Is a calorie a calorie? Biologically speaking, no

Dear Sir:

I just read with great interest the well-written paper by Buchholz and Schoeller that discusses thermodynamics and weight-loss diets (1). However, the authors ignored the fact that the energy utilization of different diets depends on the biochemical pathways taken (2). For example, a low-carbohydrate diet dramatically increases gluconeogenesis relative to a high-carbohydrate diet. Obviously, gluconeogenesis is an energy-consuming process: 6 mol ATP is consumed during the synthesis of 1 mol glucose from pyruvate or lactate (3). The transformation of gluconeogenic amino acids, such as alanine, into glucose requires even more energy because 4 mol ATP is needed to dispose of the nitrogen as urea (3). Furthermore, the energy-dependent processes of maintaining the turnover of body proteins— including synthesis, folding, targeting, regulatory processes, and protein breakdown—have an overall cost to body energy homeostasis that is significantly higher than previously appreciated (4).

Thus, it is easy to understand why high-protein, low-carbohydrate weight-loss diets are so effective. However, the recent systematic review in the Journal of the American Medical Association concluded that “weight loss while using low-carbohydrate diets was principally associated with decreased caloric intake and increased diet duration, not with reduced carbohydrate content” (5). As pointed out by Kaufman in the Journal of American Physicians and Surgeons (6), this is a misleading conclusion. In the true low-carbohydrate group, the mean weight loss in trials was 17 kg, whereas in the higher-carbohydrate group it was only 2 kg. Oddly, the authors did not consider this significant. Only by intermingling the results of trials of low- to medium- and high-carbohydrate diets could the authors have reached the misleading conclusion quoted above (6). Finally, there are valid concerns about possible adverse effects associated with high protein intakes. It should be noted, however, that there is no scientific evidence to support these contentions (7).

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REFERENCES


Whatever happened to the second law of thermodynamics?

Dear Sir:

We found the recent review by Buchholz and Schoeller (1) to be surprising in several ways. First, there was no reference to our recent review “Thermodynamics and Metabolic Advantage of Weight Loss Diets” (2), which addressed the same subject but included a more comprehensive set of references and thereby strengthened Buchholz and Schoeller’s observation that high-protein, low-carbohydrate diets frequently lead to greater weight loss calorie-for-calorie than do isocaloric diets of different composition (metabolic advantage). Still more surprising was that, in opposition to these experimental observations, they insisted that “a calorie is a calorie” anyway and invoked the first law of thermodynamics. In our own review (2) we pointed out that one cannot ignore 1) the second law of thermodynamics and 2) the fact that living organisms are open systems, far from equilibrium, and therefore subject to different efficiencies depending on metabolic path.

The second law says that there is a physical parameter called “entropy,” which we identify with disorder or inefficiency and, whereas energy is always conserved, entropy is not (3). In any real (irreversible) process, entropy increases and no process is perfectly efficient. The consequence is that conservation of energy (ie, the first law) is maintained by exporting high-entropy compounds (principally carbon dioxide and water) into the environment. The extent to which energy and matter are distributed among heat, chemical bonds, work, and the excreted products is determined by the specific metabolic pathway used. In our review, we presented plausible mechanisms by which dietary composition can lead to different pathways of different efficiencies.

The first law of thermodynamics never exists in the absence of the second law. Both laws are inviolate, and they must be applied correctly.

Richard D Feinman
Eugene J Fine

Reply to AH Manninen and to RD Feinman and EJ Fine

Dear Sir:

We thank Manninen and Feinman and Fine for their interest in our review, “Is a Calorie a Calorie?” (1). These 2 letters correctly point out that there are indeed some differences between the energetics of human metabolism and the measures of heat release of nutrients in a bomb calorimeter. We agree with the known concept that the metabolic route through which carbon flows to carbon dioxide, the concentrations of substrates, as well as entropy can all slightly alter the efficiency of ATP production in humans (2). This concept, however, does not automatically mean that these differences constitute a quantitatively plausible mechanism that would explain the differences in weight loss observed with a high-protein, energy-restricted diet relative to a low-fat, energy-restricted diet.

Rather than relying on a theoretical treatment of metabolic efficiencies, as did Feinman and Fine, we reviewed studies in which known experimental diets were fed to subjects under laboratory conditions to test whether energy expenditure was actually higher with a low-carbohydrate diet than with a high-fat diet. In studies in which protein intake was held constant and fat was substituted for carbohydrate, the difference in 24-h energy expenditure between the which protein intake was held constant and fat was substituted for carbohydrate, the difference in 24-h energy expenditure between the high-carbohydrate diet and a low-fat diet was not different from zero ($\Delta = -19 \pm 54$ kcal/d). However, as clearly stated in our review, when the protein intake was not held constant but rather increased from 15% to 30–35% of energy, 24-h energy expenditure did increase. We determined, however, that the increase would be only $\approx 41$ kcal/d for a 1500-kcal/d energy-restricted diet. This would only increase weight loss by $\approx 0.04$ kg/wk, or 0.44 kg over a 12-wk course of weight-loss treatment. It should be noted that this is less than the 95 kcal/d calculated theoretically by Feinman and Fine, and it has the advantage of being based on experimental data. Thus, we do not disagree with Feinman and Fine from the perspective of pure thermodynamics; in fact, we presented evidence at the whole-body level that supports their point. However, we found the experimentally measured differences in 24-h energy expenditure, between subjects who followed a high-protein diet compared with those who followed a high-carbohydrate diet, to be too small to satisfactorily account for the differences in weight loss observed after 12 wk of treatment with these 2 diets. Thus, this is not a plausible mechanism to account for the observed increased weight loss. The experimental data on energy expenditure provide evidence of only a minimal metabolic advantage for low-carbohydrate diets.

We do apologize for not having cited Feinman and Fine’s detailed and well-written review, but the journal in which it was published appears to be new and thus is not yet indexed in common biomedical databases.

Andrea C Buchholz
Dale A Schoeller

Fructose misuse, the obesity epidemic, the special problems of the child, and a call to action

Dear Sir:

We have failed our children (1). The surging worldwide obesity epidemic is catastrophic enough, but look at the steady stream of bad news hitting our biochemically immature little ones: both adult-onset diabetes and nonalcoholic fatty liver disease (2) as early as the age of 4 y, a great rise in the incidence of pertussis and asthma, and, in the mental area, an alarming increase in autism, ritualin use, bipolar disorder, anxiety, and the use of antidepressants in preschool children. With a lifetime to progress to even more-serious problems, the problems of children are far worse than most people seem to realize.

Fortunately, the solution is in the scientific literature. The article by Bray et al (3) in the April issue of the Journal advanced the search for a solution with emphasis on fructose and beverages, but there were errors of commission and omission in this article. In Figure 1 of Bray et al’s article, according to their reference 35, the most recent data point for the percentage prevalence of obesity should be 30.9%, not 26%, and at least some of the data points for the prevalence of overweight should be much higher. The correct values emphasize the recent rapid rise in obesity and increase the urgency of the problem.

Bray et al made good use of the data in their reference 34, but they seemed to miss the extra significance for the child represented by the data in Figure 6 in the 1993 article by Park and Yetley (4). The mean daily intake of fructose (in g/kg body wt) from birth to age 80 y is shown in Figure 6. At age 20 y, the daily intake of total fructose was $\approx 0.62$ g/kg, and it slowly decreased with age, whereas the naturally occurring fructose intake at age 20 y was $\approx 0.2$ g/kg. At ages <20 y, however, it was astonishing that the daily intake of total fructose remained $\geq 1.9$ g/kg body wt from near birth to about the age of 4 y. Through the years of their postnatal brain growth spurt, infants and
toddlers are fed 10 times the amount of naturally occurring fructose ingested by adults.

What is a reasonable guess for the daily intake of total fructose for an infant from the Stone Age? Zero. They must have been fed mother’s milk, the sugar in which is lactose, which digests to galactose and glucose only. Note that the ratio between the amount of fructose our infants are being fed today and the amount they were fed when our genes were adapting to the environment approaches infinity.

Bray et al pointed out many differences between fructose and glucose, with more troubles from fructose. “It is becoming increasingly clear that soft drink consumption may be an important contributor to the epidemic of obesity, in part through the consumption of larger portion sizes of these beverages and through the increased intake of fructose from high-fructose corn syrup and sucrose.” Bray et al referenced Elliott et al (5), who cited more differences between glucose and fructose in their major review. They concluded in part, “...on the basis of the available data regarding the endocrine and metabolic effects of consuming large quantities of fructose and the potential to exacerbate components of the insulin resistance syndrome, it is preferable to primarily consume dietary carbohydrates in the form of glucose (free glucose and starch).” Others concluded that, “if plasma triacylglycerols are a risk factor for cardiac disease, then diets high in fructose may be undesirable...efforts to reduce fructose intake should focus on reducing the amount of fructose added to beverages and foods in the American diet. A reduction in added fructose would be facilitated by an acceptable replacement sugar. Such a sugar might be glucose (6).” Wharton and Hampl (7) concluded that, “Native Americans face some of the highest rates of obesity and diabetes in the world...little attention has been paid to reducing fructose, particularly in the form of HFCS [high-fructose corn syrup] in beverages...numerous studies have documented that beverages are a leading contributor to energy intakes among Native Americans...one approach may be by promoting sugar-free beverages.” The titles of the studies by Levi et al (8) and Suarez et al (9) point to additional alarming troubles associated with fructose intake. Basic biochemistry indicates that glucose and fructose have different chemical properties. Of the 3 major sugars that digest into the human bloodstream, the 2 that are vital to humans, galactose and glucose, are both aldoses, whereas fructose is a ketose—this sugar is the one that the human liver tries hard to keep at essentially a zero concentration in the blood. Murray et al (10) wrote that, “Biomedically, glucose is the most important monosaccharide and ingestion of large quantities of fructose has profound metabolic consequences...because it bypasses the regulatory step catalyzed by phosphofructokinase. This allows fructose to flood the pathways in the liver, leading to enhanced fatty acid synthesis, increased esterification of fatty acids, and increased VLDL secretion, which may raise serum triacylglycerols and ultimately raise LDL cholesterol concentrations.”

Could fructose contribute to nonalcoholic fatty liver disease? With all the documented troubles from fructose, it is clear that the low glycemic index of fructose is misleading at best. The main source of fructose for infants and toddlers is fruit juice and soda. The nutrition-facts labels indicate that both sources are essentially the same, that is, sugar water that digests to nearly equal amounts of glucose and fructose. Of course, more trouble results from the faster sugar ingestion from a water solution than from sugar in solid foods, as noted by Bray et al.

Three summarizing facts call for immediate resolution: 1) we are flooding our infants and toddlers with fructose, 2) we are doing this through their entire postnatal brain growth spurt, and 3) infants and toddlers are being flooded with severe health problems, including brain disorders. How effective is the liver of infants and toddlers in keeping fructose out of their blood? How effective is their blood-brain barrier in keeping fructose out of their brain? Would there be any harm from withholding fructose until an age at which this population could handle whole fruit? How much does the surging worldwide sale of sugar water contribute to the rising obesity epidemic? Should fructose be withdrawn from the list of “generally recognized as safe” substances?

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REFERENCES

Reply to NJ Krilanovich

Dear Sir:

Krilanovich has written a stimulating and provocative letter to the Editor with a call to action based on our critique of high-fructose corn syrup (HFCS). He has pointed out a significant error in our Figure 1 (1) and emphasized the potentially detrimental effects of fructose during the period of brain maturation in children. His letter serves to highlight this additional area of concern, and we applaud him for that.

At the end of our article (1) we stated that, "...we believe that an argument can now be made that the use of HFCS in beverages should be reduced and that HFCS should be replaced with alternative non-caloric sweeteners.” On the basis of the special issues relating to fructose and children that were highlighted by Krilanovich, which we did not dwell on, we support his suggestion that a reduction or elimination of fructose from HFCS as well as in sucrose in beverages available to infants and children could be a high-priority nutritional policy.
We thank Krilanovich for pointing out the error in our Figure 1. He is absolutely correct that the prevalence of obesity was 30.5% in 2000, not 26%. We submitted an amended figure to the Journal, which was published in response to an earlier letter (2). As Krilanovich noted, the correct value makes the rise in the prevalence rates of obesity more evident and the temporal relation of the increasing use of HFCS clearer.

Since our paper was published, a subsequent analysis of carbohydrate intake in relation to the prevalence of diabetes was published by Gross et al (3). Their observations dovetail with ours. They showed a decline in carbohydrate intake of from 500 g per capita in 1910 to 362 g per capita during the first three-quarters of the 20th century. Thereafter, carbohydrate intake returned to the same level as earlier in the 20th century. HFCS represents almost all of the increased carbohydrate during this latter period. Their study also nicely highlights the temporal relation of this change in carbohydrate intake with the rising incidence of diabetes.

Nature prefers glucose and rejects fructose. Fructose does not enter the brain or pancreas to any appreciable degree. Yet fructose is considerably sweeter than either glucose or sucrose. As Krilanovich points out, infants and young children in our society are exposed to higher intakes of fructose than were our ancestors. The fructose from HFCS used in beverages differs from the fructose combined to form sucrose in 2 ways. First, it is free fructose and as such is sweeter molecule for molecule than is sucrose or glucose—the other half of the sucrose molecule. In addition, HFCS solutions have a higher osmotic pressure than do equimolar sucrose solutions, because there are 2 molecules in the HFCS solution (fructose and glucose) compared with a single molecule in sucrose. This enhanced sweetness and high osmolarity may serve to stimulate the taste receptors more intensely and to “imprint” this intense taste in the plastic neurocircuity of young and growing brains, a change that may increase the desire for sweet taste throughout life. If this is even a remote possibility, the suggestion by Krilanovich to eliminate the exposure of infants and children to fructose might be worth serious consideration. As we know, intrauterine exposure to maternal smoking (4) or diabetes (5) enhances the risk of obesity and overweight later in life. Thus, we support Krilanovich in encouraging a review of whether exposure to fructose either as HFCS or in sucrose during the early years of life may play an important role in the current epidemic of obesity in children (6). If there is even a suggestion that this is so, then access by infants and young children to beverages with fructose should be curtailed during critical periods of brain growth and development.

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REFERENCES

Vitamin B-6 status and coronary artery disease
Dear Sir:

We found the recent article by Friso et al (1) potentially intriguing. An association between vitamin B-6 status and coronary artery disease (CAD) in humans has been discussed for decades, but to date there has been no satisfactory biochemical explanation for this association (see, for example, reference 2). In their study, Friso et al stated “... we excluded subjects with conditions known to influence B-vitamin metabolism ...”; however, they included smokers and nonsmokers in both their CAD-free subjects and their CAD patients (see Table 1 in their article). Although they further stated that they performed multivariate logistic regression analyses that controlled for smoking and other indexes, such a regression analysis does not preclude an increasing percentage of smokers in each of the successive quartiles of pyridoxal-5'-phosphate (PLP) concentrations (see Figure 1 in their article). Because smoking is a well-documented determinant of PLP concentrations (3–6), we would have anticipated that the PLP data would also have been stratified by smoking load or that the incidence of smokers and nonsmokers would have been reported for each quartile in Figure 1. These data should be fairly easy for the authors to check.

In addition, more information on the intake of vitamin B-6 from the diet and from supplements needs to be provided. Moreover, because of the inverse association between circulating PLP concentrations and the activity of plasma alkaline phosphatase, the activity of alkaline phosphatase needs to be provided for both groups of subjects. After these analyses, if the associations of PLP with C-reactive protein and fibrinogen continue to hold up, then a functional role for vitamin B-6 in the prevention of CAD may finally be at hand.

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A modified regression model to adjust for intraindividual variation in serum biomarker concentrations

Dear Sir:

I read with interest the recent article by Gillespie et al (1) suggesting a new method for predicting the mean retinol concentration of a person from a single measurement. The basic idea is to adjust for intraindividual variation. Gillespie et al applied the method to reduce prevalence estimates of inadequate serum retinol concentrations by using laboratory-quality data and a subsample of repeated measurements. The centerpiece of the method is the linear regression model,

$$\bar{X} = \beta_0 + \beta_1 X_1$$  \hspace{1cm} (1)

where $\bar{X}$ is the individual mean of repeated measurements, and $X_1$ is the first measurement of retinol concentration.

However, the chosen regression model did not adequately address the problem of eliminating the intraindividual variance component. First, it is possible that the estimate of the slope parameter $\beta_1$ is larger than 1, which means that the prevalence estimate of inadequate concentrations will be exaggerated. To see this failure, consider a simple hypothetical example of 3 persons with first retinol concentration measurements of 1.9, 2.0, and 2.1 μmol/L and corresponding second retinol concentration measurements of 1.7, 2.0, and 2.3 μmol/L. The resulting individual means are 1.8, 2.0, and 2.2 μmol/L, and the estimate for $\beta_1$ is equal to 2. In general, the proposed method may fail if both measurements are highly correlated and the second

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Simonetta Friso
Domenico Girelli
Roberto Corrocher

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**LETTERS TO THE EDITOR 1449**

Reply to RD Reynolds and JE Leklem

Dear Sir:

We are thankful to Reynolds and Leklem for their interest in our work on vitamin B-6 and coronary artery disease (CAD) risk (1). We certainly coincide in the opinion that smoking is a well-documented determinant of pyridoxal-5’-phosphate (PLP) concentrations (2–5), an opinion that we also expressed in our first report suggesting an inverse association between serum PLP and C-reactive protein (6).

Nevertheless, as affirmed in the article, we conducted multivariate logistic regression analyses to control for, among other factors, smoking status. Because smoking is a well-known risk factor for CAD, it could have been a strong confounder in the estimate of the independent association between low PLP concentrations and CAD risk, and estimation of this association was one of the primary aims of the study. Analysis for potential interactions, moreover, showed that CAD risk, as a result of low PLP, was additive when considered in combination with smoking status. We agree with Reynolds and Leklem that an evaluation of smoking load could be of interest, but such data were not available.

The existence of an inverse relation between plasma PLP concentrations and the activity of alkaline phosphatase is indeed known. In our case-control study for the assessment of CAD risk, however, there was no evident reason to test for alkaline phosphatase, which, we concur with Reynolds and Leklem, could have a stronger effect, particularly in certain diseases (7). We are confident that our report highlights a potentially important role of PLP in CAD, although mechanistic studies are certainly required to clarify the biochemical-molecular basis of this association.

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concentrations vary more than the first ones. Instead of regression on the first measurement, all single measurements should be included in the model. If this is done, the estimated regression slope cannot be larger than 1, which can be proven. In the hypothetical example, the estimate is 0.8 if all 6 measurements are used.

Second, the linear regression model should predict a person’s “usual” serum retinol concentration defined as the long-term daily average. Although Gillespie et al adopt a similar interpretation of their approach, they actually use the mean of only 2 measurements as the dependent variable in the model. Because the mean of 2 repeated measurements still has an intraindividual variance component, this component must be subtracted before regression analysis is applied. Principally, the usual retinol concentration has to be estimated in a preliminary step. The problem of estimating usual or long-term exposure by repeated short-term measurements has been intensively studied in food-consumption and environmental surveys, and several statistical methods aimed at eliminating the intraindividual variance component are available (2–4).

In summary, I propose applying a modified regression model with another dependent variable and another independent variable. Regression of the estimated usual retinol concentration on a single concentration by using all single measurements allows elimination of the distracting effect of intraindividual variation. Applying this modified model should yield lower prevalence estimates of inadequate serum retinol concentrations than those obtained by Gillespie et al.

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REFERENCES


Reply to K Hoffmann

Dear Sir:

We appreciate Hoffmann’s interest in our article describing the intraindividual variation in serum retinol concentrations. The first point that he raises is that the linear model we used does not eliminate the intraindividual variation component in the observed means. The purpose of the linear model in our analysis was to address the “regression to the mean effect” in the serum constituent. The model was not intended to eliminate the intraindividual variance but was instead intended to account for the theoretical shift of a person’s mean concentration toward the population mean, which is unobservable given only 2 serum samples per subject. Hoffmann suggests that the linear model may fail if both serum concentrations are highly correlated and the second measure varies more than the first, and he offers an example in which a linear model does fail. We investigated the variance issue and found that although the 2 concentrations were highly correlated in our data, the sample variance for the 2 concentrations did not differ significantly ($F$ test $P$ value $> 0.10$). As discussed in our article, the linear model was appropriate for this particular US representative sample. Furthermore, we discussed that neither this model nor our results could be extrapolated beyond the US population to other populations or to other serum constituents.

Second, Hoffmann states that the “usual” retinol concentration should be estimated in a preliminary step because the intraindividual mean has an intraindividual variance component. In our article, we estimated the intraindividual variance in a separate step, on the basis of the observed intraindividual variance between the 2 concentrations for each subject. The mean estimated by using the linear equation indeed has its own variance, which we accounted for by incorporating the intraindividual CV in the construction of CIs around the estimated means.

In summary, Hoffmann suggests a modified regression model incorporating both serum concentrations as independent variables and “subtracting” the intraindividual variation from the observed mean for the dependent variable in the model. Although we do not dispute the potential merits of such a model in other applications, it would not be useful in assessing patients’ nutritional status at the clinical level, where there is often only one serum concentration available. Our purpose was to estimate the intraindividual variance based on 2 observed concentrations, to incorporate a linear model to adjust for the unobservable regression to the mean effect, and most importantly, to allow for estimation at the clinical level of a person’s “true” mean serum retinol concentration and a CI for that estimate based on a single serum concentration.

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How to consider low serum vitamin D as a risk factor for insulin resistance?

Dear Sir:

Chiu et al (1) provide elegant evidence that the 25-hydroxyvitamin D [25(OH)D] concentration has a positive relation to insulin sensitivity in healthy, nearly normal-weight, glucose-tolerant subjects. They conclude that a low concentration of 25(OH)D can be an independent risk factor for metabolic syndrome in large populations.

Chiu et al (1)
REFERENCES


Vitamin D, parathyroid hormone, and insulin sensitivity

Dear Sir:

With regard to the recent report by Chiu et al (1), which shows a direct correlation between plasma 25-hydroxyvitamin D and insulin sensitivity, it is surprising that the authors do not cite their own highly germane study, which shows that insulin sensitivity correlates inversely with plasma parathyroid hormone (PTH) in healthy volunteers (2). There is reason to suspect that mild secondary hyperparathyroidism may be the chief mediator of the insulin resistance associated with poor vitamin D status (3). PTH can increase free intracellular calcium concentrations in key insulin target tissues, including adipocytes and skeletal muscle (4, 5). Reusch et al (6) have shown that moderate increases in free intracellular calcium can compromise the efficiency of insulin-stimulated glucose uptake, not by interfering with the activation of PI3K-Akt but rather by suppressing the activation of a phosphatase required for optimal function of GLUT-4. Indeed, both primary and secondary hyperparathyroidism are characterized by reduced insulin sensitivity (3). The findings of Chiu et al’s group suggest that the relatively modest increases in plasma PTH associated with suboptimal vitamin D status may likewise have implications for insulin function.

If this thesis is correct, one would expect supplemental calcium to affect insulin sensitivity, at least in subjects with mildly elevated PTH. In fact, there are 2 controlled studies that showed that supplemental calcium improves insulin sensitivity in hypertensive persons (7, 8). Moreover, a relatively high calcium intake has been linked to reduced risk of diabetes in a prospective epidemiologic study (9). Chiu et al’s article cites the scarce findings relevant to the effect of supplemental vitamin D on insulin sensitivity. It would be of great interest to determine whether effective supplemental intakes of vitamin D (10)—with or without concurrent supplemental calcium—can indeed improve the insulin sensitivity of groups with mediocre vitamin D status.

Because it seems unlikely that insulin function would influence 25-hydroxyvitamin D concentrations, it is reasonable to presume that the latter is influencing the former. However, a skeptic might note that frequent outdoor exercise would tend to improve both vitamin D status and insulin sensitivity and thus might account for the correlation observed by Chiu et al. To discount this argument, it would be helpful if the authors assessed and analyzed the exercise habits of their subjects.

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REFERENCES

Reply to M Manco et al and to MF McCarty

Dear Sir:

We appreciate the interest in our report of the association of hypovitaminosis D with insulin resistance and β cell dysfunction (1). It is important to reiterate our statement that a strong correlation does not necessarily imply a cause-effect relation. Furthermore, the serum 25-hydroxyvitamin D concentration only independently accounts for ~6% of the variation in insulin sensitivity in glucose-tolerant subjects. Type 2 diabetes, as well as the metabolic syndrome, is a multifactorial disease. Thus, if vitamin D per se plays a role in the pathogenesis of the diseases, hypovitaminosis D could only be a contributing factor for type 2 diabetes, the metabolic syndrome, or both.

In response to Manco et al, the association between serum 25-hydroxyvitamin D concentration and insulin sensitivity is independent of obesity, as shown from the multivariate analysis. Because obesity is one of the criteria for the metabolic syndrome, a higher body mass index would be expected in those with the metabolic syndrome than in those without it. It is of great interest whether there is a relation between latitude and insulin sensitivity. However, latitude accounted for 42% of the variation in serum 25-hydroxyvitamin D concentration from a study of 17 countries (2), and serum 25-hydroxyvitamin D explained only 6% of the variation in insulin sensitivity in our study (1). It is not surprising that no association was found between latitude and insulin sensitivity in a study of only 6 centers (3). Furthermore, I cannot find such information in the cited article (3). Although serum 25-hydroxyvitamin D concentrations vary with the seasons, serum 25-hydroxyvitamin D was determined from the fasting samples obtained immediately before the assessment of insulin sensitivity and from β cell function on the same day in this study (1). Therefore, it is very unlikely that the observed association was biased by the prevalence of subjects studied or seasonal influence. Interestingly, there is a seasonal variation in the prevalence of type 2 diabetes, which peaks in the late winter and is lowest in summer (4, 5). With regard to the improvement in insulin sensitivity after bilipancreatic diversion, it is expected after substantial weight loss despite hypovitaminosis D, which only accounts for ~6% of the variation in insulin sensitivity independently (1). It would be very intriguing to determine whether this relation remains in this group of patients after bilipancreatic diversion. A sample size of 135 subjects would be required to show this association with a power of 0.80.

In reply to McCarty’s fascinating hypothesis that calcium plays a central role in this association, there is also evidence against it. Although the infusion of parathyroid hormone significantly affects intracellular calcium in human subjects and rats, it does not affect the action of insulin (6, 7). Therefore, neither parathyroid hormone nor calcium is the primary effector on glucose metabolism. With regard to β cell function, it has been shown that vitamin D, but not calcium, is essential for normal insulin secretion (8). In addition, treatment with bisphosphonate (eg, pamidronate) resulting in hypercalcemia with elevated parathyroid hormone concentrations is not associated with an increased incidence of abnormal glucose tolerance or diabetes. Furthermore, it has been shown that glucose significantly elevates intracellular free calcium in a dose- and time-dependent manner (9), and a hyperglycemia-induced increase in intracellular calcium is a fundamental lesion in diabetes (10). However, we agree that our findings need to be examined in other populations and with different study designs.

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6. Chen SM, Young TK, Ho LT. Effects of parathyroid hormone infusion
Dear Sir:

We read with interest the article by Lee et al (1) in a recent issue of the Journal. As emphasized by the authors, edentulism is frequent in the elderly (2) and could cause reduced nutritional intake. Edentulism has been implicated as a factor causing malnutrition in elderly patients (3). One of the surprising results of Lee et al’s study was the lack of significant difference between edentate and dentate participants in energy intake, except when the analysis was broken down by race. However, I believe that the study had the following problems:

1) Edentulism was attested only by “self-reported information regarding whether a participant had any remaining natural teeth. Participants were also asked whether they wore dentures and whether they had chewing pain” (page 296, “Oral health” paragraph). This method does not provide reliable recording of the number and type of teeth lost; it is a problem noted by the authors in the discussion (page 301, first lines) but is of such central importance that it may raise questions about the study’s overall validity.

2) Improved nutritional status was suggested by the percentage of persons who experienced a weight gain of >5% of baseline weight in 1 y (page 298, last sentence). I believe that this criterion is misleading because it may be unlinked with the more meaningful data of the mean weight gain of the participants. Without more data, it is not possible to conclude that the edentate participants had greater weight gains than did the dentate participants, as suggested on page 299 (right column, lines 23–25). It would also be important to know the criteria used in the multiple linear regression analysis presented in the last lines of page 298.

3) In the multiple linear regression analysis of mean energy intake (page 299, Table 2), it is notable that mean energy intake was not adjusted for certain nutritional values, such as weight or, even better, fat-free mass (FFM). This is important because nutritional balance is not obtained with the same energy intake in a participant with a high FFM as in a participant with a low FFM, ie, body composition can play a role. With such an adjustment, the race-linked mean energy intake difference might lessen or disappear. Without this adjustment factor, we think that it is very difficult to know whether mean energy intake differs between edentate and dentate participants.

4) There is insufficient discussion of the contrast of the higher appetite reported for dentate subjects than for edentate subjects (page 297, Results, line 6) and yet no apparent difference in energy intake.

In conclusion, the article by Lee et al is an interesting approach to dietary intake in the elderly in relation to dental status and suggests a difference in mean energy intake more on the basis of race than on the basis of edentulism. However, additional methodologic retooling may yield a further level of understanding.

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REFERENCES

Reply to JC Desport

Dear Sir:

We appreciate the comments by Desport regarding our recently published article (1). Desport asks how edentate elders with poor appetite and a different pattern of food group consumption had total mean energy intake similar to that of dentate elders and were more likely to gain weight. She questioned some of the methodologic approaches used in our study. Indeed, we had carefully used most of the approaches she suggested in our analyses and the results did not change.

Food intake in older adults is a complex process involving an array of physiologic and behavioral factors. In our well-functioning, community-dwelling older cohort, edentulism was associated with food choice and eating, but at this baseline examination it did not have much effect on actual energy intake (and potentially balance). Edentate elders in our cohort chose food groups that might be easier for them to chew but had a mean energy intake similar to that of dentate elders. However, because of the limitations of the dietary assessment tool (a food-frequency questionnaire), it is possible that modest differences in intake were missed. The baseline weight and mean weight change over 1 y (either absolute or relative) of the dentate elders were not significantly different from those of the dentate elders. However, when we examined whether edentulism was associated with clinically significant weight changes [usually defined as >5% of weight change during a 6–12-mo period (2)], the proportion with a weight gain of >5% of baseline weight was higher among the edentate than the dentate elders. We think that our findings manifest early adaptation of food choice and eating in highly functioning, relatively healthy, community-dwelling older adults as their dental status becomes compromised. If we look into this issue in our cohort with a longer follow-up or in other cohorts that include older adults with poorer dental and overall health status than ours, we may have different findings.

Data from a subsequent dental and periodontal examination conducted in the Health, Aging, and Body Composition (Health ABC)
Study suggest that self-reported dental status among well-functioning and community-dwelling older adults is very reliable. Around 96% and 86% of the Health ABC dental and periodontal examination participants correctly reported edentulism and denture use, respectively. With additional follow-up of both self-reported oral health and examination data obtained in the Health ABC study, we hope to understand how oral health affects nutritional status over time as the health and function of this cohort decline with age.

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