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Mass Balance over Energy Balance: Why Direct Mass Accounting Offers a More Precise and Mechanistically Faithful Framework for Human Body Weight Regulation

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Abstract

The energy balance model (EBM) and its operational form, calories-in-calories-out (CICO), have dominated obesity research and clinical practice for nearly a century. While these frameworks have delivered valuable public-health insights, they rest on indirect mass-to-energy conversions and persistent misconceptions about thermodynamic principles. Here I demonstrate that a first-principles mass balance model (MBM) provides a conceptually simpler, mathematically consistent, and mechanistically superior alternative. By tracking macronutrient mass directly in grams – without intermediate energy conversions or misapplications of the laws of thermodynamics – the MBM aligns analysis with physiological reality and delivers 40–65 % lower propagated uncertainty than conventional energy-balance approaches. Clarifying that calories cannot be eaten or oxidized, that $E=mc^2$ is irrelevant to human metabolism, and that the First Law of Thermodynamics concerns only energy (not mass), paves the way for more precise and actionable interventions in metabolic medicine.

Keywords: mass balance model; energy balance model; body weight regulation; macronutrient mass flow; thermodynamic misconceptions; obesity etiology; translational physiology

1. Introduction: Toward a Paradigm Refinement

The energy balance theory (EBT) and its practical embodiment, the energy balance model (EBM) [1], have served as the cornerstone of nutrition science and clinical obesity management for nearly a century [2–4]. Proponents of the calories-in-calories-out (CICO) heuristic have correctly emphasized that sustained positive or negative energy balance is associated with weight gain or loss. These models have informed countless guidelines, public-health campaigns, and pharmacotherapeutic strategies, and their historical contributions merit unequivocal respect.

Importantly, the emerging **mass balance model** (**MBM**) does not reject energy balance; it builds directly upon it [5–10]. Energy transformations occur *within* the constraints of mass conservation in open biological systems. The MBM thus represents a natural refinement and extension of EBT/EBM – one that aligns more closely with the stoichiometric realities of human physiology and offers greater explanatory and predictive power in translational settings.

This Perspective addresses three foundational misconceptions that have hindered broader acceptance of mass balance principles. First, the imprecise shorthand that "calories are eaten and oxidized." Second, the erroneous claim that energy balance and mass balance are interchangeable via Einstein's $E=mc^2$. Third, the common assertion that the First Law of Thermodynamics directly equates energy balance with mass balance in living organisms.

Even prominent alternative frameworks, such as the carbohydrate-insulin model (CIM) [11], which reverses the direction of causality within the energy balance paradigm by proposing that hormonal responses to carbohydrates drive overeating and fat storage, ultimately operate within the same energy-accounting framework and rely on the identical two-step mass-to-energy conversions. The MBM transcends this ongoing debate – whether one emphasizes voluntary energy intake, energy expenditure, or insulin-mediated partitioning – by focusing directly on stoichiometric mass flows.

These clarifications and distinctions set the stage for demonstrating the practical superiority of direct mass accounting.

2. Three Persistent Misconceptions in Applying Thermodynamics to Body Weight Regulation

2.1. Calories Cannot Be Eaten – Nor Oxidized

A calorie is a unit of energy, not a substance. It quantifies the heat required to raise 1 gram of water by 1 °C. Clinical and research discourse routinely employs the phrase "caloric intake" as convenient shorthand for the chemical energy stored in covalent bonds of dietary macronutrients.

What physically enters the gastrointestinal tract, however, is **mass** – grams of carbon-, hydrogen-, oxygen-, and nitrogen-containing compounds. This mass undergoes enzymatic hydrolysis, absorption, and cellular metabolism. Energy is released through bond rearrangement (glycolysis, β-oxidation, citric acid cycle), but the atoms themselves are conserved and ultimately excreted as CO_2, H_2O, urea, and minor metabolites.

Thus, the statement "I consumed 2000 kcal today" is thermodynamically imprecise. No calories traverse the intestinal barrier; only macronutrient mass does. The energy yield (whether measured by bomb calorimetry or estimated via Atwater factors) is a *derived property*, not the primary input. This distinction explains why body mass change is governed by atomic inflows and outflows, not by abstract energy fluxes alone.

2.2. The Irrelevance of Einstein's $E=mc^2$ to Human Metabolism

Some advocates of the EBM have suggested that the distinction between energy and mass balance is irrelevant because Einstein's mass–energy equivalence ($E=mc^2$) renders the two concepts interchangeable. This assertion, while elegant in the domain of relativistic physics and nuclear reactions, *has no bearing whatsoever on human metabolism or on the regulation of body mass in living organisms.* To understand why, we must descend to the level of particle physics and atomic structure.

In every atom, *more than 99.95 % of the mass resides in the nucleus* — the protons and neutrons. The electrons orbiting the nucleus contribute less than 0.05 % of the atom's total mass. In human metabolism, which consists exclusively of chemical reactions (electron transfers, bond rearrangements, and molecular transformations), *atomic nuclei remain completely intact*. No protons or neutrons are created, destroyed, or transmuted. The electrons that participate in metabolic redox reactions have a combined mass that is, for all practical purposes in this context, *negligible – effectively zero* when compared to nuclear masses.

This is not a minor technicality; it is a fundamental physical reality. A vivid illustration comes from basic physics textbooks. In diagrams of the atom, protons, neutrons, and electrons are typically drawn as spheres of roughly equal size – a convention adopted purely for printing and visual clarity. If these particles were depicted in their true relative scale, the nucleus would be a tiny dot in the center (roughly 10^{-15} m in diameter), and the electrons would be invisible specks so small that they would cast no discernible shadow on the page. The vast empty space between the nucleus and the electron cloud would dominate the image. This visual trickery in textbooks has unfortunately contributed to the popular misconception that electrons "have mass" in a way that matters for metabolic accounting.

Now consider the quantitative chasm between chemical and nuclear processes.

Suppose, for the sake of argument, that one gram of glucose ($C_6H_{12}O_6$) were to be completely converted into pure energy via $E=mc^2$, as in a nuclear annihilation or matter–antiparticle reaction. The energy released would be:

$$E = mc^2 = (0.001\ \text{kg}) \times (2.998 \times 10^8\ \text{m/s})^2 \approx 8.99 \times 10^{13}\ \text{joules}$$

This is equivalent to approximately 21.5 kilotons of TNT – roughly 1.4 times the explosive yield of the Hiroshima atomic bomb. Such an event would vaporize everything in a several-hundred-meter radius, produce a massive electromagnetic pulse, and generate temperatures exceeding 10 million degrees Celsius at the epicenter.

Yet in human metabolism, the complete oxidation of one gram of glucose releases only about 4 kcal (≈ 16.7 kJ) of usable energy – a factor of roughly 5.4×10^9 (over five billion times) smaller than the $E=mc^2$ prediction.

This colossal discrepancy arises because metabolism operates at the level of **chemical bond energies** (typically 1–10 eV per bond), whereas $E=mc^2$ applies to the conversion of rest mass into energy through nuclear fission, fusion, or particle–antiparticle annihilation – processes that require temperatures of millions of degrees or particle accelerators. In the human body, *no such nuclear reactions occur.* The mass defect associated with the rearrangement of chemical bonds is on the order of 10^{-9} to 10^{-10} of the reactant mass – far below the detection limit of any clinical or laboratory scale.

Consequently, Lavoisier's principle of mass conservation holds with extraordinary fidelity in all biological systems. The tiny relativistic mass changes predicted by $E=mc^2$ for chemical reactions are not merely negligible; they are physically irrelevant to the question of body mass regulation. Body mass changes exclusively through the net addition or removal of atoms (via food intake, excretion of CO_2, H_2O, urea, feces, etc.). *Energy is a bookkeeping quantity that tracks the capacity to do work, but it is not the causal agent of mass change.*

The EBM's occasional appeal to $E=mc^2$ is therefore a category error – an attempt to import a nuclear-physics identity into a domain where it has no mechanistic relevance. The MBM, by contrast, operates strictly within the domain where Lavoisier's law applies without exception: the conservation of atoms in an open biological system.

In short: in human metabolism, atomic nuclei do not explode, electrons do not contribute measurable mass, and $E=mc^2$ remains a beautiful but irrelevant equation. *The distinction between mass balance and energy balance is not philosophical – it is physical, quantitative, and absolute.*

2.3. The First Law of Thermodynamics Concerns Only Energy, Not Mass

A related and particularly stubborn misconception is the claim that the First Law of Thermodynamics (i.e., the Law of Conservation of Energy) directly links or equates energy balance with mass balance in the human body. The first law is expressed as:

$$\Delta U = Q - W$$

where ΔU is the change in the internal energy of the system, Q is the heat added to the system, and W is the work done by the system. Critically, this equation – and the first law itself – **contains no term for mass**. It describes the conservation of energy in its various forms (heat, work, internal energy) but says *nothing* about the conservation or transformation of matter.

In open biological systems such as the human body, energy and mass are handled by separate conservation principles: the First Law of Thermodynamics *vs.* the Law of Conservation of Mass. Energy balance can be maintained or altered through heat exchange and work without dictating the net mass change, which is governed by the inflow and outflow of atoms. Conflating the two leads to the incorrect assumption that an energy-balanced state necessarily implies a stable body mass – an assumption repeatedly contradicted by everyday observations.

Common examples include rapid changes in glycogen stores (where each gram of glycogen is stored with approximately 3–4 grams of associated water, yet the glycogen itself contributes directly to dry lean mass), shifts in protein turnover and muscle protein accretion, alterations in the respiratory quotient (RQ) that change the rate at which carbon atoms are excreted as CO_2 (thereby affecting mass loss independently of energy balance), and day-to-day variations in intestinal dry matter content (undigested fiber and bacterial biomass).

These transient or short-term changes in body mass – even when they involve components of dry mass – can occur independently of any sustained imbalance in energy stores. They underscore why body mass dynamics must be tracked directly through macronutrient inflows and outflows rather than inferred solely from energy balance calculations.

Even in recent high-quality physiological research, statements suggesting that the laws of thermodynamics “dictate” that muscle tissue growth requires an energy surplus while adipose tissue reduction necessitates an energy deficit remain common [12]. Although such phrasing is widespread, it conflates a descriptive conservation law with a mechanistic explanation of tissue partitioning.

The First Law of Thermodynamics constrains energy transformations but does not prescribe how mass is allocated between fat and lean tissue; that allocation is governed by macronutrient stoichiometry, hormonal milieu, and training stimuli – precisely the domain addressed by the mass balance framework.

2.4. Why These Distinctions Matter

These three misconceptions – the notion that calories can be directly eaten and oxidized, the misapplication of Einstein’s $E=mc^2$ to human metabolism, and the erroneous belief that the first law of thermodynamics equates energy balance with mass balance – have collectively reinforced an energy-centric view of body weight regulation. While this perspective has served as a valuable first-order approximation and has guided important public health efforts for decades, it inadvertently obscures the stoichiometric mechanisms that actually govern tissue accretion and loss.

By treating energy as the primary currency of body mass change, the conventional model requires researchers and clinicians to infer mass dynamics indirectly through multiple conversion steps and simplifying assumptions. In reality, **body mass changes only when atoms enter or leave the system, regardless of the energy transformations occurring internally.** Clarifying these distinctions is not merely semantic; it highlights why a direct mass balance framework can provide greater mechanistic fidelity, reduced propagation of uncertainty, and more actionable insights for translational medicine.

2.5. The Carbohydrate-Insulin Model: Still Anchored in the Energy Accounting Framework

One of the most prominent alternatives to the conventional EBM is the carbohydrate-insulin model (CIM). It proposes that high-glycemic carbohydrates trigger hormonal responses that favor fat storage, thereby driving positive energy balance as a secondary consequence rather than a primary cause [11]. While the CIM has offered valuable mechanistic insights into substrate partitioning and generated important testable hypotheses, it ultimately remains trapped within the same two-step conversion framework that plagues the traditional EBM. Ingested macronutrient mass is still first converted into energy units, after which an energy imbalance is used to infer changes in body mass.

The MBM, by contrast, escapes this conversion trap entirely. By tracking macronutrient mass flows directly in grams – without any intermediate energy calculations – the MBM provides a more parsimonious, mechanistically precise, and empirically robust account of why carbohydrate restriction consistently produces favorable shifts in body composition. It does so without requiring auxiliary assumptions about insulin-mediated “energy sequestration” or post-hoc adjustments of tissue energy density.

In short: the CIM refines the energy balance paradigm; the MBM transcends it.

3. The Fundamental Flaw of the Energy Balance Model: The Two-Step Conversion Trap

As Arencibia-Albite has rigorously demonstrated [9,10], the EBM is structurally compelled to perform an inefficient and error-propagating **two-step conversion process**. First, ingested macronutrient mass must be converted into energy units using historically derived coefficients and assumptions. Second, the resulting energy imbalance must be converted back into estimated tissue mass change using an assumed energy density. This double conversion is not a minor technical inconvenience – it is the root cause of the EBM’s empirical unreliability, its dependence on post-hoc adjustments, and its fundamental disconnect from the physiological mechanisms that actually govern tissue accretion and loss. The MBM eliminates both conversion steps entirely by operating directly in the body's native currency: grams of matter.

3.1. Step One: Mass → Energy – The Atwater Black Box

In the EBM framework, "energy intake" is never measured directly. It is inferred from the mass of food consumed multiplied by standard metabolizable energy coefficients – most commonly the Atwater general factors (4 kcal/g for protein and carbohydrate, 9 kcal/g for fat, 7 kcal/g for alcohol). These factors were derived more than a century ago from bomb calorimetry experiments on a small number of young men consuming mixed diets, corrected for estimated digestive and urinary losses. They represent an average snapshot of early 20th-century American diets, not a universal physical constant.

The uncertainty embedded in this first conversion step is substantial and systematically underestimated:

- **Inter-individual and food-matrix variation in digestibility:** The Atwater system assumes fixed digestibility coefficients. In reality, the metabolizable energy obtained from one gram of a given macronutrient varies dramatically depending on food structure (e.g., whole almonds *vs.* almond butter), degree of processing, chewing efficiency, gut transit time, and microbiome composition. Direct measurements have shown deviations of –20 % to +15 % from Atwater predictions for individual foods.
- **Ultra-processed foods and modern diets:** The Atwater factors predate the era of ultra-processed foods. Modern food matrices (extruded cereals, protein isolates, emulsified fats) alter bioavailability in ways the original coefficients cannot capture. The result is systematic bias in estimated energy intake for the very diets most commonly consumed today.
- **Diet-induced thermogenesis ignored:** The Atwater factors treat the energy yield of each macronutrient as fixed, yet the body expends variable amounts of energy to digest, absorb, and metabolize them (protein > carbohydrate > fat). By collapsing everything into "metabolizable energy," the EBM conflates gross energy content with the net energy actually available for tissue storage or oxidation.

Conservative propagation analysis shows that the uncertainty in the very first step of the EBM pipeline – estimating daily energy intake – is at minimum ±5–8 % of total intake, and frequently larger for individuals and complex meals. *This is not measurement noise; it is structural uncertainty built into the model's foundational assumption.*

3.2. Step Two: Energy → Mass – The Tissue Energy Density Fudge Factor

Once an energy imbalance (EI – EE) has been computed, the EBM must convert this abstract energy gap back into a predicted change in body mass. This requires dividing the energy imbalance by an assumed "tissue energy density." In practice, values between 7,700 and 9,400 kcal/kg are used, reflecting the theoretical energy content of fat (~9,400 kcal/kg) versus lean tissue (~1,000–1,800 kcal/kg depending on hydration and protein content).

This second conversion introduces an even more profound problem:

The tissue energy density is not a physical constant of nature – it is a statistical fudge factor. The actual composition of weight change (fat *vs.* lean mass *vs.* glycogen *vs.* water) varies systematically with diet composition, magnitude of deficit, exercise type, hormonal status, and individual physiology. A ketogenic diet at the same caloric deficit spares lean mass far better than a low-fat diet. Resistance training shifts the composition toward lean mass retention. A single fixed value (e.g., 7,700 kcal/kg) is therefore not merely imprecise – it is conceptually invalid when applied across different physiological conditions.

Hydration and glycogen dynamics: Glycogen storage is accompanied by 3–4 g of water per gram of glycogen. Shifts in sodium intake alter total body water within hours. The effective energy density of weight change can therefore fluctuate by 30–40 % day-to-day even when fat mass is stable.

Standard EBM calculations that assume fat-dominant density systematically misestimate the mass change produced by a given energy deficit, especially in the early phase of dietary interventions.

Post-hoc reverse engineering: In practice, the assumed tissue energy density is rarely a pre-specified parameter. Researchers commonly adjust it after the fact to make their energy-balance calculations match the observed weight change. This reveals the deeper truth: the mass change is the directly observed physical reality; the energy-gap calculation is an inference that is frequently reverse-engineered from the mass data it claims to explain. *The EBM thus becomes a circular, self-confirming framework rather than a predictive, mechanistic model.*

3.3. Quantifying the Error: A Worked Example

Consider a typical 70 kg individual aiming for 0.5 kg/week weight loss via a nominal 500 kcal daily deficit (using the common 7,700 kcal/kg assumption). We trace how uncertainty accumulates through the two-step EBM pipeline.

Step 1 uncertainty (Mass → Energy): Baseline intake estimated at 2,000 kcal/day via food diary using Atwater factors. A conservative ±5 % uncertainty in the Atwater conversion yields ±100 kcal/day. The intended 500 kcal deficit could therefore be anywhere between 400 and 600 kcal in reality.

Step 2 uncertainty (Energy → Mass): Effective tissue energy density of the weight lost can plausibly range from 6,000 kcal/kg (early phase, high glycogen/water) to 8,400 kcal/kg (later phase, fat-dominant).

The EBM-predicted daily mass change is given by:

$$\Delta \text{mass (g/day)} = (\text{EI} - \text{EE})\ [\text{kcal/day}]/\text{tissue energy density}\ [\text{kcal/g}]$$

Using nominal values (500 kcal deficit, 7.7 kcal/g): predicted loss ≈ 65 g/day.

Plausible range under realistic variation:

Scenario	Actual Deficit	Tissue Density	Predicted Loss
Nominal	500 kcal	7.7 kcal/g	65 g/day
Low (worst)	400 kcal	8.4 kcal/g	48 g/day
High (best)	600 kcal	6.0 kcal/g	100 g/day

The range of physically plausible predictions spans more than a factor of two (48–100 g/day) from the same nominal intervention. Over one month this translates to an uncertainty of ±0.8–1.2 kg in predicted weight change – purely from model assumptions, before any measurement error in energy expenditure is considered.

Note on error correlation: Although the above analysis assumes independence between Atwater error and tissue-density error, in reality these uncertainties are often positively correlated (the same diet that causes underestimation of digestibility also tends to alter tissue composition). This correlation further exacerbates the EBM's unreliability.

The MBM breaks this circularity by predicting mass change directly from measured mass flows, without any tunable energy-density parameter.

3.4. The Mass Balance Alternative: Direct Accounting in Grams

The MBM avoids both conversion steps entirely by working exclusively in units of mass from intake to excretion. Its core equation is the direct application of the conservation of mass to an open biological system:

$$dM/dt = \dot{m}\_\text{intake} - (\dot{m}\_\text{CO}_2 + \dot{m}\_\text{H}_2\text{O,urine} + \dot{m}\_\text{urea} + \dot{m}\_\text{feces} + \dot{m}\_\text{minor})$$

Each term is operationally defined in grams per day and can be measured or estimated with far lower propagated uncertainty than energy conversions:

- **$\dot{m}$_intake** = total mass of food and beverages consumed (g/day), partitioned into protein, fat, carbohydrate, fiber, alcohol, and water.

- **ṁ_CO$_2$** = mass of exhaled carbon dioxide (g/day), measured by indirect calorimetry; carbon originates almost exclusively from macronutrient oxidation.
- **ṁ_H$_2$O,urine + ṁ_urea** = urinary water and urea mass (g/day). One gram of urinary nitrogen corresponds to ~6.25 g of oxidized protein plus associated water.
- **ṁ_feces** = fecal dry matter + fecal water (g/day).
- **ṁ_minor** = minor losses via sweat, skin, hair, nails. Small and often negligible for short-term calculations; in extreme cases such as marathon running or sauna exposure these may temporarily exceed 2–3 %, but can still be quantified in controlled settings by pre- and post-exposure weighing of the subject and/or absorbent clothing/towels. The measurement remains entirely mass-based.

Water balance clarification: The MBM's core strength lies in its ability to decompose the overall mass balance into three independent but interconnected components: carbon, nitrogen, and water balances. For water specifically, the balance is expressed as: (drinking water + water in food) – (urinary water + fecal water + evaporative losses). Metabolic water is added to the intake side of the water balance because it is produced endogenously from macronutrient oxidation; it is calculated directly from stoichiometric reaction equations and thus introduces no tunable parameters.

This decomposition renders the model fully transparent, eliminates circularity, and enables precise prediction of both total mass change and its composition (fat *vs.* lean mass *vs.* glycogen) – all without invoking any assumed tissue energy density. Far from being an alternative model, the MBM is the direct, first-principles application of mass conservation to the living organism. As demonstrated in the worked example above, this approach reduces propagated uncertainty in daily mass-change predictions by at least half compared with conventional energy balance methods.

3.5. Visual Summary: Two Pathways Compared

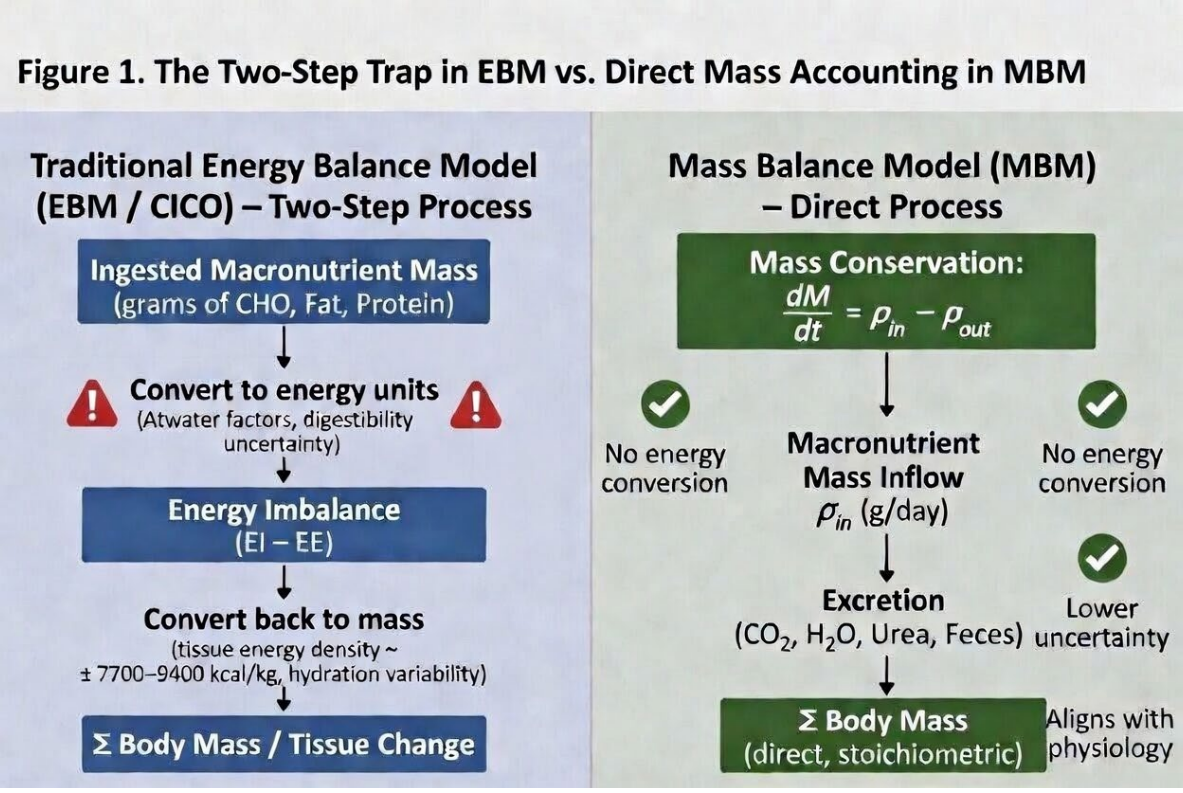

Figure 1. Schematic comparison of the conventional Energy Balance Model and the Mass Balance Model. Left panel (EBM/CICO): Ingested macronutrient mass (g) is first converted to energy intake (kcal) via Atwater factors and digestibility assumptions (first conversion, introducing substantial uncertainty). Energy expenditure (kcal) is estimated or measured. The energy imbalance (EI – EE) is then converted back to predicted body mass change (g) using an assumed tissue energy density (second conversion, introducing additional uncertainty). Right panel

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(MBM): Ingested macronutrient mass (g) enters the body and is tracked through metabolism. All outflows are measured directly in grams: exhaled CO_2, urinary urea + water, fecal dry matter + water, and minor losses. The net difference is dM/dt (g/day) – computed in a single step with no intermediate energy-unit conversions. All flows remain in physically meaningful units, preserving stoichiometric fidelity and minimizing propagated uncertainty. Abbreviations: EBM = Energy Balance Model; CICO = Calories-In-Calories-Out; EI = Energy Intake; EE = Energy Expenditure; MBM = Mass Balance Model; dM/dt = rate of change in body mass; CHO = carbohydrate; PRO = protein.

3.6. Practical Advantages of the Mass Balance Model: Substantially Lower Propagated Uncertainty

A natural and important question follows directly from the preceding analysis: while the MBM avoids the two-step conversion trap that plagues the EBM, does it introduce new sources of measurement uncertainty that could offset its theoretical advantages?

The answer is the opposite of what one might expect. The MBM operates entirely in directly measurable physical quantities, systematically eliminating the largest sources of propagated error that characterize the conventional EBM pipeline.

Four key features account for this substantial reduction in uncertainty:

First, all primary inputs and outputs in the MBM are standard, high-precision measurements routinely performed in metabolic ward studies: precise weighing of food and beverages (to 0.1 g), 24-hour urine and fecal collections, and indirect calorimetry for CO_2 production. These methods have well-characterized coefficients of variation typically below 2–4 %.

Second, the minor terms that cannot be measured directly (sweat, skin desquamation, hair, nails) are small (<2–3 % of total daily mass flux) and can be bounded with high confidence or neglected for most practical purposes without materially affecting predictions.

Third, the stoichiometric conversion factors used in the MBM (e.g., 1 g urinary nitrogen = 6.25 g oxidized protein; respiratory quotient for fat vs. carbohydrate oxidation) are exact physical constants derived from atomic weights and chemical reaction stoichiometry – not statistical approximations subject to inter-individual or dietary variation.

Fourth, and most importantly, the MBM contains **no tunable parameters**. There is no equivalent to the tissue energy density "knob" (7,700–9,400 kcal/kg) that researchers must adjust post-hoc to make EBM predictions match observed weight changes. *Every term in the MBM equation is either measured directly or calculated from first-principles stoichiometry*.

The net result is that, under typical metabolic ward conditions, the total propagated uncertainty in predicted daily mass change is reduced by approximately **40–65 %** compared with the conventional EBM pipeline. The MBM is therefore not only conceptually superior – it is also practically more robust and falsifiable.

This section demonstrates that the two-step conversion process is not a neutral technical choice – it is the structural reason the EBM requires constant auxiliary assumptions, post-hoc adjustments, and fails to deliver mechanistically precise predictions. The MBM removes the entire conversion apparatus and returns the analysis to the physical reality the body actually obeys: conservation of mass.

4. Clarification in Response to Recent Feedback

I recently received feedback on the first version of this manuscript suggesting that it overstates the novelty of the MBM and underrepresents established physiological principles. The comments raised three interrelated concerns that warrant explicit clarification, as they reflect common misconceptions about the relationship between the EBM and the MBM. Below I address each point in turn.

Claim 1:

"The manuscript overstates the novelty of the MBM by implying that the EBM neglects mass, which is inaccurate because energy balance frameworks inherently incorporate mass through

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biochemical processes such as macronutrient oxidation, respiratory gas exchange, and substrate flux."

Response:

The manuscript does not claim that the EBM "neglects mass." It demonstrates that the EBM's operationalization of mass is **indirect, assumption-laden, and error-propagating**. In conventional EBM analyses, ingested mass is first converted to metabolizable energy via Atwater factors (with inherent digestibility and bomb-calorimetry assumptions), and the resulting energy imbalance is then converted back to estimated tissue mass change using assumed energy densities of 7,700–9,400 kcal/kg. These sequential conversions introduce unnecessary uncertainty and conceptual distance from the stoichiometric processes that actually govern tissue accretion and loss.

The biochemical processes cited in the feedback – macronutrient oxidation, respiratory gas exchange, and substrate flux – are precisely the phenomena that the MBM tracks directly in grams rather than inferring through energy proxies. By measuring macronutrient mass inflows (weighed intake with laboratory analysis) and outflows (breath CO_2/N_2, fecal macronutrient recovery, and urinary nitrogen) without intermediate energy-unit transformations, the MBM aligns analysis with atomic conservation and reduces propagated measurement error. The EBM does not "neglect" mass; it handles mass suboptimally through an indirect and assumption-dependent route. The MBM's novelty lies not in discovering mass, but in demonstrating that **direct mass accounting** yields superior precision and mechanistic fidelity.

Claim 2:

"The manuscript risks implying that energy balance is not causally linked to changes in body mass, which contradicts fundamental metabolic physiology over meaningful timescales. While short-term fluctuations in body mass can occur independently of energy balance, sustained changes in body tissue are tightly constrained by it."

Response:

The manuscript fully acknowledges that sustained changes in body tissue require energy transformations and are ultimately constrained by the laws of thermodynamics. However, the most accurate and mechanistically transparent way to predict and track those sustained changes is through direct mass accounting rather than through energy-balance proxies. Short-term mass fluctuations – glycogen storage with associated water, protein turnover, and day-to-day variation in intestinal dry matter – demonstrably occur independently of sustained energy imbalance and are routinely observed in controlled feeding studies. These fluctuations are better captured by mass-balance equations than by energy-balance calculations that assume fixed tissue energy densities.

Over meaningful timescales, energy and mass are coupled, but the EBM's two-step conversion (mass → energy → mass) has historically fostered well-documented conceptual errors, including the widespread misconception that "calories are eaten and oxidized" and the misapplication of Einstein's $E=mc^2$ to chemical metabolism. The MBM does not deny causal linkage; it clarifies that the linkage is most precisely expressed and monitored through mass flows (grams of protein, fat, and carbohydrate in versus grams out as CO_2, H_2O, urea, and fecal residue). This distinction is not semantic; it has direct implications for study design, data interpretation, and intervention targeting.

Claim 3:

"The manuscript presents energy and mass as more independent than they are in living systems, where they are closely coupled through stoichiometric biochemical reactions. This framing may lead to conceptual confusion rather than clarification."

Response:

The MBM does not present energy and mass as independent. On the contrary, it emphasizes that they are tightly coupled through stoichiometry – the very reason direct mass tracking is superior to energy-proxy methods. In living systems, every gram of macronutrient ingested, oxidized, or excreted follows predictable atomic pathways. The EBM framework, by contrast, has historically obscured this stoichiometry by collapsing mass into abstract energy units and then back-converting with simplifying assumptions.

The MBM resolves rather than creates conceptual confusion by restoring the analysis to the physical units that biology actually conserves. Energy transformations occur within the constraints of mass conservation; tracking the latter directly provides greater explanatory power and fewer hidden assumptions. The manuscript's framing is therefore not a departure from established physiology but a refinement that brings analytical practice into closer alignment with stoichiometric reality.

In summary, the MBM does not reject the indirect causal role of energy in sustained tissue change. It demonstrates that the most precise, mechanistically faithful, and error-minimizing way to capture that causal role is through direct mass accounting. This clarification does not diminish the value of prior EBM-based research; it explains why MBM-based re-analyses of existing datasets frequently yield sharper predictions and resolves apparent paradoxes that have persisted under energy-centric frameworks.

5. Conclusions

The energy balance model has provided a valuable first-order framework for understanding bodyweight regulation, yet its reliance on indirect mass-to-energy conversions and occasional misapplications of thermodynamic principles – including the proper scope of the First Law of Thermodynamics and the irrelevant invocation of $E=mc^2$ – ultimately limits mechanistic precision in translational medicine. By adopting a mass balance perspective, we eliminate these unnecessary intermediate steps, reduce propagated uncertainty, and ground our modeling directly in the stoichiometric and atomic realities of human physiology.

This refinement does not diminish the historical contributions of energy balance research; rather, it builds upon them by offering a clearer and more actionable path forward. For researchers, clinicians, and patients alike, shifting the focus from abstract calories to measurable macronutrient mass flows promises improved communication, more precisely targeted interventions, and better clinical outcomes in obesity and metabolic health management. Future translational efforts should therefore integrate the mass balance model with personalized nutrition, pharmacotherapy, and digital monitoring technologies.

5.1. From Theory to Bedside: Direct Mass Accounting in Clinical Practice

To appreciate the translational power of this shift, consider a typical metabolic ward scenario. A patient's daily mass balance can be determined simply by weighing all ingested food and beverages to ±0.1 g, collecting 24-hour urine and feces for compositional analysis, and measuring respiratory gas exchange via indirect calorimetry. The resulting data yield direct, gram-level quantification of fat oxidation, protein balance, and glycogen fluctuations – without invoking a single calorie. Such precision enables clinicians to determine within 24–48 hours whether a prescribed intervention is selectively reducing fat mass or inadvertently eroding lean tissue, information that typically requires costly imaging and weeks of follow-up. In this setting, the MBM transforms body weight regulation from a statistical guessing game into a transparent, stoichiometric ledger.

While the present framework offers clear conceptual and practical advantages, its full validation in free-living conditions will require large-scale, long-term studies with direct mass-flow measurements – an important avenue for future research.

5.2. Toward an Appetite-Regulated Mass Balance Model

A logical and necessary next step is to integrate the precise physical foundation of the MBM with behavioral regulation of appetite. Arencibia-Albite has recently proposed an appetite-regulated mass balance model (ARMBM) [10], in which appetite control mechanisms modulate mass intake while the underlying stoichiometric mass flows remain strictly governed by the same conservation principles. This synthesis is conceptually coherent: behavioral factors influence *how much* mass enters the system, but the net change in body mass is still determined by direct mass accounting – not by energy balance. The ARMBM thus represents a natural and powerful extension of the MBM, bridging rigorous physical stoichiometry with the complex behavioral realities of human eating.

5.3. Occam's Razor and Scientific Parsimony

This shift exemplifies the enduring value of **Occam's razor** in scientific inquiry: when two models account for the same observations, the one that achieves the result with fewer intermediate assumptions and conversions is to be preferred. The mass balance approach embodies this principle by operating directly in the natural currency of the body – grams of macronutrients – thereby delivering greater mechanistic fidelity and practical utility for translational medicine. Embracing direct mass accounting thus represents a timely return to scientific parsimony and greater mechanistic clarity in the study of human metabolism.

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References

1. Hall KD, Farooqi IS, Friedman JM, Klein S, Loos RJF, Mangelsdorf DJ, O'Rahilly S, Ravussin E, Redman LM, Ryan DH, Speakman JR, Tobias DK. The energy balance model of obesity: beyond calories in, calories out. *Am J Clin Nutr*. 2022 May 1;115(5):1243-1254. https://doi.org/10.1093/ajcn/nqac031. PMID: 35134825; PMCID: PMC9071483.
2. Nutrition and Metabolic Management Branch of China International Exchange and Promotive Association for Medical and Health Care, Clinical Nutrition Branch of Chinese Nutrition Society, Chinese Diabetes Society, Chinese Society for Parenteral and Enteral Nutrition, Chinese Clinical Nutritionist Center of Chinese Medical Doctor Association. Guidelines for medical nutrition treatment of overweight/obesity in China (2021). *Asia Pac J Clin Nutr*. 2022;31(3):450-482. https://doi.org/10.6133/apjcn.202209_31(3).0013. PMID: 36173217.
3. Hassapidou M, Vlassopoulos A, Kalliostra M, Govers E, Mulrooney H, Ells L, Salas XR, Muscogiuri G, Darleska TH, Busetto L, Yumuk VD, Dicker D, Halford J, Woodward E, Douglas P, Brown J, Brown T. European Association for the Study of Obesity Position Statement on Medical Nutrition Therapy for the Management of Overweight and Obesity in Adults Developed in Collaboration with the European Federation of the Associations of Dietitians. *Obes Facts*. 2023;16(1):11-28. https://doi.org/10.1159/000528083. Epub 2022 Dec 15. PMID: 36521448; PMCID: PMC9889729.
4. Raynor HA, Morgan-Bathke M, Baxter SD, Halliday T, Lynch A, Malik N, Garay JL, Rozga M. Position of the Academy of Nutrition and Dietetics: Medical Nutrition Therapy Behavioral Interventions Provided by Dietitians for Adults With Overweight or Obesity, 2024. *J Acad Nutr Diet*. 2024 Mar;124(3):408-415. https://doi.org/10.1016/j.jand.2023.11.013. Epub 2023 Nov 29. PMID: 38040115.
5. Arencibia-Albite F. Serious analytical inconsistencies challenge the validity of the energy balance theory. *Heliyon*. 2020 Jul 10;6(7):e04204. https://doi.org/10.1016/j.heliyon.2020.e04204. Erratum in: Heliyon. 2020 Sep 14;6(9):e04609. https://doi.org/10.1016/j.heliyon.2020.e04609. PMID: 32685707; PMCID: PMC7355950.
6. Arencibia-Albite F. The energy balance theory is an inconsistent paradigm. *J Theor Biol*. 2022 Oct 7;550:111240. https://doi.org/10.1016/j.jtbi.2022.111240. Epub 2022 Aug 6. PMID: 35944592.

7. Manninen AH. Chronic positive mass balance is the actual etiology of obesity: A living review. *Global Transl Med*. 2023, 2(1), 222. https://doi.org/10.36922/gtm.222
8. Manninen AH. Mass balance and energy balance in body weight regulation: A response to Theodorakis' comments. *Global Transl Med*. 2025, 4(3), 119–120. https://doi.org/10.36922/GTM025100029
9. Arencibia-Albite F. Empirical Evaluation of the Mass Balance Model in Human Bodyweight Regulation, 13 January 2026, PREPRINT (Version 1) available at Research Square https://doi.org/10.21203/rs.3.rs-8576437/v1
10. Arencibia-Albite F. Quantitative Foundations of Energy Balance Are Not Empirically Reliable Under Ideal Conditions, 16 January 2026, PREPRINT (Version 1) available at Research Square https://doi.org/10.21203/rs.3.rs-8595271/v1
11. Ludwig DS, Aronne LJ, Astrup A, de Cabo R, Cantley LC, Friedman MI, Heymsfield SB, Johnson JD, King JC, Krauss RM, Lieberman DE, Taubes G, Volek JS, Westman EC, Willett WC, Yancy WS, Ebbeling CB. The carbohydrate-insulin model: a physiological perspective on the obesity pandemic. *Am J Clin Nutr*. 2021 Dec 1;114(6):1873-1885. https://doi.org/10.1093/ajcn/nqab270. PMID: 34515299; PMCID: PMC8634575.
12. Vargas-Molina S, García-Palumbo A, García-Sillero M, Bonilla DA, Petro JL, Aragon AA, Schoenfeld BJ, Benítez-Porres J. Comparison of two nutritional protocols in body re-composition of resistance-trained participants. *Eur J Appl Physiol*. 2026 Apr 6. https://doi.org/10.1007/s00421-026-06209-6. Epub ahead of print. PMID: 41940947.