



# Methodology fact sheet: Assessing energy expenditure

## Background

- Accurate assessment of energy expenditure is crucial to comprehensive clinical trials focused on pharmaceuticals or nutraceuticals for weight management.
- Total energy expenditure (TEE) can be divided into three components: resting energy expenditure (REE), diet-induced thermogenesis (DIT) and activity induced energy expenditure (AEE).
- The standard measurement methods are: indirect calorimetry for REE and DIT; spiroergometry for AEE; and the doubly labeled water method for total energy expenditure.

## How do indirect calorimetry and spiroergometry work?

**Indirect calorimetry** is a non-invasive, very accurate and highly reproducible method for assessing REE and DIT. Rather than directly measuring heat production to estimate energy expended, it monitors oxygen consumption and carbon dioxide production over time. Based on these measurements, energy expenditure can be calculated using specific formulas.

The subject is at rest during the measurements, which take approximately 30 minutes. It is essential that the subject has refrained from physical activity for more than 48 hours; has fasted overnight (for at least 10 hours) and not eaten a large or protein-rich meal the previous evening; and has had sufficient sleep.

**Spiroergometry** is also based on oxygen consumption and carbon dioxide production. However, the measurements are performed while the subject is performing physical activity (e.g., on a cycle ergometer). It is used to assess AEE, metabolism, cardiovascular performance and respiration, giving insights into the energetics of physical exercise and the pathogenesis of metabolic diseases. The procedure takes approximately 60 minutes.

## Advantages of indirect calorimetry and spiroergometry

- They yield precise and accurate measurements for the individual.
- They enable the determination of contributors to TEE. Indirect calorimetry enables the measurement of REE and DIT, as well as the resting metabolic rate (RMR). Spiroergometry enables the measurement of DIT and activity.
- They can be applied to quantify the oxidation rates of substrates.

## Challenges with indirect calorimetry and spiroergometry

- A very high level of standardization is necessary at every stage of the process, including standardization in the manner of preparation of the subjects.
- The high equipment costs are a barrier for some clinics and labs.

## Share of TEE

REE accounts for ~60–70% of total energy expenditure. AEE accounts for ~20–30% and DIT accounts for ~8–15%

## Substrate metabolism

Indirect calorimetry can also be used to identify the specific kind of energy substrate (carbohydrate, lipid or protein) being metabolized by the body at a given time.

## Protein oxidation rate

The protein oxidation rate can be measured using spiroergometry. This is based on urinary nitrogen excretion over a 24-h period.

## How does the doubly labeled water method work?

At Profil, we use the doubly labeled water method for TEE evaluations. The technique involves enriching the body water of the subject with isotopes of hydrogen and oxygen ( $^2\text{H}$  and  $^{18}\text{O}$ ), and then determining the elimination rates of the two isotopes.

$^2\text{H}$  and  $^{18}\text{O}$  in body water are diluted and eliminated in almost the same ways. The difference is that  $^{18}\text{O}$  is also eliminated as  $\text{CO}_2$  in exhaled air, giving it a faster elimination rate. This can be used to calculate  $\text{CO}_2$  production as a measure of energy expenditure.

The doubly labeled water method is the method of choice for assessing TEE under free-living conditions because it is only necessary to collect spot urine samples at defined points over a period of 1 to 2 weeks to calculate isotope dilution and elimination.

## Advantages of the doubly labeled water method

- It yields accurate measurements of individual TEE under free-living conditions.
- It is a non-invasive technique, relying solely on urine samples.
- It requires only naturally occurring stable isotopes, so there is no radiation involved.

## Challenges with the doubly labeled water method

- $^{18}\text{O}$  is expensive to purchase.
- Only highly experienced laboratories can successfully perform isotope analysis.

## Further reading

1. Heise, T., et al. 2016. Similar risk of exercise-related hypoglycaemia for insulin degludec to that for insulin glargine in patients with type 1 diabetes: a randomized cross-over trial. *Diabetes Obes. Metab.* 18(2): 196–199.
2. Engeli, S., et al. 2018. Effect of sacubitril/valsartan on exercise-induced lipid metabolism in patients with obesity and hypertension. *Hypertension* 71(1): 70–77.
3. Muscelli, E., et al. 2016. Metabolic consequences of acute and chronic empagliflozin administration in treatment-naive and metformin pretreated patients with type 2 diabetes. *Diabetologia* 59(4): 700–708.
4. Lamers, D. 2018. Determining energy expenditure in clinical trials. Profil Webinar. [profil.com/energy-expenditure-webinar](https://www.profil.com/energy-expenditure-webinar)

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