Dear Sir:

I read with interest the article by Domouzoglou and Maratos-Flier (1), which summarizes current knowledge on fibroblast growth hormone 21 (FGF21) and provides insights into the potentially promising applications of this factor in the treatment of nonalcoholic fatty liver disease, obesity, and type 2 diabetes. Studies in mice fed a ketogenic diet greatly contributed to the understanding of the physiologic roles of FGF21.

Domouzoglou and Maratos-Flier emphasize that ketogenic diets lead to weight loss and improvement in insulin sensitivity (1). Although I agree with the effect on body weight, I am more skeptical about the effect of ketogenic diets on insulin sensitivity. Indeed, using the hyperinsulinemic-euglycemic clamp technique, which is the gold standard to assess insulin sensitivity, we recently showed that mice fed a ketogenic diet developed profound hepatic insulin resistance compared with mice fed regular feed pellets, as reflected by decreased suppression of endogenous glucose production during the clamp (2). Importantly, this effect was observed with the same ketogenic diet used in previous studies (3, 4). In our study, hepatic insulin clamp (2). Importantly, this effect was observed with the same ketogenic diet developed profound hepatic insulin resistance compared with mice fed regular feed pellets, as reflected by decreased suppression of endogenous glucose production during the clamp (2).

In human studies, however, HOMA-IR and QUICKI are frequently used as surrogate markers of insulin sensitivity. An important study comparing a low-carbohydrate diet with a low-fat diet in severe obesity reported a significant improvement in insulin sensitivity in patients on the low-carbohydrate diet using the QUICKI index (5). On the basis of our findings in mice (2), this apparent improvement in insulin sensitivity may be questionable. Moreover, in healthy nonobese men, a high-fat, low-carbohydrate diet was shown to reduce the ability of insulin to suppress endogenous glucose production compared with a low-fat diet and an intermediate-fat diet in the same subjects, suggesting the development of insulin resistance (6).

In summary, although low-carbohydrate, high-fat ketogenic diets are effective in achieving weight loss, they can induce hepatic insulin resistance, at least in mice, secondary to the development of nonalcoholic fatty liver disease. Therefore, caution needs to be used before recommending such diets to obese patients, and clinicians should wait for more thorough and well-designed studies that include measurement of insulin sensitivity using the hyperinsulinemic-euglycemic clamp technique with a concomitant assessment of the potential accumulation of fat in the liver.

The author had no conflicts of interest to disclose.

François R Jornayvaz

Department of Internal Medicine
Yale University School of Medicine
New Haven, CT 06536
E-mail: francois.jornayvaz@yale.edu

REFERENCES

1. Domouzoglou EM, Maratos-Flier E. Fibroblast growth factor 21 is a metabolic regulator that plays a role in the adaptation to ketosis. Am J Clin Nutr 2011;93:901S–5S.

doi: 10.3945/ajcn.111.019646.
Reply to FR Jornayvaz

Dear Sir:

We thank Jornayvaz for his interest and comments on our recent review article and the editors for giving us the opportunity to address them (1).

At issue is the nature of the effect of a ketogenic diet on insulin sensitivity. As shown by both us and Jornayvaz, insulin and glucose concentrations are low in mice that consume a ketogenic diet (2, 3). Indeed, we compared mice fed a ketogenic diet with mice subjected to calorie restriction similar to that used for longevity studies and found that insulin and glucose concentrations in mice fed a ketogenic diet were lower than those observed in calorie-restricted mice (2). We additionally showed that ob/ob mice fed this diet showed marked improvement in both basal insulin and glucose concentrations and in the glycemic response during a glucose tolerance test as well as the lowering of glucose during an insulin tolerance test (4). Furthermore, we and many others have shown that healthy humans who consume a ketogenic diet have very low fasted glucose and insulin concentrations and improved insulin sensitivity (5–7).

Thus, in both rodents and humans consuming a ketogenic diet, insulin and glucose homeostasis appear to be improved when assessed by multiple methods including baseline insulin and glucose concentrations and insulin (Figure 1) and glucose tolerance tests or when calculated by using a homeostasis model assessment of insulin resistance or a quantitative insulin sensitivity check index. In this regard, our results agree with those of Jornayvaz. In contrast, under conditions of a euglycemic-hyperinsulinemic clamp, ketogenic diet–fed animals appear to have increased insulin resistance because they require lower rates of glucose infusion (3). We agree with Jornayvaz that the hyperinsulinemic-euglycemic clamp is a critically important technique for assessing insulin sensitivity for most metabolic states. However, our assessment is that the very nature of the clamp makes it difficult to draw conclusions about insulin sensitivity for ketogenic diet–fed animals (5). We and many others have shown that healthy humans who consume a ketogenic diet have very low fasted glucose and insulin concentrations and improved insulin sensitivity (5–7).

With regard to fatty liver associated with ketogenic diets, it is important to note that even in the context of the most extreme carbohydrate restriction, as in the case of children who consume the most extreme ketogenic regimen for many years as an effective treatment of epilepsy, the overall health effects have not been well defined (10).

None of the authors declared a conflict of interest.

Eleni M Domouzoglou
Patricia C Chui
Adam R Kennedy
Eleftheria Maratos-Flier

Division of Endocrinology
Beth Israel Deaconess Medical Center
Center for Life Sciences
3 Blackfan Circle
Boston, MA 02215
E-mail: emaratos@bidmc.harvard.edu

REFERENCES
1. Domouzoglou EM, Maratos-Flier E. Fibroblast growth factor 21 is a metabolic regulator that plays a role in the adaptation to ketosis. Am J Clin Nutr 2011;93:901S–5S.


6. Dushay J, Chiu PC, Gopalakrishnan GS, Varela-Rey M, Crawley M, Fisher FM, Badman MK, Martinez-Chantar ML, Maratos-Flier E. Increased fibroblast growth factor 21 in obesity and nonalcoholic fatty liver disease. Gastroenterology 2010;139:456–63.


doi: 10.3945/ajcn.111.019786.

---

Less is more? Is permissive underfeeding in critically ill patients necessary?

Dear Sir:

The randomized controlled study reported by Arabi et al (1) shows that permissive underfeeding in critically ill patients is associated with lower mortality rates than those associated with target feeding. As the authors describe, the results agree with some previously published studies that investigated the caloric intake in medical intensive care units (ICUs) and showed that lower caloric intake, as recommended by the medical societies, is associated with better outcomes in ICU patients (2, 3). On the other hand, the benefit of achieving the caloric target to prevent malnutrition in terms of outcome improvement has been addressed in several studies (4–6) and was included in major guidelines on nutritional therapy (7, 8).

In an attempt to explain the conflicting results of these studies, and taking the consequences of the Arabi et al. study into account, several questions arise. First, 1587 patients were assessed for eligibility for this study, but only 240 patients were included. By the definition of the exclusion criteria, a considerable number of patients who might have benefited from enteral nutrition were excluded from the study. Another confounding factor, which might have influenced the results, is the fact that the patients who discontinued intervention were included in the analysis. As the authors describe, interventions were stopped if a Do-Not-Resuscitate order was written or if a patient became brain dead. There are no details provided on the numbers of patients with these conditions, and a possible influence cannot be ruled out because 25–30% of the included patients were admitted with a traumatic brain injury. The results for these included patients might also have influenced the results for the length of stay in the ICU, which was shorter for patients in the permissive underfeeding group, without reaching statistical significance.

Another aspect, which is not well described in this study, was the calculated energy requirement of the patients. The mean height of the patients was 164.0 cm. The mean (±SD) BMI (in kg/m²) was 28.5 ± 7.4, indicating that many patients were obese. The actual body weight and a value of ~24 kcal/d were probably used to calculate the energy requirement of the patients. The calculated average ideal body weight using 164.0 cm on average from this patient group would be 60.7 kg for men and 55.9 kg for women, which would lead to much lower calculated energy requirements for the study patients than those used in the study (7). Recent studies show that there is a relation between the amount of energy and protein administration and clinical outcomes, which is influenced by preexisting nutritional status (9). Certain subgroups of patients (eg, those with a BMI <25 or >35) had the highest association of amount of energy and negative outcome in a survey of 167 ICUs across 37 countries (9). Arabi et al (1) provides no information on preexisting malnutrition in the study patients or on the results of a screening at admission. The progression of the patient’s weight can also be of interest, even though this is not a validated parameter in clinical routine. The patients were fed only via an enteral route; no parenteral nutrition was given. There might have been a subgroup of malnourished patients, who would have shown a benefit from additional parenteral nutrition.

One problem of the study was addressed by the authors. The achieved caloric intake was below the value planned at the beginning of the study. These difficulties are well documented in the literature (10); a possible reason for the low intake in this study might also be the study design because the nutritional groups were not blinded.

A fact that might also have influenced the results is the amount of protein the patients received. The achieved protein intake was higher in the permissive underfeeding group (47.5 ± 21.2 compared with 43.6 ± 18.9 g/d; P = 0.14), without reaching statistical significance. The amount of protein is much closer to the calculated protein requirement for each patient than the energy intake by calories.

In our opinion, the lack of implementation of nutrition guidelines is still a problem in many countries, resulting in adverse outcomes for patients in intensive care. Studies such as the one presented by Arabi et al (1) should not result in minimizing the problem of nutrition. An individual approach to each patient, in consideration of the individual risk of malnutrition, is indispensable in settings in which patients with high risk of adverse outcomes are treated.

Neither of the authors declared a conflict of interest.

Marc Kastrup
Claudia Spies

Department of Anaesthesiology and Intensive Care
Charité–University Medicine Berlin,
Campus Virchow-Klinikum and Campus Charité Mitte
Augustenburger Platz 1
13353 Berlin
Germany
E-mail: claudia.spies@charite.de

REFERENCES


patients is associated with adverse outcomes. JPEN J Parenter Enteral Nutr 2010;34:280–8.

doi: 10.3945/ajcn.111.018333.

Reply to M Kastrup and C Spies

Dear Sir:

We thank Kastrup and Spies for their comments. As with other randomized controlled trials, inclusion and exclusion criteria are selected to help answer the study question. Therefore, in our trial, which addresses caloric intake in enteral feeding, we included patients who received enteral feeding and excluded those who received oral feeding. For a meaningful intervention, we included patients if they were expected to stay in the intensive care unit (ICU) >48 h. In addition, patients with a very poor prognosis, including those with Do-Not-Resuscitate status, brain death, terminal illness, or postcardiac arrest, were also excluded because they were not candidates for human research or because their inclusion would not contribute to answering the study question. The numbers of patients in whom the intervention was discontinued are shown in Figure 1 in our article along with the reasons for discontinuation (1). All patients were included in the analysis according to the intention-to-treat principle.

To address the potential effect modification of traumatic brain injury as raised by Kastrup and Spies, we tested for the interaction of traumatic brain injury and the intervention by using multivariate logistic regression modeling and observed no significant interaction ($P = 0.37$). Similarly, we observed no interaction between BMIs (in kg/m²) of <25, 25–35, and >35 and the intervention ($P = 0.16$).

The use of weight as an outcome for nutritional intervention in the ICU has limited value for several reasons, including the lack of accuracy of measurement in the ICU setting in addition to the presence of many other factors that affect weight, including fluid balance in particular. The point regarding the achieved caloric intake has already been addressed as a limitation in the original article.

We strongly believe in evidence-based nutritional practice, which requires properly conducted studies including randomized controlled trials; and we believe our current and previous studies support this approach (1–3). Our current trial was in line with this evidence-based practice because we implemented early enteral feeding in both arms, which is supported by level I evidence. We fully agree that the lack of implementation of nutrition generally is still a significant problem in many ICUs, especially in relation to not initiating early nutritional support and frequent unjustified feeding interruptions. Our study examined a very specific question regarding the dose of caloric intake in the setting of appropriate, evidence-based, early initiation of enteral feeding (4), which is an area that has not been adequately studied (5, 6). We agree that our study should not be misinterpreted as evidence to support inadequate feeding. In fact, our caloric intake in the permissive underfeeding group equals or exceeds what is achieved by many studies and is given to many critically ill patients.

None of the authors had a conflict of interest.

Yaseen M Arabi
Hani M Tamim
Abdulaziz Al-Dawood
Muhammad Al-Sultan

College of Medicine
King Saud Bin Abdulaziz University for Health Sciences
King Abdulaziz Medical City
Riyadh
Saudi Arabia
E-mail: yaseenarabi@yahoo.com

REFERENCES


A lack of epidemiologic evidence to link consumption of monosodium L-glutamate and obesity in China

Dear Sir:

We are writing to comment on a recent publication in the Journal entitled “Consumption of monosodium glutamate in relation to
incidence of overweight in Chinese adults: China Health and Nutrition Survey (CHNS)” by He et al (1).

We wish to call to your attention that some sections of this article are inadequately described, unclear, or questionable. Because these involve essential aspects of the study design and methods, they need clarification for proper interpretation of the results.

1) The design is that of an “open-cohort, ongoing nationwide survey,” which needs further clarification. Were the same individuals from the selected households reassessed? The lost-to-follow-up rate was never addressed. At the individual level, the follow-up for all of the interim surveys between the first survey and 2006 was 52% (He et al’s reference 17). The mean follow-up period was 5.5 y, but the survey period described in this study encompasses 15 y (1991–2006), which is a critical period in modern Chinese history with the outmigration of rural people. Many of the survey provinces would have witnessed this phenomenon, especially in China. Furthermore, whereas the incidence of overweight doubled in females compared with lower socioeconomic status, etc. Further, bias—eg, urban compared with rural populations, higher education, and even in this group there was significant underreporting of caloric intake. This study did not validate other nutrients. Therefore, one would expect less educated rural populations to have greater difficulty in reliably quantifying individual amounts of foods consumed.

2) Because the key variable for this study is monosodium glutamate (MSG) as a determinant of incident overweight, reliable and valid quantification of MSG is critical. It appears that individual MSG consumption was derived from a 3-d difference in the weight of the MSG shaker at the household level and then by estimating individual MSG consumption based on the proportion of foods consumed. A similar method was used to estimate MSG from soy sauce. However, one questions the reliability of this approach for several reasons:

- Because Chinese meals are traditionally shared from common dishes, reliably estimating individual shares consumed at each meal on the basis of a 3-d recall in this setting would be most difficult. A reference for validation of the China Health and Nutrition (CHNS) dietary methods was provided (He et al’s reference 21). However, this study was carried out in a highly selected (ie, volunteer) urban group, and even in this group there was significant underreporting of caloric intake. This study did not validate other nutrients.

- Even though the authors dismiss the contribution of MSG in prepared foods, we respectfully disagree. Given the ubiquitous presence of MSG in many packaged foods such as instant noodles, limiting assessment to direct use and soy sauce leads to only partial assessment and can introduce bias—eg, urban compared with rural populations, higher compared with lower socioeconomic status, etc. Furthermore, it is unclear if the MSG content of foods eaten at restaurants, work-site canteens, market food stalls, etc, was included. Given the rapidly changing use of consumer products in China and the lack of a centralized up-to-date nutrient database (He et al’s reference 19), it would be most difficult, if not impossible, to even approximate total daily MSG consumption without significant errors or bias.

- Last and most important, we have a major concern with the validation of MSG intake reportedly used in this study. The reference cited (He et al’s reference 20) was actually for assessing adherence to a high-fiber diet in a cancer control trial via using urinary riboflavin excretion as a marker of fiber intake. This reference does not even mention MSG. Thus, it is puzzling how the correlation coefficient of 0.82 was derived by using this riboflavin excretion method. This point needs clarification to properly interpret the key study finding.

3) As with the lack of a centralized, updated nutrient database, a similar situation exists for physical activity. The database used in this study is the Ainsworth Compendium of Physical Activities (He et al’s reference 26). Whereas this compendium captures a wide range of commonly performed physical activities in the United States, it is woefully inadequate and even inappropriate for China. One doubts that this compendium can provide metabolic equivalent task values for the activities of rural Chinese such as a farmer plowing land by walking behind oxen or a woman stooping all day planting rice.

Questionable reliability of measures of the 2 most important determinants of BMI—ie, energy intake and physical activity—can introduce significant confounding into the statistical analyses examining the role of MSG. In addition, those factors that had been previously reported as significant determinants of increased BMI—eg, car ownership, restaurant meals (2), etc—were not included in the present study for data analysis. This potential confounding is further compounded by the questions raised above regarding the reliability of MSG intake assessment.

Finally, to infer causality between MSG and risk of overweight on the basis of the study findings, it may be useful to apply the following Hill criteria, which have been widely used in epidemiology (3).

STRENGTH OF THE ASSOCIATION

The observed associations in this study are relatively weak, with ORs all <1.5. As noted above, the statistical models, although very technically elaborate, lack sensitivity for accommodating significant confounders as noted above. Hence, the question remains as to whether the study findings might be due to bias, confounding, miscategorization, or even chance.

DOSE-RESPONSE RELATION

The dose-response of the outcome by quintiles of MSG intake is not consistently linear (He et al’s Table 4). Even though the trend test was statistically significant, the lack of a consistent linear relation across the MSG quintiles and the outcome is troubling.

TEMPORALITY

There should be parallel time trends between MSG intake and the incidence of overweight. Despite a century of MSG use in Asia, the increased prevalence of overweight/obesity is a recent phenomenon, especially in China. Furthermore, whereas the prevalence of overweight in the parent survey doubled in females and tripled in males between 1989 and 1997 (He et al’s reference 23), MSG intake did not. Even in the current study, the median values of the quintiles of MSG consumption did not show a consistent upward trend with time, whereas there was an increasing trend for BMI (He et al’s Table 1).
CONSENSUS

Given the limited studies of MSG, it should be noted that, although He et al previously reported a linkage between MSG and BMI in another cohort (their reference 11), a 5-y study conducted in Jiangsu, one of the provinces included in this study (their reference 33), failed to show such a relation.

PLAUSIBILITY

The animal model studies that the authors cited as the potential mechanism are not applicable because the amount used to induce hypothalamic lesions in the rodent model was extremely high, and it was via direct injection. However, the authors in referring to a study by Hermanussen (He et al’s reference 14) stated that “oral MSG use at a level similar to the amount typically added to food had a significant potential for damaging the hypothalamic regulation of appetite.” We disagree because the amount given to Wistar rats was 5 g/d, far exceeding the median intake of the Chinese population surveyed, which was merely 327 mg/d (median cumulative intake of 1.8 divided by 5.5 y). Thus, MSG intake per unit of body weight was exponentially higher in the rodent model.

The authors also speculated on a link between D-glutamate presence in MSG and the effects. However, commercial MSG is made by controlled fermentation to contain >99% L-glutamate. Rundlett and Armstrong (4) found that foods to which MSG was added had lower relative percentage of the D-enantiomer (usually <0.8%) than those foods without MSG added and showed that D-glutamate presence could be related to the relative amounts of other food ingredients such as cheese.

Finally, even though observational studies often provide useful information for hypothesis formulation, given the significant questions and concerns raised in this study, it is premature to even generate a plausible hypothesis on MSG intake and obesity.

The current epidemic of obesity is worldwide, including in Asia. Because MSG has been extensively used as a flavoring agent in Asia, it could also potentially play an important role of enhancing palatability and acceptability of calorie-reduced diets. Until further confirmatory information becomes available, extreme caution needs to be exercised not to raise undue public safety concerns regarding MSG consumption.

RGB and MS are employed by Ajinomoto USA Inc, a producer of MSG. LW is the executive director of The Glutamate Association.

Robert G Bursey
Scientific and Regulatory Affairs
Ajinomoto Corporate Services LLC
1120 Connecticut Avenue
Washington, DC 20036

Lisa Watson
The Glutamate Association
Washington, DC

Miro Smriga
Scientific and Regulatory Affairs
Ajinomoto Corporate Services LLC
1120 Connecticut Avenue

REFERENCES


doi: 10.3945/ajcn.111.020727.

Reply to RG Bursey et al

Dear Sir:

We thank Bursey and Watson for their comments on our study and for calling scientists’ attention to the importance of studying monosodium glutamate (MSG) consumption and risk of obesity.

As noted by Bursey and Watson, the population within the modern China is dynamic. Our study included data from 1991 to 2006, and participants contributed various amounts of person-time in this open cohort. The average follow-up period was 5.5 y (range: 2–15 y). Of the >10,000 participants who had MSG data available, ~7000 who were not overweight when they initially entered the cohort and who were examined in at least one follow-up examination were included in the incidence estimation. As we discussed, although the possibility cannot be completely excluded, our findings are less likely to be substantially biased by loss to follow-up because of the following reasons: 1) it is unlikely that the cases of loss to follow-up are associated with both MSG intake (exposure) and overweight (outcome) and 2) the results are fairly robust and consistent between incidence estimation and prevalent OR assessment in the entire cohort.

In our study, dietary data were collected at both the household and individual levels by multiple 24-h recalls (a common diet-measurement instrument) plus a direct weighing technique, which may provide more accurate information than using a 24-h recall method alone. This includes direct measurement of MSG, sodium, and soy sauce intake on a daily basis over 3 d for sample households. Measurement errors in diet assessment are inevitable regardless of the eating habits of study populations. Nevertheless, the dietary data we collected would enable us to rank the participants and estimate the relative risks (1). Particularly for measuring MSG intake, there is no existing perfect method, especially for a large cohort study. As we acknowledged, MSG consumption assessed in the present study and in previous studies was likely to be underestimated because of missing information on MSG in processed foods. However, MSG from other sources represents a relatively small portion of MSG in the Chinese diet as compared with added MSG, including MSG from soy sauce in food preparation. Of note, riboflavin is an established adherence biomarker that has been used in nutrition-related studies to monitor compliance (2). We successfully adopted this biomarker to validate MSG consumption in our study. The Spearman’s correlation coefficient between individual MSG intake, as assessed from three 24-h recalls combined with a direct weighing technique, and MSG...
measurement by using a urinary riboflavin marker was 0.82 ($P < 0.01$), which indicates that the MSG measurement in our study is reliable and informative at least for ranking participants and for estimating the relative risks, even though we might not accurately quantify the absolute amount of MSG intake.

Bursey and Watson arbitrarily conclude that the Compendium of Physical Activities developed by Ainsworth et al (3), which we used in our study, “is woefully inadequate and even inappropriate for China.” In fact, we worked with researchers from Ainsworth’s group and with Ainsworth herself and successfully quantified physical activity in Chinese and other populations with methods modified from the Compendium of Physical Activities (3–5). In addition, all dimensions of physical activity as measured by the China Health and Nutrition Survey have been found to predict incident obesity, something not often found in other measures of obesity (6–8). As for energy intake assessment, the validation data from an independent research group using the best objective measurement—doubly labeled water method—have indicated that our measurement was as good as or even better than other established diet-measurement instruments used in the United States (9).

Hill’s perspectives on causal inference have been discussed by epidemiologists for decades (10). We are afraid that Bursey and Watson might ignore the fact that causal relation may not be established by a single observational study. This was why we concluded that “further studies are needed to confirm our findings, to elucidate the mechanisms of action, and to establish causal inference.”

We strongly agree that more evidence is required before we can make any definitive conclusion on MSG and obesity. Assertions of no link between these 2 from the MSG/glutamate industry may not be helpful to future research in terms of scientific merit in this field.

None of the authors reported any conflicts of interest.

Ka He
Shufa Du
Pengcheng Xun
Barry Popkin

Department of Nutrition
Gillings School of Global Public Health
University of North Carolina at Chapel Hill
2221 McGavran-Greenberg
Campus Box 7461
Chapel Hill, NC 27599
E-mail: kahe@unc.edu

Sangita Sharma

Department of Medicine
University of Alberta
Alberta
Canada

Huijun Wang
Fengying Zhai

National Institute for Nutrition and Food Safety
Chinese Center for Disease Control and Prevention
Beijing
China

REFERENCES

6. Tudor-Locke C, Neff LJ, Ainsworth BE, Addy CL, Popkin BM. Omis-

8. Bell AC, Ge K, Popkin BM. The road to obesity or the path to pre-


doi: 10.3945/ajcn.111.020818.