulin spikes. Make your muscles more sensitive with the habits in Chapters 2 to 5.

1.2 GLUT4: the door glucose has to go through

Glucose cannot simply diffuse into muscle. It needs a transporter, GLUT4, and at rest most GLUT4 sits inside the cell, stored in small vesicles. Insulin sensitivity is, at its core, how easily those vesicles get moved to the surface.

THE SCIENCE

The insulin pathway. When insulin binds its receptor on the muscle cell, it triggers a relay of signals:

1. The insulin receptor activates **IRS-1** (insulin receptor substrate 1).
2. IRS-1 activates **PI3-kinase**, which activates **Akt** (also called protein kinase B).
3. Akt phosphorylates **AS160** (also called TBC1D4). In its resting state, AS160 acts as a brake that keeps GLUT4 vesicles inside the cell.
4. Once AS160 is switched off, the brake is released. GLUT4 vesicles fuse with the cell membrane and glucose flows in.

The same Akt signal also drives glycogen storage (through GSK-3) and feeds into mTOR, the growth pathway. That is why a muscle with good insulin signaling stores carbohydrate as glycogen and stays in a better anabolic environment.

The contraction pathway: the backdoor. Muscle contraction moves GLUT4 to the surface through a separate route that does not need insulin at all. It runs through energy and calcium sensors activated during work, mainly **AMPK** (activated when ATP drops), calcium-dependent kinases, and the protein Rac1. This is why exercise lowers blood glucose even in people with severe insulin resistance.

Where the two pathways meet. Both routes converge on AS160 and its sister protein TBC1D1. This convergence explains one of the most powerful facts in this guide: insulin and exercise do not just add up, they multiply. In a study of healthy volunteers, an insulin clamp alone produced glucose uptake of about 8.7 mg/kg/min, and light cycling alone about 1.4. Combined, uptake reached about 15.1 mg/kg/min, far more than the sum. More than 85% of that glucose went into skeletal muscle (DeFronzo et al., 1981).

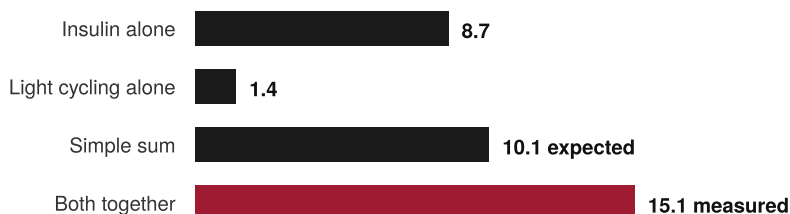


Figure 1. Insulin and exercise multiply, they don't just add up. Glucose uptake, mg/kg/min, healthy volunteers; the cycling value is the rise above resting uptake. DeFronzo et al., 1981.

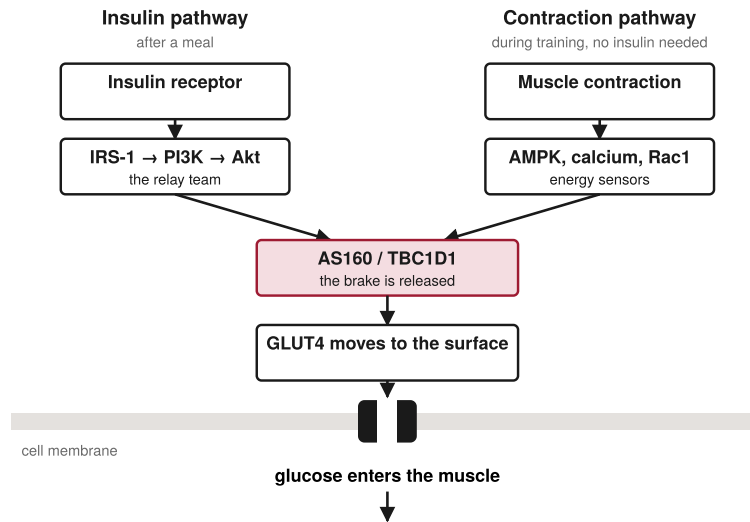


Figure 2. Two pathways, one door. Insulin and contraction take different routes but release the same brake, which is why training and carbohydrate together move far more glucose into muscle than either alone.

The post-workout window, explained properly. After a training session, AS160 stays phosphorylated for hours, even after Akt and AMPK activity have returned to baseline (Vendelbo et al., 2014). In human studies using one-legged exercise, the previously trained leg responds more strongly to insulin than the rested leg, and AS160 appears to be the link (Treebak et al., 2009). The “anabolic window” is not 30 minutes. It is a period of several hours in which the trained muscle is primed to take up glucose at lower insulin levels. Chapter 2 shows how to exploit it.

In Plain English

Glucose gets into muscle through doors called GLUT4.

Insulin opens them, and so does muscle contraction, through a separate key. After training, the doors stay easier to open for hours. That is why carbs eaten around your workout are far more likely to end up in muscle than in fat.

Do this: Put your biggest carb meal in the hours right after training.

1.3 How muscle goes deaf to insulin, and the athlete’s paradox

Muscle insulin resistance is not caused by “eating carbs”. It is mostly caused by fat stored in the wrong form, in the wrong place, in a muscle that does not burn it.

THE SCIENCE

Lipid intermediates jam the signal. When more fatty acids enter muscle than its mitochondria can burn, some are converted into reactive lipid intermediates. Two matter most:

- **Diacylglycerols (DAG).** Certain DAG species, especially at the cell membrane, activate enzymes called novel protein kinase C isoforms (PKC θ and PKC ϵ). These enzymes put a “stop” tag on IRS-1, the first runner of the relay team, which blocks the insulin relay before it reaches Akt. In healthy, lean volunteers, a lipid infusion raised muscle DAG, activated PKC θ and caused insulin resistance, in that order (Szendroedi et al., PNAS 2014).
- **Ceramides.** These sphingolipids, built in larger amounts from saturated fat, block Akt directly. Of all the lipid intermediates, ceramide shows the most consistent link with insulin resistance in human muscle (Amati et al., Diabetes 2011).

End of the free sample

Thanks for reading. The full guide picks up from here.

You have just read the introduction and the opening of Chapter 1. The complete guide continues with:

- How muscle goes “deaf” to insulin, and the athlete’s paradox
- How to measure your own insulin sensitivity from a standard blood test
- Training, nutrition, supplements, sleep, stress, alcohol and cold, each with its evidence
- Hour-by-hour templates for bulking, rest and cutting days, and an 8-week plan

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