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PERSPECTIVE

"Calories in, calories out" and macronutrient intake: the hope, hype, and science of calories

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Howell S, Kones R. "Calories in, calories out" and macronutrient intake: the hope, hype, and science of calories. *Am J Physiol Endocrinol Metab* 313: E608–E612, 2017. First published August 1, 2017; doi:10.1152/ajpendo.00156.2017.—One of the central tenets in obesity prevention and management is caloric restriction. This perspective presents salient features of how calories and energy balance matter, also called the "calories in, calories out" paradigm. Determinants of energy balance and relationships to dietary macronutrient content are reviewed. The rationale and features of the carbohydrate-insulin hypothesis postulate that carbohydrate restriction confers a metabolic advantage. According to this model, a large amount of fat intake is enabled without weight gain. Evidence concerning this possibility is detailed. The relationship and application of the laws of thermodynamics are then clarified with current primary research. Strong data indicate that energy balance is not materially changed during isocaloric substitution of dietary fats for carbohydrates. Results from a number of sources refute both the theory and effectiveness of the carbohydrate-insulin hypothesis. Instead, risk for obesity is primarily determined by total calorie intake.

calories in, calories out; metabolic adaptation; thermic effect of food; CHO-insulin hypothesis; laws of thermodynamics; obesity; low-carbohydrate diet; energy expenditure; metabolic advantage; NuSI

Approach to Obesity, Calories, and Energy Balance

OBESITY HAS REMAINED a substantial and increasing contributor to the global burden of disease, with current prevalence estimates of 5% in children and 12% in adults, representing more than a twofold increase since 1980 (11). In the United States, over 66% adults are overweight, 33% are obese, and the proportion of very obese is growing rapidly (18). Despite mechanistic and clinical advances in management, all highlight the central importance of energy imbalance (34).

Since 1824, nutritionists have used the calorie, a unit of energy (heat), to measure the ability of food to fuel work, either biochemical or physical (24). Buttressed by many well-designed studies, common experience, and 95 million Google search results later, obesity is now attributed to excessive calorie consumption in relation to the work expended. This is popularly expressed as "calories in, calories out"; creating a deficit causes weight loss, whereas excess, regardless of macronutrient type or quality (or decreasing energy expenditure), leads to weight gain.

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Calories "in," consumed in food, are self-explanatory. Calories "out" consists largely of resting energy expenditure (REE), the energy requirement or basal metabolism of the body "at rest" in the absence of external work. REE is chiefly dependent on lean body and fat-free mass, and accounts for 60–70% of total energy expenditure. It is also highly variable, due to interindividual differences in metabolic rates and the size of internal organs. The second component of calories out is physical activity, which may be considered the sum of basal activities of daily living and purposeful physical activity, or "exercise." The third, and typically the smallest, component of total energy expenditure is the thermal effect of food (TEF, or diet-induced thermogenesis). TEF is the energy associated with a postprandial rise in metabolic rate and covers energy expended to process food, usually amounting to ~10% of ingested calories (17). This accepted estimate may vary, since TEF differs among macronutrients: largest for protein, intermediate for carbohydrate, and smallest for fat.

In response to reduced energy intake, metabolic adaptation or adaptive thermogenesis occurs, referring to a decrease in energy expenditure (5). Any lean body mass that is lost over time will lower REE. For these reasons, the inability to lose weight as diets progress and prevent weight regain is explained by these adaptations (38). Although a decline in the metabolic rate during periods of calorie deprivation certainly occurs and may be contributory, whether the magnitude is commonly greater than predicted by changes in TEF and body composition so that it exceeds the original calorie deficit prescribed for weight loss is controversial (10, 40). In fact, good adherence to calorie-reduction diets may be sufficient to overcome the degree of ordinary adaptive thermogenesis encountered. The experiences chronicled in the National Weight Loss Registry clearly support this contention (42). Curiously, the degree of metabolic adaptation may occur independently of total baseline body fat, and may persist for considerable periods of time, even when energy balance is achieved at a lower body weight. Unfortunately, some observers have misinterpreted the data just presented by proclaiming that calorie balance and applications such as portion control are irrelevant or archaic; such a conclusion is misguided and has the potential to undermine significant progress.

In summary, during underfeeding, the older equivalency of a loss of 1 lb. of fat from a 3,500 calorie dietary deficit no longer holds, to the extent that energy intake, expenditure, and weight are interrelated. Nonetheless, this remains a useful clinical approximation with the proviso that the discrepancy will represent metabolic adaptation. Thermodynamic interpretation of events, however, still applies: the caloric energy

derived from oxidizing calories in will be the same in an intact human as in the bomb calorimeter, i.e., calories out, after adjustments are made for conditions, form of energy produced, and reaction products.

In view of the alarming magnitude of the dual epidemics of obesity and Type 2 diabetes, both of which drive other risk factors and cardiovascular disease, lowering their prevalence and severity has become a global public health challenge (22). There is no medical treatment capable of reliably preventing or treating obesity in the long term. Several recent well-designed and resource-intensive initiatives have not been able to reverse this trend. Accordingly, the possibility that varying the macronutrient content of diets might improve weight management has received considerable attention. The advantage of higher protein intakes in weight loss and maintenance due to improved satiety, high TEF, lower ghrelin levels, and improved gluconeogenesis and plasma triacylglycerol concentrations is generally acknowledged (23, 31). Barriers to wider adoption of high-protein diets include acidosis, an association between high branched-chain amino acid intakes and metabolic disease, and renal and bone effects (6). There are also some concerns that the rise in levels of insulin growth factor-1 produced by animal protein, in conjunction with a Western diet, may promote aging, cancer, and cardiovascular disease.

In addition to protein, isocaloric manipulation of dietary content of CHO and fats to produce meaningful weight loss has been the subject of intense debate. This perspective focuses on the evidence that a low-CHO diet, due to a "metabolic advantage," produces greater weight loss than a low-fat diet, calorie for calorie. In other words, energetically, is a carbohydrate calorie different from a fat calorie?

Energy Effects of Varying Macronutrient Intake

When rates of energy expenditure and substrate oxidation were continuously measured in volunteers, classic studies reported that dietary fat intake, as opposed to mixed diets, failed to promote fat oxidation (33). These data implied that raising dietary fat consumption was obesogenic. Short-term, mixed-diet overfeeding studies in humans have indicated that there is high energy economy during overfeeding, so that all energy ingested in excess of maintenance requirements is accounted for either as energy stored as fat (75%) or as energy expenditure (25%) (32). Sonko et al. (35) reported a dose-dependent relationship between the amount of fat ingested fat and fat metabolism in the immediate postprandial period. About 26% of the fat was oxidized, with this amount inversely and significantly correlated with the dose ingested, implying that ingested quantities over ~50 g in normal resting adults were stored as fat. Therefore, taken together, fat ingestion does not promote fat oxidation. Rather, the opposite occurs: as the amount of fat consumed rises, the proportion that is oxidized falls.

Abbott et al. (1) assessed body energy balance, along with carbohydrate (CHO), fat, and protein balances in 27 men and 27 women over a 24-h period in a respiratory chamber. Overall energy balance was correlated with fat balance in men and women ($r = 0.79$ and 0.72, respectively), with the relationship approaching unity in both men (1.16 ± 0.18) and women (0.80 ± 0.15). Since there were no correlations between energy balance and either CHO or protein balances, it was concluded that CHO and protein stores were tightly regulated by adjusting oxidation to intake. These data strongly suggested that imbalance between energy in and energy out was buffered by body fat stores, resulting in a large proportion of fat stored during daily fluctuations in energy balance.

As mentioned, data on thermic effect of CHO and protein is widely published and consistent. Acheson (2) reported diet-induced thermogenesis values of 20–30% for protein, 5–10% for CHOs, and 0–3% for fat. A review by Westerterp (39) noted a similar macronutrient oxidation hierarchy across ventilated hood and respiration chamber studies of diet-induced thermogenesis. Mixed-diet protocols consumed at energy balance resulted in diet-induced energy expenditure of 5–15% of total 24-h energy expenditure. Energy expenditure was greater with high-protein consumption, but less with high-fat consumption. The latter has implications for the largely anecdotal acceptance of ketogenic or very low CHO on the basis of satiety, appetite control, and decreased caloric intake (30). To the contrary, Westerterp-Plantenga (41) reported higher satiety scores with high-protein and high-CHO diets during meals ($P < 0.001$) and over a 24-h period ($P < 0.001$), compared with a high-fat diet. Greater satiety scores were attributed to high-protein content as compared with high carb content. Most likely, any satiety benefit from very low CHO or ketogenic diets is derived solely from protein content; the impact on overall food intake has never been measured in a controlled environment.

The CHO-Insulin Hypothesis

In the 1970s, Atkins (2a) postulated that *1*) severe restriction of CHO would confer a substantial metabolic advantage, and therefore *2*) large amounts of fat could be consumed without significant weight gain. Since then, a plethora of publications and lay articles have conflated the cause of obesity generally with the purported metabolic advantage of low-CHO consumption. A third matter, whether unnecessary addition of simple sugars to the American diet is associated with ill health, is related to these questions, but is not the subject of debate.

Using data from animal models, Ludwig and Friedman (27) proposed that high CHO intakes induce an internal starvation response by chronically simulating insulin secretion, inhibiting lipolysis and the release of fatty acids, and driving fat into adipocytes for storage. This purportedly "starves" metabolically active muscle, heart, and liver, leading to hunger and overeating. When combined with a metabolic adaptation in energy expenditure, obesity follows. Their "carbohydrate-insulin" hypothesis also predicts that lowered CHO intake then reduces insulin levels, restores lipolysis, allows metabolism of fat by other cells, thereby leading to loss of weight. Hence, high insulin levels are associated with weight gain and adaptive suppression of energy expenditure (EE), whereas low-CHO intake releases this maladaptive block to permit fat oxidation. A person consuming low CHO can burn more calories than one consuming higher amounts of CHO without commensurate weight gain: the so-called metabolic advantage. The CHO-insulin hypothesis directly challenges the collective data from the classical work cited above. Moreover, even though insulin does inhibit lipolysis, this property per se is not an independent cause or predictor of fat mass. Another inconsistency is that when insulin levels are high in obese individuals, plasma fatty

acid and glucose levels are not low, in contrast with the "cellular starvation" portrayal basic to the CHO-insulin hypothesis.

Motivation

Scientific interest in calories in, calories out was piqued by Feinman and Fine (9) who declared that "a calorie is a calorie" violated the second law of thermodynamics, viz., in irreversible reactions an energy imbalance is not only required, but essential, as entropy increases. These authors maintained that different thermic effects of macronutrients illustrate this principle. Buchholz and Schoeller (3) disagreed, stating that thermodynamic theory dictates that a calorie is a calorie independent of dietary macronutrient composition. In their view, any greater loss of weight reports in early studies of low-CHO/high-protein diets was not due to either macronutrient-specific differences in the availability of dietary energy or changes in EE. Several articles, however, continued to maintain that the calories in, calories out paradigm was untenable (27, 36). A salient point was that both Ludwig's and Feinman's works complemented each other, with the latter solidifying Ludwig's biological claims. The surrounding climate concerning the CHO-insulin hypothesis involved molecular biologist and author, Marion Nestle, author of "*Why Calories Count: From Science to Politics*" (28, 28a). She argued that total calories, regardless of macronutrient ratios, mattered, citing 1964 metabolic ward results from obese patients consuming controlled low-calorie diets with differing macronutrient composition (20). Gary Taubes, a prolific journalist, also published a book which effectively demonized consumption of CHOs (37). To validate his theory, Taubes formed the Nutrition Science Initiative (NuSI) to fund and sponsor research studies designed to demonstrate the efficacy of CHO-restricted diets (29).

NuSI Study Findings

One of these was a NuSI study, co-sponsored by the National Institutes of Health, seeking to determine if an isocaloric low-CHO ketogenic diet (KD) resulted in changes in EE, respiratory quotient (RQ), and body composition (14). A metabolic ward design was used, enrolling 17 overweight or obese men that were fed a high-CHO baseline diet (BD) for 4 wk and a KD with clamped protein for another 4 wk. Each subject was evaluated for two consecutive days per week in metabolic chambers to assess EE, sleeping EE (SEE), and RQ. Dual-energy X-ray absorptiometry was used to assess body composition and doubly labeled water EE_{DLW} assessed average EE of the final 2 wk of each BD and KD period. Researchers found all subjects lost body fat and weight coinciding with an overall negative energy balance ~300 kcal/day. The KD diet showed increases in $EE_{chamber}$ (57 ± 13 kcal/day, $P = 0.0004$) and SEE (89 ± 14 kcal/day, $P < 0.0001$) and a decrease in RQ (-0.111 ± 0.003, $P < 0.0001$). The average EE increased by (151 ± 63 kcal/day, $P = 0.03$). There was a decrease in the rate of body fat and fat-free mass loss along with greater protein utilization. Contrary to Taube's beliefs, these data demonstrated that the KD was associated with almost undetectable increases in EE and no increase in body fat loss. A protest concerning the small size and potential inaccuracy of calculations in this study was made (26); a reply provided specific explanations justifying the interpretations made (15).

Hall's Review

Hall (13) subsequently presented how premises of the CHO-insulin hypothesis were demarcated sufficiently to allow experimental verification. Two recent studies, including the NuSI study, met the controlled conditions for verification (12, 14). The first premise of decreased insulin secretion and the second of increased fat oxidation were met. The third premise of increased body fat loss was falsified by the finding that even though insulin secretion was reduced, both studies consistently resulted in less body fat loss with CHO restriction diets than isocaloric diets when protein was equated. According to the CHO-insulin hypothesis, when insulin levels fall, body fat would also decrease.

Rebuttal

Since release of the data and Hall's interpretation, there have been several exchanges in which Ludwig (25) argued Hall was incorrect in both areas. The text was based on speculation mixed with incomparable and tangential studies: two observational, one animal, one controlled trial, and one systematic review. One valid argument was that the NuSI study was not randomized and possessed no control of carry-over effects of the diets.

The validity of Ludwig's assertions fades when study design, study intent, measuring standards, and evidence from other controlled studies are considered. The NuSI study design was rigorous and meticulously controlled, regardless of random allocation of diet sequence. Ludwig cited his own randomized study, but failed to mention this study used outpatient feeding and there was no control over dietary adherence (7); in contrast, the NuSI study used a metabolic ward design to control all conditions, food consumed, and nutrient composition of each diet. The measures used by NuSI researchers represent the "Gold Standard" of nutrition and metabolism research, which included dual-energy X-ray absorptiometry, doubly labeled water, and metabolic chamber assessments, among an array of others.

Evidence

Hall et al. (12) randomly assigned 19 obese female and male subjects to either a diet with a 30% calorie restriction from CHO or a diet with 30% calorie restriction from fats. A crossover design was used to expose subjects to both diet conditions, while controlling for any diet related carry-over effect. A washout period was included after the initial diet condition for a period of 2 to 4 wk before the second diet condition. The degree of sophistication, rigor, and control of this study was exceptional even for controlled trial designs. The researchers measured metabolic rate, fat oxidation, rate of fat loss, RQ, body composition, and several hormones including insulin and C-peptide. The low-fat diet had no effect on insulin levels; however, the low-CHO diet resulted in a 22% decrease in insulin secretion, as measured by 24-h urinary excretion of C-peptide. The low-fat diet resulted in less weight loss (-1.3 ± 0.16 kg) than the low-CHO diet (-1.85 ± 0.15 kg). The low-fat diet resulted in a lower fat oxidation rate (-31.2 ± 31 kcal/day) than the low-CHO group (403 ± 30 kcal/day), although the low-fat diet contained less fat. However, the low-fat diet resulted in a 463 ± 37 g reduction in

body fat across the 6-day period compared with a 245 ± 21 g loss over the 6-day period in the low-CHO diet.

Findings here are supported by a systematic review and meta-analysis conducted by the Cochrane Collaboration (19), which assessed the relationship between total fat intake and body weight in adults and children. Randomized controlled trials (RCTs) and cohort studies were included that compared lower vs. total fat intake and measured effects of body fatness by using body weight, body mass index (BMI), or waist circumference. The required length of RCTs was ≥6 mo and ≥1 yr for cohorts. A total of 33 RCTs and 10 cohort studies were included in the analysis. Trial analysis indicated diets with lower total fat corresponded with lower relative body weight (1.6 kg, 95% CI −2.0 to −1.2 kg, $i^2 = 75\%$, 57,735 participants). The majority of heterogeneity was explained by meta-regression, which indicated greater reduction in total fat intake and lower baseline fat intake corresponded with greater relative weight loss. Sensitivity analysis preserved the significant effect of low-fat diet on weight. Lower total fat intake resulted in lower BMI (−0.51 kg/m^2, 95% CI −0.76 to −0.26, nine trials, $i^2 = 77\%$) along with waist circumference (0.3 cm, 95% CI −0.58 to −0.02, 15,671 women, one trial). No signals of adverse effects on lipid levels or blood pressure were found. The researchers concluded lower total fat intake leads to small, statistically significant and clinically meaningful long-term reductions in body weight in adults with baseline fat intakes of 28–43% of energy intake with study duration of 6 mo to greater than 8 yr.

A recent systematic review and meta-analysis offers strong and comprehensive evidence on the relationships between dietary composition, energy balance, mechanism, and risk for obesity (16). This investigation included 32 controlled feeding studies ($n = 562$) with isocaloric substitution of dietary CHO for fat, but dietary protein content remained equal. As the proportion of dietary CHO to fat changed, daily EE and body fat were carefully followed. This allowed a direct comparison of effectiveness of low-fat and low-CHO diets across a wide range of study conditions in the original measurement scale without use of a standardized effect size. The pooled weighted mean difference in EE was 26 kcal/day higher with the lower fat diets ($P < 0.0001$). The rate of body fat loss, pooled weighted mean difference of 16 g/day, was greater with lower fat diets. Visual inspection of forest plots revealed only 6 out of the 32 studies carried more than a negligible advantage in EE for the low-CHO diet. Only 3 out of 32 studies showed an improvement in body fat loss with the low-CHO diet, whereas the overwhelming majority showed greater body fat loss with the low-fat diet.

These results were opposite to those predicted by the CHO-insulin hypothesis, and refute any so-called metabolic advantage to preferential CHO-feeding.

Thermodynamics and Theory vs. Actual Data

Does discussion of thermodynamics clarify the discussion or obfuscate, and can such arguments supersede data? Although one can appreciate the applicability, the discourse may only add complexity and detract from the importance of the message from rigorous data and experimental design (9, 20, 21). Arguing that the second law of thermodynamics does not preclude changes equivalent to a metabolic advantage of low-CHO diets is unhelpful when it is used to explain a phenomenon which likely does not occur; it also offers no plausible or testable mechanism. The lack of evidence supporting the CHO-insulin hypothesis, combined with a failure to account for much related mechanistic research and common observations, does not require thermodynamic theory. Rather, there is an obligation to answer the research question posed with data, however interesting philosophy and theory may be. The scientific method demands that an extraordinary claim requires extraordinary proof, even though the low-CHO approach is popular. Feinman and Fine (9) developed the theoretical argument that low-CHO diets confer a substantial metabolic advantage through differences in macronutrient composition and, subsequently, different metabolic pathways. An extensive review by Buchholz and Schoeller (3) sought to assess this difference with actual data to elucidate thermodynamic mechanisms for increased rates of weight loss in those consuming high-protein diets and/or low-CHO diets. They found the difference in EE was small, possibly accounting for less than 33% of the difference in weight loss between diets, and warned against misinterpretation of such details as a thermodynamic advantage between diets. They concluded that different diets result in a difference in EE, shift in energy balance, and difference in weight loss with the laws of thermodynamics intact.

When queried about Buchholz and Schoeller's paper (3), Fine did not respond with actual study data, but rather with another theoretical paper about modeling. The response was a short thermodynamic discussion using the general phrases "living organisms are open systems, far from equilibrium," "whereas energy is always conserved, entropy is not", and "both laws are inviolate and must be applied correctly" (8). The follow-up by Buchholz and Schoeller (4) concisely summarized the current state of evidence in obesity research: "Instead of using a theory as evidence in itself, we sought to determine if the theoretical underpinning of the metabolic advantage was quantitatively meaningful?" They found a ~41 kcal/day increase in EE with a 1,500 kcal/day diet, as opposed to the 95 kcal/day estimate proposed by Feinman and Fine (8). In addition, Buchholz and Schoeller emphasized that the experimental data provided evidence of only a nominal low-CHO metabolic advantage. For these reasons, experimental proof of the core of the CHO-insulin theory remains lacking, and restatement in different ways does not constitute evidence.

Conclusion

The CHO-insulin hypothesis predicted that lowering dietary CHO significantly should cause insulin levels to fall, leading to release of fat from adipocytes that would *1*) increase fat loss and *2*) increase EE to claimed amounts in the range of ≥350 cal/day (range 400–600). Neither of these effects was observed in two current and highly rigorous metabolic ward studies, one of which was the actual NuSI study being discussed.

Weight gain or loss is not primarily determined by varying proportions of CHO and fat in the diet, but instead by the number of calories ingested. Changes in EE, which metabolic pathways are used and other considerations are quite modest when compared with caloric intake. Until high-quality, metabolic ward primary data become available indicating otherwise, a calorie is still a calorie.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

S.H. and R.K. conceived and designed research; S.H. and R.K. analyzed data; S.H. drafted manuscript; S.H. and R.K. edited and revised manuscript; S.H. and R.K. approved final version of manuscript.

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