# DO THE OBESE HAVE LOWER BODY TEMPERATURES? A NEW LOOK AT A FORGOTTEN VARIABLE IN ENERGY BALANCE

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## ABSTRACT

Understanding the pathogenesis of obesity is now more important than ever, given the remarkable world-wide epidemic. This paper explores the potential role of core temperature in energy balance, and develops the hypothesis that basal temperature and changes in the temperature response in various situations contribute to the enhanced metabolic efficiency of the obese state. The argument is based on the important contribution that heat production makes in establishing the basal or resting metabolic rate, as well as on an analysis of the adaptive role played by changes in temperature in response to environmental challenge. If this hypothesis is validated, new therapeutic approaches may ensue.

## Total Energy Expenditure and the Energy Balance Equation

In sedentary humans, estimates suggest that physical activity accounts for about 10% of energy expenditure, while basal or resting metabolic rate (RMR) accounts for about 80%, and adaptive thermogenesis rounds out the remaining 10%. The latter refers to sympathetically mediated heat production in response to cold or dietary intake. RMR, in turn, has two major components: "essential" heat, which constitutes about 1/3$^{rd}$ of RMR, represents the energy required to maintain cellular integrity and the ionic environment; the second component of RMR is heat production for homeothermy which amounts to about 2/3$^{rds}$ of the metabolic rate [1–3]. Although these estimates are rough and may underestimate the contribution of physical activity depending on the definition of "sedentary," overall they imply that up to 50% of energy expenditure in sedentary man is dedicated to maintaining a constant core temperature. This extraordi-

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nary observation is validated by the fact that the metabolic rate of a mouse is many-fold higher than that of a lizard of the same weight [3].

What does this mean in terms of energy balance? Consider the energy balance equation:

$$\text{Energy Intake} = \text{Energy Output} + \text{Storage}$$

When intake is equal to output, the individual is in energy balance, and there is no change in storage (fat). Increases in any of the components of energy expenditure would expand the range of intakes over which energy balance could be maintained. Conversely, decreases in any of the output components would reduce the range of intakes over which balance could be achieved.

Can this simple tautological expression help to understand the current epidemic of obesity and its related disorders? Does it help to understand why humans are heir to obesity? Is there more to obesity than "gluttony and sloth"? And if so, what is the basis of the differences between lean and obese?

## Metabolic Efficiency

In this context, metabolic efficiency refers to individual differences in the dissipation of calories as heat. In a classic overfeeding experiment involving twin pairs, a three-fold variation in weight gain was noted among the participants who consumed an additional 1000 kcal/day, 6 days per week, for three months, while maintaining a sedentary life-style and limiting activity [4]. Some of the subjects dissipated almost no portion of the increased calories while others dissipated as much as 60%. The differences were greater between twin pairs than within twin pairs, implying an inherited disposition to metabolic efficiency.

Those who dissipate excess calories may be said to have a less efficient metabolism than those who store ingested calories as fat with less dissipated as heat. Those with the more efficient metabolism resist famine better, but have a predisposition to become obese when faced with an abundant food supply and in the presence of dietary excess. Given the ever increasing prevalence of obesity in the US and the world, understanding the basis of these differences in metabolism is of critical importance [5].

## Compartments of Energy Output

The three major compartments of energy expenditure include: physical activity, adaptive or facultative thermogenesis and basal or resting metabolic rate (RMR).

***Physical Activity.*** In sedentary man, purposeful and non-purposeful movement account for about 10% of total energy output [2]. In people who are physically active, the activity component of energy output is, of course, correspondingly greater. In the study of metabolic efficiency described above, differences in activity were unlikely causes of the differences in weight gain, pointing to differences in metabolic efficiency as the cause of differences in weight gain.

***Adaptive (Facultative) Thermogenesis.*** This category also accounts for about 10% of total energy expenditure. Heat is generated by chemical reactions that address a physiologic need, most notably cold exposure (non-shivering thermogenesis) or dietary intake (diet-induced thermogenesis). The processes that generate heat in these situations are regulated by the sympathetic nervous system. Thyroid hormones play a permissive role [6]. In rodents and small mammals, and in human neonates, brown adipose tissue (BAT) is the site of heat production [3, 7]. The role of BAT in large primates has been controversial, but recent evidence utilizing PET scanning suggests that functional BAT can be demonstrated in adult humans [8, 9]. The potential role for BAT aside, it is well established that sympathetic stimulation increases heat production in humans, that stimulation of the sympathetic nervous system (SNS) underlies dietary thermogenesis, and that suppression of the SNS with fasting or low energy diets decreases energy expenditure [6, 10]. A robust capacity for dietary thermogenesis could act as a buffer against weight gain; a diminished capacity, on the other hand, would decrease the range of intakes over which energy balance could be achieved. In the later case the more efficient metabolism would constitute a thermogenic handicap.

Since the SNS is the mediator of adaptive thermogenesis (supressed with fasting, increased with overfeeding), it is reasonable to ask whether diminished SNS activity accounts for the enhanced metabolic efficiency in the obese. This is a plausible explanation since inherited models of rodent obesity do, in fact, have diminished sympathetic activity [11, 12]. Overfed models of obesity in rodents, however, as well as obese humans have increased rather than diminished sympathetic activity [13–16]. Any impairment, therefore, in dietary thermogenesis is not due to diminished SNS activity. It is possible, however that the thermogenic response to SNS stimulation might be blunted in the obese. This would be consistent with data suggesting that dietary thermogenesis may be diminished in the obese.

***Basal or Resting Metabolic Rate.*** The term resting metabolic rate is usually employed because it assumes less about the "basal" state than basal metabolic rate (BMR), although for practical purposes the two

terms are generally considered equivalent. As noted above, in completely sedentary man, resting metabolic rate (RMR) is considered to account for about 80% of total energy expenditure [2]. In the physically active, RMR may be substantially less depending on the degree of activity.

RMR (or BMR), in turn, is comprised of two components: essential energy expenditure and the energy required for homeothermy. The former refers to the energy utilized in maintaining cellular structure and function, including protein turnover, ionic gradients (calcium, sodium) and the like. The latter is the metabolic cost of maintaining core temperature at approximately 37 degrees C. It has been estimated that the cost of homeothermy is about 2/3rds of the BMR [2]. This is consonant with the well recognized observation noted above that the metabolic rate of a mouse is 8 to 10 times greater than that of a lizard of the same body weight [3]; since the components of essential energy expenditure should be similar in both poikilotherms and homeotherms, the clear implication is that maintaining the higher temperature is the cause of the increased metabolic rate. If the RMR is 80% of total energy expenditure, then approximately 50% of total energy is expended in the maintenance of homeothermy. RMR is generated by mitochondrial metabolism regulated by thyroid hormones with a minor contribution from the SNS.

## Metabolic Rate in the Obese

Despite the compelling evidence for a thermogenic handicap in the obese, a clear demonstration of weight-related differences in metabolic efficiency has not been forthcoming. A likely explanation for the failure to definitively demonstrate differences in energy expenditure in direct comparisons between lean and obese involves factoring for body size. Energy expenditure is measured by oxygen consumption, and this requires normalizing for the mass of metabolizing tissue. This conundrum-how to compare a 150 kg person with a 70 kg person-has never been successfully resolved. Factoring by body surface area or by lean body mass (the usual method) has theoretical as well as practical limitations [17]. The measurement error in lean body mass determination, for example, is large enough to swamp a physiologically important difference in oxygen consumption. Core temperature, on the other hand, can be measured precisely and is independent of body size, thereby avoiding this conundrum.

## The Case for Core Temperature

Five points indicate the potential importance of lower core temperature as a factor in the enhanced energy efficiency associated with obesity:

***Substantial Contribution to RMR.*** Maintenance of a core temperature of 37 degrees C is the major factor in generating an RMR. As much as 50% of total energy expenditure might be due to homeothermy in truly sedentary humans.

***Effect of Temperature on Metabolic Rate.*** It has been known since early in the 20th century that a rise in temperature is associated with an increase in metabolic rate. Each degree C rise in temperature is associated with a 10–13% increment in oxygen consumption [18]. The elevation in temperature itself is responsible for speeding up metabolism.

***Metabolic Rate and Core Temperature Vary Among Individuals and in Different Populations.*** There is an inverse relationship between mean annual ambient temperature and RMR in different geographic regions. RMR is higher in arctic climes and lower in the tropics [19–22]. RMR, furthermore, is known to vary among individuals by as much as 600 Kcal per day [3].

***Fall in Temperature is a Physiologic Adaptation to Decreased Energy Intake.*** Given the quantitative significance of temperature maintenance in overall energy expenditure, it should come as no surprise that a fall in temperature is part of the adaptive response to energy deprivation. During starvation both energy output and temperature drop [10, 23]. Hypoglycemia, an acute state of energy deprivation, is likewise associated with hypothermia [24–26]. Recent studies also demonstrate that Fibroblast Growth Factor 21, a ligand generated in the liver under the regulation of peroxisome proliferator-activated receptor $\alpha$ (PPAR$\alpha$), mediates lipid mobilization during fasting and induces a fall in temperature (shallow torpor) in mice [27]. All of there observations indicate that lower temperature is an important part of the metabolic response to diminished energy intake.

***Precedence in the Animal World.*** Genetically obese rodents (*ob*/*ob* mice, *fa*/*fa* rats) have lower temperatures than lean control animals [28–31]. Hibernation, and the lesser state of shallow torpor, which are utilized by many mammalian species, are associated with substantial falls in core temperature [32, 33]. Some indigenous human populations also undergo torpor, an exaggeration of the normal fall in core temperature during nighttime sleep [34].

## Potential Impact of Temperature on Metabolic Efficiency

Temperature might be involved in enhancement of metabolic efficiency in the following ways: lower basal core temperature set point; greater nocturnal temperature fall; lesser temperature rise during

exercise; lesser post-prandial temperature rise; and a greater temperature fall during fasting or decreased energy intake as in therapeutic dieting. Some studies in humans have suggested a lower body temperature in the obese but others have not [35–37].

***Quantitative Significance.*** Some rough estimates of the impact of temperature on energy balance are of interest. A positive caloric balance of 3500–4000 Kcal results in the deposition of one pound of fat. Walking one mile burns about 100 kcal. A one degree C increase in core temperature, by increasing metabolic rate 10–13%, would lead to an increase in caloric expenditure of 100 to 130 Kcal/day, assuming a caloric intake of 2000 Kcal/day, and assuming that temperature accounts for 50% of total energy production. This would increase the range of dietary intake over which an individual could maintain energy balance by a corresponding amount. Conversely, one degree C lower temperature would impose a thermogenic handicap of 100–130 Kcal/day which might amount to 3000–4000 kcal per month or one pound of fat. These calculations are gross approximations only, but they serve to indicate that lower temperatures might contribute significantly to metabolic efficiency. Temperature may thus be a component of a thrifty metabolic phenotype.

## Summary: Core Temperature and the Pathogenesis of Obesity

"Gluttony and sloth", over eating and lack of exercise, obviously play an important role in the genesis of obesity. But the decisive demonstration that individuals differ in metabolic efficiency indicates that other factors are also at play. Evidence summarized here suggests that lower core temperature in the obese may be one such factor. Studies of body temperature in the obese under different circumstances (exercise, sleeping, after meals) are feasible and may reveal important differences between lean and obese. If this proves to be the case, a new therapeutic target, body temperature, may emerge.

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## DISCUSSION

**Luke, Cincinnati:** Pheochromocytoses and thyrotoxicosis cause higher temperatures. Is this related to this?

**Landsberg, Chicago:** Well both of those have a significant increase in metabolic rate by different mechanisms, frequently by core temperature, but it's not exclusively by core temperature, because they sweat a lot; and so they defend their temperature but have a lot of increased energy production.

**Chapman, Jackson:** Body temperatures tend to be lower in patients who are in renal failure, uremic. Have there been any studies on weight gain that occurs in uremia?

**Landsberg, Chicago:** That's a good point. I am not aware of any. Maybe some of the nephrologists know.

**Boyer, New Haven:** Interesting talk, Leu. There is some recent exciting data from France that indicates that bile acids affect thermogenesis, I think through some way of regulating the thyroid. This would explain, perhaps, the fasting-feeding effects, since in fasting, bile acids will stay in the gallbladder rather than being circulated; and it might also explain the complications from ursodeoxycholic acid therapy, where weight gain is one of the hydrophobicity of bile being decreased. Could you comment on that possibility?

**Landsberg, Chicago:** That is an interesting thing to pursue. We don't know what underlies these changes. I suspect that thyroid hormone is importantly involved and

that thyroid-regulated mitochondrial metabolism in cells throughout the body is apt to be important.

**Boyer, New Haven:** Perhaps alterations in the enterohepatic circulation of bile acid might be playing a role here via a target for therapy.

**Hochberg, Baltimore:** So one of the populations which has this metabolic efficiency and has been extensively studied are the Pima Indians in the southwest, particularly in Arizona, and there are lots of data through NIDDK from their research station. Do you know if anybody has ever looked at body temperature in this group?

**Landsberg, Chicago:** This is the only group that has been looked at in this way, and they had two reports on temperature in the obese Pimas. One reported that it was increased and one reported that it was decreased. It depends on how you look at it. So I think we need further studies.