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Nutrition Discussion Forum

Body-weight change during over- and underfeeding as an indicator of adaptive thermogenesis

Macias (2004) designed a study to determine if there is a homeostatic control of human body weight by measuring body-weight changes after an experimental modification of energy ingested. Outcome measures were the trend in body weight as determined daily over several weeks at 07.00 hours and the amount of weight lost in an 8 h overnight period. The author concludes that the study demonstrated there is a homeostatic control of weight, and described an index of energy expenditure calculated from weight loss. In an invited commentary, Van Baak (2004) confirms that the observed changes in overnight weight loss support adaptive changes in energy expenditure during over- and underfeeding. The methodology is striking for its simplicity compared with the measurement of energy expenditure with direct and indirect calorimetry. However, as stated by both authors, a change in body weight cannot be directly converted into a change in energy expenditure.

Sanctorius (1614) demonstrated how a subject loses weight while seated in a chair suspended from a balance. The weight loss was ascribed to 'insensible perspiration'. Benedict & Wardlaw (1932) indicated that men's insensible weight loss fluctuates between 15 and 60 g/h. The insensible loss is the sum of the weight of water vapour given off and the difference in weight of CO₂ produced and O₂ consumed. A subject oxidising pure fat produces 0.7 mol CO₂ for each mol O₂ consumed. The weight of 0.7 mol CO₂ produced ($0.7 \times 44 = 31$ g) is thus nearly the same as the corresponding weight of O₂ consumed (1 mol O₂ = 32 g). The insensible weight loss is therefore almost equal to the weight of the water lost by evaporation. The other extreme is a subject oxidising pure carbohydrate where 1 mol CO₂ is produced for 1 mol O₂ consumed. Then, insensible water loss equals evaporative water loss plus 12 g/mol O₂ consumed and CO₂ produced.

The contribution of overnight energy expenditure to overnight weight loss can be calculated with the information presented earlier. The minimum is zero at pure fat oxidation. The maximum is reached at pure carbohydrate oxidation. Overnight energy expenditure is assumed to be equivalent to BMR and can be calculated with the Harris & Benedict (1919) equation. At pure carbohydrate oxidation, the energy equivalent of O₂ consumed is 473 kJ/mol (Brouwer, 1957). In that case, at the weight-maintenance diet in the study of Macias (2004), the weight loss due to energy expenditure is 54 g in 8 h for subject A, and 60 g in 8 h for subject B. The observed weight loss (the sum of the weight of water vapour given off and the difference in weight of CO₂ produced and O₂ consumed) was, respectively, 262 and 272 g in 8 h. Thus, 0 to 20% of overnight weight loss was due to energy

expenditure. The size and the potential variation of the contribution of energy expenditure to the overnight weight loss do not allow the weight loss to be used as an accurate indicator of energy expenditure.

In a situation where the carbohydrate:protein:fat ratio of the oxidation substrate changes, there is a simultaneous change in the energy expenditure-induced weight loss, even at an unchanged level of energy expenditure and an unchanged evaporative water loss. During underfeeding, the oxidation substrate changes to relatively more fat, resulting in a decrease of overnight weight loss. With overfeeding, the oxidation substrate changes to relatively more carbohydrate, resulting in an increase of overnight weight loss. Thus, overnight weight loss decreases irrespective of adaptive thermogenesis with an energy-restricted diet and increases irrespective of adaptive thermogenesis when overfeeding. Indeed, as stated by Macias (2004), overnight reduction of body weight cannot be directly converted to a change in energy expenditure. Therefore, unfortunately, the conclusion that the observed changes in overnight weight loss support adaptive changes in energy expenditure during over- and underfeeding cannot be drawn.

The other aspect of the study, the day-to-day trend in body weight as a function of dietary intake, underfeeding or overfeeding with a fixed activity pattern, also has to be interpreted with great care. The energy density of the body stores ranges from 4 MJ/kg for glycogen and lean tissue to 32 MJ/kg for fat tissue (Westerterp, 1994). The body-weight change over the first week after the experimental change in energy intake was 1.4 kg or more. After the transition week, body-mass change reached a constant value of about 0.4 kg/week. The explanation for the relatively large body-mass change in the transition week is a change in glycogen stores, with an eight times lower energy density as fat tissue. Thus, the observed diuresis in the first week of underfeeding is a reflection of the glycogen-associated water loss.

We are left with the value of the constant weight change, over the second to the fifth week after the change in energy intake at an unchanged activity pattern, of 0.4 kg/week with a hypo- and hyperenergetic diet. Macias (2004) calculated a theoretical minimum weight change of 0.75 kg/week for a situation without adaptive thermogenesis. The observed value can also be compared with a calculated value from a simulation model including adaptive thermogenesis (Westerterp *et al.* 1995). It is a continuous-time dynamic model with energy intake and energy expenditure as input variables, where energy expenditure is the sum of diet-induced energy expenditure and BMR multiplied by a factor for physical activity. In a negative energy balance there is a lowering of BMR per unit body mass depending on the size of the energy deficit. In a positive energy balance there is an energy cost to convert the surplus for storage.

The assumption is a change in energy intake at an unchanged activity pattern. The simulated weight change for the two subjects, taking adaptive thermogenesis into account, appears to be 0.6 kg/week instead of the observed 0.4 kg/week. This leaves 0.2 kg/week unexplained. The most probable explanation for the discrepancy is a decrease in the activity-induced energy expenditure during under- and overfeeding, even while subjects tried to do the same things as during the weight-maintenance interval (Velthuis-te Wierik *et al.* 1995).

Finally, why did the subjects not return to their initial weight in stage 2 of the study, after equivalent hypo- and hyperenergetic intervals? Interestingly, subject A and subject B each were nearly 1.0 kg heavier after they consumed overall a weight-maintenance diet over 16 to 17 weeks, including a 5-week interval with 38% underfeeding and a 5-week interval with 38% overfeeding. An explanation is a decrease in the activity-induced energy expenditure during under- and overfeeding, as mentioned earlier. Adaptive thermogenesis reduced the weight change during under- and overfeeding. The end result was an increase in body weight.

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Klaas R. Westerterp

Department of Human Biology
Maastricht University, PO Box 616
6200 MD Maastricht
The Netherlands
k.westerterp@hb.unimass.nl
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Body weight. Time to start learning from Sanctorius again – Reply by Macias

I would like to thank Professor Westerterp for his interest in my study (Macias, 2004) and his mention of Sanctorius (1614). This mention is not casual as I conceived my study thinking about Sanctorius and his weighing chair (Fig. 1). For decades, Sanctorius worked, ate, slept and made love in his chair to see his weight homeostasis in action. He discovered that the weight of his excreta was less than that of his food and drink. We now know that the difference is not a salutary way of sweating off internal toxins; apart from that, current knowledge of our body-weight clockwork is in essence where Sanctorius left it.

Westerterp poses several objections to my study, concluding that there is nothing in it in the way of demonstrating a human weight set point (a 'ponderostat'). He reasonably assumes that oxidation substrates may change from relatively more carbohydrates at overfeeding to relatively more fat at underfeeding, which would mean less weight lost per unit of energy spent. The catch of such an assumption is that we do not know what the dynamic of that change is. Glycogen can be replenished in the absence of food intake even after exercise (Fournier *et al.*



Fig. 1. Sanctorius Sanctorius (1561–1636) in his weighing chair. Image courtesy of the Blocker History of Medicine Collections, Moody Medical Library, The University of Texas Medical Branch, Galveston, TX, USA.

2002). At the moderate food restriction of my study, body-weight fall did not follow an uninterrupted downward trajectory but that of a tapering curve with blips suggestive of glycogen replenishment. I think I made it clear that overnight weight loss cannot be directly converted to energy expenditures. Furthermore, I described that my weighing instrument was not precise enough, which could be now added to Westerterp's objections. Alas, for weighing individuals, Sanctorius' contraption was more precise than the best gadget I could get four centuries later! As a result, I resorted to statistical calculations and I stated that future studies will require more precise instruments that allow static weighing.

Given our difficulties in interpreting physiological weight loss, should we forsake Sanctorius' approach and be happy only measuring energy expenditures? Let us first consider methodological worries. The total daily energy expenditure is generally measured after the excretion of water labelled with isotopes, followed by calculations with formulas (Seale *et al.* 1989; Amatruda *et al.* 1993). The resting metabolic expenditure is measured under a 'hood calorimeter', analysing fractions of gases flowing out of the hood and calculations with formulas (Rodriguez *et al.* 2002). The thermal effect of food is calculated against pre-feeding values with measuring at 30, 120 and 240 post-feeding minutes (Leibel *et al.* 1995). Finally, there is no way to measure directly the expenditure from activity, which is calculated as the difference between total energy expenditure and the sum of the other measured components. From these complexities, it is not surprising that the results from different studies are discordant, often cancelling each other out (Granata & Brandon, 2002). I argued that we need to break such a methodological impasse with a different approach.

If we consider the difficulties of measuring energy expenditures, food standardisation, activity control and weight measurement are more reproducible. Nevertheless, the assumption that human intake cannot be standardised made energy measurements the hub of studies during the twentieth century. I designed the overnight weight loss as a straightforward index of the resting metabolism, even though it is not necessarily equivalent to calorimetric determinations. But to engage in a discussion of the superiority of surrogate markers will go full circle to the methodological impasse. As I said, the simple fact that we do not know the relative changes of metabolic substrates at under- and overfeeding makes assumptions invalid, so I will not defend calculations. For the time being, I can only say that losing more or less weight after eating more or less is an important metabolic adaptation whose significance cannot be easily denied.

Westerterp's objections say nothing about what I described as the most striking fact in favour of a ponderostat; the same diet that causes weight gain can cause weight loss. Westerterp, however, pretends that everything can be inferred from calculations and assumptions. And when calculations do not fit because some weight is left over, he infers that the activity was for certain not well controlled. This is stretching inference too much, because that simply did not happen. I think I know all too well; I was there. We could as well argue that a hot sandwich

has more energy than a cold one; the uncertainty principle applies even to exact sciences. A strict control of activities, to the last movement of our pinkies, is impossible. Yet, our activities could be reasonably well controlled within one building in the lecture rooms, laboratories and library. We had to deviate from transportation only one block for weekly food shopping and occasional visits to the bank. Being that the RMR is the main consumer of energy (Leibel *et al.* 1995; Garrow, 2000), it is improbable that minor deviations from sedentary activities explain the observed phenomena. An ecological model explains what may happen when we are overfed; the set point seems to function rather as a settling point with new levels maturing after continuously demanding the upper limit (Egger & Swinburn, 1997).

I wonder if scepticism represents prevalent feelings for considering self-experimentation unworthy. Despite its long and productive history, self-experimentation is no longer a driving force in medicine (Altman, 1972). This is unfortunate because self-experiments can do many things more easily than conventional experiments. When Westerterp questions my ability to control activities he is judging my study with a rigour that we do not usually exert for conventional research. Multi-authorship and technical complexities, however, make reproducibility difficult, even for honestly conducted studies, to say nothing of those involving scientific fraud and post-result cooking of data. Straightforward designs promote authors' accountability. I am confident that the methods I described can be replicated even by non-experts, requiring only motivated subjects and a good scale. From my experience as a human guinea-pig, I think that we could learn a good deal about nutrition by experimenting on ourselves. Do you want to experiment what dyspepsia is? Overfeed yourself for weeks and you will feel it full-blown; then read any review on dyspepsia and you will find nowhere overfeeding as a cause. Some functional dyspepsias could be a good defensive mechanism against overfeeding!

Over theory, facts should take precedence. First, the very same diet that kept weight unchanged was able to cause weight loss or gain. Second, under the isoenergetic diet, day-to-day weight variations were surprisingly small. Third, and yes, we lost more weight overnight when we ate more and less when we ate less. A rose is a rose; we must come with fact-driven calculations and not the other way round. Theoretical calculations, however elegant, cannot substitute facts and they cannot convince me that everything is moonshine. To start with, let us try to confirm in others the existence of the facts I reported in two subjects; it may be worthy, they are facts newly reported in literature. To follow, let us honour or reject the existence of those facts. To finish, let us explain what happens. Sanctorius' approach still makes sense, as makes sense his teaching that we should rely first on sense experience, second in reasoning and lastly on authority.

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Alejandro E. Macias

Guanajuato University School of Medicine at Leon
Mexico, 20 de Enero 929

Leon
Guanajuato 37320

Mexico

aaeemmh@yahoo.com

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