Advancing Obesity Drug Development Through Gold-Standard Energy Expenditure Measurement: The Role of Doubly Labeled Water and Modern Deployment Platforms

Overview of Obesity as a Global Health Challenge

Obesity has emerged as one of the defining health challenges of the 21st century, impacting individuals across all age groups and socioeconomic backgrounds. Despite unprecedented advances in therapeutics, the fundamental drivers of weight regulation remain incompletely measured in clinical research, particularly the role of energy expenditure.

According to the World Health Organization, in 2022, 43% of adults worldwide were classified as overweight, with nearly 1 billion individuals living with obesity, more than double the number recorded in 1990. Additionally, over 150 million children and adolescents are affected, representing the fastest-growing group. [1]

Multiple factors contribute to this global rise, including the increased availability and consumption of calorie-dense and processed foods, greater sedentary behavior associated with modern transportation and screen use, and structural barriers to accessing healthy foods or safe environments for physical activity. Genetic predisposition and early-life exposures also increase susceptibility to weight gain. [2]

Obesity is associated with increased incidence of type 2 diabetes, cardiovascular disease, certain cancers, metabolic-associated fatty liver disease (MAFLD), and diminished physical function. Its economic burden already exceeds hundreds of billions of dollars annually and is projected to reach trillions globally by 2035. [3, 4, 5]

In the United States, approximately 40% of adults are classified as having obesity. This prevalence contributes to increased healthcare expenditures, reduced productivity, and the widening of health disparities among population groups. [5]

Core Physiology of Energy Balance and Weight Regulation

Body weight is determined by the balance between caloric intake and energy expenditure, a process regulated by complex physiological systems. The hypothalamus plays a central role in controlling appetite and energy utilization by responding to hormones such as leptin and ghrelin. These feedback mechanisms contribute to maintaining long-term weight stability. [9, 10]

Total daily energy expenditure (TDEE) reflects the sum of processes through which the body expends energy to sustain life and support activity: basal metabolism, nutrient processing, and physical movement. Understanding these components is essential for interpreting treatment effects in obesity trials

Resting Energy Expenditure (REE)

Resting energy expenditure, also known as basal metabolic rate, represents the energy required to sustain essential physiological functions such as respiration, thermoregulation, and cellular maintenance during rest. In most adults, this component accounts for approximately 60 -70% of total daily energy expenditure. REE is largely determined by fat-free mass, especially muscle and organ tissue, making it a key variable in weight regulation.

Thermic Effect of Food (TEF)

The energy cost of digesting and assimilating nutrients accounts for approximately 10% of daily expenditure, varying by meal size, macronutrient composition, and metabolic regulation.

Physical Activity Energy Expenditure (PAEE)

This component includes structured exercise and habitual movement. It is the most variable fraction of TDEE, ranging from ~15% in sedentary individuals to over 50% in highly active ones.

Non-Exercise Activity Thermogenesis (NEAT)

Non-exercise activity thermogenesis (NEAT) refers to the energy expended for daily activities such as fidgeting, maintaining posture, and performing household tasks. NEAT varies substantially among individuals, influenced by occupational demands, environmental context, and behavioral patterns.

Thermoregulation

When ambient temperature deviates from thermoneutrality, additional energy is required to maintain core temperature through shivering or heat-dissipation mechanisms. Although this energy expenditure is minimal under laboratory conditions, it may be significant in real-world settings and is increasingly recognized as relevant in obesity research.[6-8]

A comprehensive understanding of energy expenditure and its components, as well as how they adapt in obesity and during weight loss, is crucial in the development of obesity drugs. Objective measurement of energy expenditure provides mechanistic insight by distinguishing metabolic effects from appetite-mediated effects, supports differentiation between therapeutic classes, and aligns with increasing regulatory expectations for evidence supporting the mechanism of action in metabolic-modifying therapies.

Influence of obesity and weight loss on EE dynamics

In individuals with obesity, absolute EE is typically higher than in lean individuals due to larger body mass, but when adjusted for body composition, the metabolic rate per unit of lean mass may be slightly lower. This altered energy efficiency may contribute to difficulty in weight regulation.

Weight loss induces predictable reductions in EE, largely due to the loss of metabolically active lean mass and reduced energy demands of a smaller body. However, this decline often exceeds what is expected from changes in body mass alone. This phenomenon, known as adaptive thermogenesis, reflects the body's biologically hardwired response to perceived energy deficits and is characterized by disproportionate reductions in REE and physical activity energy expenditure.[11]

Clinically, adaptive thermogenesis can undermine weight loss efforts and long-term maintenance by reducing daily caloric needs to levels that are unpredictable. It also persists after weight stabilization in many individuals, contributing to weight regain, a major challenge in obesity treatment. Understanding these EE dynamics is essential for designing interventions that preserve lean mass and mitigate metabolic slowing.

Methods to Assess Energy Expenditure

Gold Standard Approaches

Accurate measurement of energy expenditure (EE) is crucial for understanding metabolism and evaluating interventions in obesity and weight loss research. Multiple techniques are available, each differing in precision, feasibility, and context of application. Among these, direct calorimetry, indirect calorimetry, and the doubly labeled water (DLW) method are considered the gold standards for assessing human metabolism.

Direct Calorimetry

Direct calorimetry measures energy use by tracking the body's heat production inside a special insulated chamber. This method provides a continuous and accurate measurement of metabolic energy, making it the theoretical gold standard for human energy metabolism. Still, it is technically complex and requires expensive, specialized equipment, as well as careful environmental control. Participants must stay inside the chamber for the entire test, which can be uncomfortable. Due to the high costs and limited availability, direct calorimetry is rarely employed in routine clinical or research settings.

Indirect Calorimetry

Indirect calorimetry is considered the practical gold standard for clinical and research use. It estimates energy use by measuring the amount of oxygen a person breathes in and the amount of carbon dioxide they exhale, often using devices such as a metabolic cart, a face mask, or a canopy. This information helps calculate energy expenditure and illustrates how the body utilizes various fuels, including carbohydrates and fats.

When performed correctly, indirect calorimetry yields reliable results that align with those from direct calorimetry. It is used in many settings, from intensive care units for nutrition planning to research studies on obesity. Newer portable systems enable the measurement of energy use at the bedside or in other locations, making the method more flexible and accessible. In specialized research centers, whole-room metabolic chambers can measure energy expenditure continuously over 24 hours or longer, providing high-resolution metabolic data under controlled conditions. However, their cost, infrastructure requirements, and restrictive living environment limit their widespread clinical use.

Even with its benefits, indirect calorimetry still needs trained staff, careful procedures, and regular equipment checks to ensure accurate results. While it is less expensive than direct calorimetry, the costs, time, and expertise required mean it is mostly used in specialized centers.

Doubly labeled water (DLW)

The DLW method is the gold standard for measuring total daily energy use in real-life conditions. After drinking water labeled with stable isotopes, the rate at which these isotopes are eliminated in urine or saliva reflects carbon dioxide production, providing a precise estimate of total energy expenditure over several days without altering normal behavior. DLW captures the average energy expenditure across the measurement period, rather than day-to-day fluctuations. While short-term changes in energy expenditure can be detected in response to major shifts in activity or metabolism, it does not provide a daily resolution. Additionally, the method is relatively expensive, requires specialized analytical equipment, and repeated back-to-back assessments typically necessitate a wash-out period to avoid dose overlapping.

Together, direct calorimetry, indirect calorimetry, and DLW constitute the gold-standard framework for human metabolic energy assessment across controlled and free-living environments.[12-14]

From Laboratory Gold Standard to Real-World Solution

DLW Challenges and Complexities

Historically, the doubly labeled water (DLW) method has been primarily implemented in academic or specialized research settings, and it is less frequently used in multi-center or later-stage clinical trials. The main barriers have included the technical complexity of kit preparation, sample collection, and isotopic laboratory analysis.

With the advent of specialty providers such as Calorify, which have leveraged their scientific expertise to develop and deploy robust, scalable processes suitable for large-scale, multi-center clinical research, the picture has changed significantly, and DLW has now become a viable, widely usable, and applicable research method.

These methodological advancements, including the use of off-axis integrated cavity output spectroscopy (OA-ICOS), automated sample processing, and optimized analytical workflows, have transformed DLW from a highly specialized research assay into a scalable and clinically deployable tool for metabolic assessment.

By reducing the need for on-site laboratory visits and enabling consistent, reproducible analysis across sites, these systems have expanded access to energy expenditure measurements in both centralized and decentralized studies. As a result, DLW technology can now be applied in real-world clinical research to generate the metabolic insight once confined to academic labs, positioning energy expenditure measurements as a practical and robust component of obesity and metabolic research.

Deployment and Advantages in Clinical Trials

In clinical research, a decentralized and automated DLW workflow may offer several operational advantages. DLW kits can be shipped directly to participants' homes, enabling remote sample collection and return without the need for on-site calorimetry or laboratory visits. Each test requires only a single oral dose of labeled water and a limited number of urine collections over several days, making the method well-suited to decentralized and hybrid study designs.

Compared to traditional calorimetry and site-based metabolic assessments, this approach enables the measurement of total energy expenditure in real-world conditions without disrupting participants' routines or relying on specialized facilities. It reduces logistical complexity, site workload, and overall study costs while enhancing accessibility, compliance, and data representativeness across diverse populations.

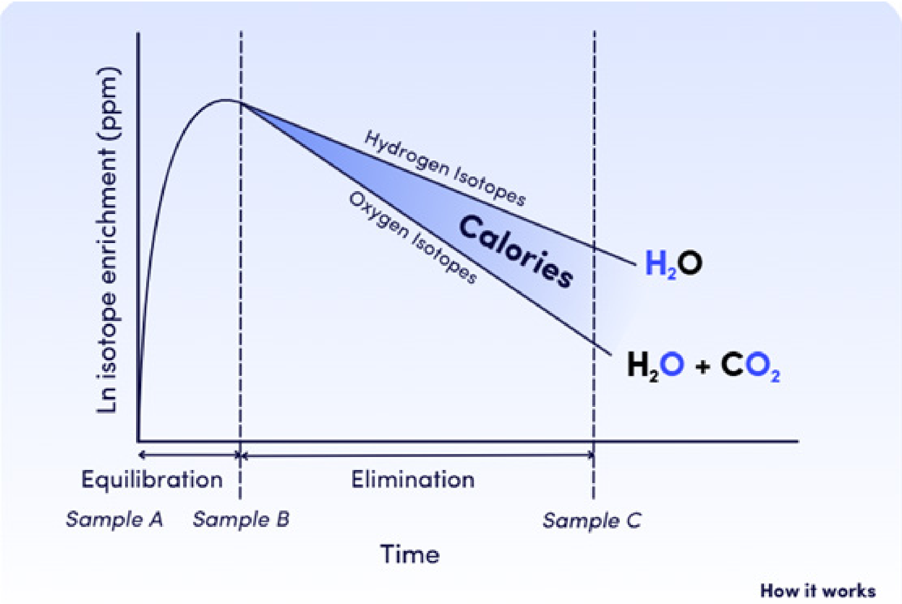

Figure Description:

Principle of the Doubly Labeled Water (DLW) Method for Measuring Energy Expenditure
The graph illustrates the change in isotope enrichment over time following administration of doubly labeled water containing stable hydrogen and oxygen isotopes. During the equilibration phase, both isotopes distribute uniformly within the body water pool (Sample A → Sample B). Thereafter, during the elimination phase, hydrogen isotopes are lost only as water (H_2O), whereas oxygen isotopes are eliminated as both water and carbon dioxide ($H_2O + CO_2$). The difference between the elimination rates of the two isotopes reflects carbon dioxide production, which is used to calculate total energy expenditure (caloric output).

Applications in Obesity Clinical Trials

Energy expenditure is a central determinant of weight loss efficacy and metabolic adaptation; however, it remains infrequently measured in clinical trials for obesity. Integrating DLW-based assessments provides objective insight into how therapeutic interventions influence caloric utilization, metabolic efficiency, and body composition over time.

In trials of anti-obesity medications, energy expenditure data can help distinguish pharmacologically driven metabolic effects from changes in energy intake alone. Similarly, in lifestyle or combination intervention studies, it allows for direct measurement of compensatory metabolic responses that often confound traditional endpoints such as body weight and BMI. Because the method is compatible with decentralized and hybrid study models, it can be deployed across heterogeneous study settings, improving real-world relevance and supporting the generation of rigorous, regulator-ready metabolic data.

By incorporating DLW-based energy expenditure measurements, approaches such as those exemplified by Calorify, obesity trials can move beyond weight-centric outcomes toward a more mechanistic understanding of metabolic changes, supporting a more precise evaluation of therapeutic efficacy, durability, and physiological impact.

Future Directions

As the science of metabolism advances, measurement of energy expenditure is expected to play an increasingly important role in obesity and metabolic disease research. Integrating these assessments into clinical trials will enhance the mechanistic understanding of treatment effects, metabolic adaptation, and weight maintenance, providing a more comprehensive view of energy balance beyond weight or body composition alone.

Emerging technologies now make it feasible to conduct these measurements in decentralized and longitudinal study designs, allowing repeated assessments across diverse populations and real-world settings. Combining energy expenditure data with complementary measures, such as continuous activity monitoring, dietary intake tracking, and biomarker or multi-omics profiling, will enable a more nuanced characterization of metabolic phenotypes and therapeutic responses.

Looking ahead, the ability to accurately quantify total energy expenditure at scale has the potential to transform obesity and metabolic research, bridging the gap between controlled laboratory insights and real-world clinical outcomes.

Calorify and ProSciento: Enabling Metabolic Innovation

The evolution of DLW technology has expanded access to the gold-standard measurement of energy expenditure in clinical research. Systems such as Calorify's automated, scalable DLW platform provide a practical pathway to implement these assessments in decentralized and multi-center studies with standardized analytical rigor.

ProSciento brings complementary expertise in early-phase and translational metabolic research, including protocol design, advanced phenotyping, functional assessments, and regulatory-aligned scientific execution. Drawing on deep experience across obesity, diabetes, and cardiometabolic programs, ProSciento supports the integration of DLW-based energy expenditure measurement alongside body composition imaging, muscle function evaluation, and biomarker and metabolic profiling.

Together, this scientific and operational framework enables the generation of high-quality metabolic data, provides mechanistic insight, and facilitates a more precise evaluation of therapeutic candidates—advancing the field toward more rigorous and informative obesity and metabolic disease trials.

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