RESEARCH
Review

The Effects of Increased Protein Intake on Fullness: A Meta-Analysis and Its Limitations

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ARTICLE INFORMATION

Article history:
Submitted 17 July 2015
Accepted 8 January 2016
Available online 3 March 2016

Keywords:
Dietary protein
Fullness
Appetitive sensations
Human preload studies
Meta-analysis limitations

http://dx.doi.org/10.1016/j.jand.2016.01.003

ABSTRACT

Background Higher protein intake has been implicated in weight management because of its appetitive properties. However, the effects of protein intake on appetitive sensations such as fullness have not been systematically assessed. Meta-analysis is a useful technique to evaluate evidence of an intervention's effect on testable outcomes, but it also has important limitations.

Objective The primary aim of this study was to synthesize the available evidence on the effect of protein intake on fullness using a quantitative meta-analysis and a secondary directional analysis using the vote-counting procedure. A tertiary aim was to address limitations of meta-analyses as they pertain to findings from this meta-analysis.

Design We searched multiple databases for interventional studies that evaluated the effect of increased protein intake on fullness ratings. Inclusion criteria for both analyses were as follows: healthy human participants, preload studies that utilized intact dietary protein, delivery of protein load orally, and studies reporting fullness as an outcome. For the meta-analysis, an additional criterion was that the studies also needed to report 2- to 4-hour area under the curve value for fullness.

Results Five studies met all criteria for the meta-analysis. Twenty-eight studies met all criteria for the directional analysis. The meta-analysis indicated higher protein preloads have a greater effect on fullness than lower protein preloads (overall effect estimate: 2,435.74 mm.240 min, (95% CI 1,375.18 to 3,496.31 mm.240 min; $P<0.0001$). The directional analysis also revealed a positive effect on fullness with higher protein preloads ($P<0.01$). Many related scientifically rigorous studies were excluded from the analysis because analytical criteria required a narrowly focused research question.

Conclusions The present analyses show that higher protein preloads increase fullness ratings more than lower protein preloads under tightly defined conditions. Extrapolation of findings to common conditions outside the specified criteria of this analysis must be made cautiously, as must speculation about the influence of fullness sensations on ingestive behavior, body weight, and various health outcomes.
J Acad Nutr Diet. 2016;116:968-983.

THE HIGH PREVALENCE AND ATTENDANT ECONOMIC, social, and health costs of overweight and obesity are well known. Adherence to a nutritionally adequate and balanced diet that meets, but does not exceed, energy needs, is the best approach for weight management. A healthy diet is lower in cost[1] and has reduced risk of adverse side effects compared to pharmacologic or surgical interventions. Diets emphasizing higher protein content have been popular for weight management. Such diets reportedly have high satiety value, yield less metabolizable energy because of their high thermogenic effect, and aid in maintenance of lean body mass, which also can enhance energy expenditure.[2] Although well documented, the latter two properties make limited contributions to energy balance.[3] Thus, the primary mode of protein's action is thought to be based on its appetitive properties.

The aminostatic theory of feeding regulation, proposed in the 1950s,[4] held that low circulating amino acid concentrations were a signal that prompted hunger sensations and the motivation to eat. However, this theory did not receive convincing support and subsequent work revealed that, rather than amino acid concentrations impacting hunger, dietary protein was an effective stimulus for the release of gut peptides associated with fullness or satiation.[5] Fullness is defined as the sensations that lead to the cessation of an

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ingestive event and, thus, determines portion size. Satiety is composed of sensations that determine the interval between ingestive events. The strong satiation and satiety properties of protein[6-8] are often cited as the primary mechanism for the benefits of higher protein diets for weight management in short-term clinical trials.[9,10] However, questions about longer-term effectiveness[10-13] and potential adverse health consequences associated with high protein intake[14,15] have attracted considerable research interest. Several scholarly reviews of evidence related to protein and weight management[16-21] and satiety[22] have been published, but none has focused exclusively on the proposed primary mode of action, enhanced fullness. This was the aim of the present meta-analysis.

Meta-analysis has emerged as a preferred technique to critically and objectively evaluate the evidence from multiple independent trials pertaining to an intervention's effect on some identified outcome. The advantages of the approach are its low cost, rapid execution, objectivity, and power. A well conducted meta-analysis yields a statistically testable outcome for a well-defined question using the maximal amount of published data that conform to *a priori* described methodologic criteria. The process is transparent and reportedly less susceptible to bias. However, the technique is also fraught with limitations that are not as well recognized.[23] For example, to adequately delineate the question under study, it is often defined so narrowly that the outcome may not actually address the issue of concern. In addition, to ensure the suitability of merging data from multiple independent trials, decisions must be made regarding methodologic parameters used in each.[24] This improves validity, but typically yields insights based only on a small percent, rather than the totality of evidence pertinent to the question. The present review also addresses a number of these limitations as they pertain to the findings.

Four questions are commonly posed in research studies to capture different dimensions of appetitive sensations; ie, hunger, desire to eat, fullness, and prospective consumption. *Hunger* refers to sensations related to the onset of an eating or drinking event and is traditionally viewed as a reflection of energy need. The "desire to eat" may drive the onset or continuation of eating and is commonly regarded as mediated by cognitive and sensory factors. Thus, one may have a strong desire to eat in the absence of hunger based on an anticipated rewarding effect of consuming a palatable item such as a dessert. *Fullness* is the term used to indicate the sensation responsible for terminating an eating event. Thus, hunger is most strongly linked to eating initiation, whereas fullness is more closely associated with portion size. Hunger and fullness are reportedly driven by different physiologic systems with ghrelin regarded as a hunger hormone (although this has been questioned)[25] and cholecystokinin, glucagon-like peptide-1, and peptide YY are representative of satiation/satiety hormones.[5] Prospective consumption refers to the amount of food that could be eaten at a given point in time and reflects both the energy and rewarding properties of an item and the physiological state of the individual. Although all four questions are routinely asked in an appetite study, hypotheses should be more targeted because of the specificity of the sensations and mechanisms that underlie them. In the case of protein, the preponderance of evidence indicates that it activates satiation/satiety hormone release and so should be most strongly tied with fullness ratings. On this basis, we focused our review on papers that measured this specific sensation. Clearly fullness does not capture the totality of sensations that modulate ingestive behavior. So, while fullness is the logical choice, it admittedly fails to provide a complete picture of protein's effect on appetite.

There is a body of literature on the effects of selected amino acids or different sources of protein (eg, animal, plant) on appetitive sensations. No clear, reproducible, stronger effect of one source has emerged over the others,[26,27] although no single study has compared all sources of protein. Often trials of isolated amino acids or proteins have proof of principle designs that entail supraphysiological doses and experimental controls that do not relate well to customary eating practices. This hampers interpretation of the findings. For this meta-analysis, the decision was made to include only trials that used intact dietary proteins consumed in foods. This led to the exclusion of many papers that could have helped clarify the effects of protein on fullness. Still, they were excluded because the greater variance they would introduce in the stated outcome variable would likely have obscured the hypothesized treatment effect.

The purpose of this investigation was to do both a quantitative meta-analysis and a secondary directional analysis of the effect of protein intake on fullness.

METHODS

Data Sources

Peer-reviewed published articles, including randomized trials, systematic reviews, and meta-analyses, were identified by searching the following electronic databases on December 12, 2013: PubMed (http://www.ncbi.nlm.nih.gov/pubmed), Web of Science (http://webofknowledge.com), Cochrane Library (http://www.thecochranelibrary.com/view/0/index.html), PsycINFO (http://www.apa.org/pubs/databases/psycinfo/), and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) (http://www.ebscohost.com/nursing/products/cinahl-databases/cinahl-complete). Bibliographies of relevant review articles were also searched to ensure appropriate studies had been located using the search criteria that follows. When necessary, relevant articles not yet included in indexing services were added to the list of possible studies to consider for inclusion.

Inclusion Criteria

For the full meta-analysis, studies had to meet all of the following criteria.

1. Study used human participants.
2. Participants were healthy (eg, without chronic diseases).
3. Study was interventional in nature (eg, not observational).
4. Study utilized intact dietary protein as the protein intervention (eg, no specific amino acid supplements).
5. The protein load was consumed orally.
6. Study used a preload design.
7. Study measured and reported fullness as an outcome.