Review

EASL JOURNAL OF HEPATOLOGY

The nutritional geometry of liver disease including non-alcoholic fatty liver disease (NAFLD)

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Summary

Nutrition has a profound effect on chronic liver disease, especially non-alcoholic fatty liver disease (NAFLD). Most observational studies and clinical trials have focussed on the effects of total energy intake, or the intake of individual macronutrients and certain micronutrients, such as vitamin D, on liver disease. Although these studies have shown the importance of nutrition on hepatic outcomes, there is not yet any unifying framework for understanding the relationship between diet and liver disease. The Geometric Framework for Nutrition (GFN) is an innovative model for designing nutritional experiments or interpreting nutritional data that can determine the effects of nutrients and their interactions on animal behaviour and phenotypes. Recently the GFN has provided insights into the relationship between dietary energy and macronutrients on obesity and ageing in mammals including humans. Mouse studies using the GFN have disentangled the effects of macronutrients on fatty liver and the gut microbiome. The GFN is likely to play a significant role in disentangling the effects of nutrients on liver disease, especially NAFLD, in humans.

Keywords: Nutrients; Macronutrients; Fatty liver; Geometric Framework for Nutrition; Protein leverage.

Received 14 August 2017; received in revised form 6 October 2017; accepted 10 October 2017

Introduction

The intimate relationship between diet and physiology confers nutrition with considerable potential for the primary prevention, management and treatment of human disease.[1,2] There are several reasons why this potential has yet to be realised, prominent among which is the prevailing practice of focussing on single nutrients, both as putative causes of disease and as potential cures, rather than considering the interactions among nutrients and other dietary constituents.[1,3] In this review, we begin by framing the challenges posed both to science and clinical practice by the complex concatenation of multilevel interactions between nutrients, foods and diets. Next, we introduce an approach called the Geometric Framework for Nutrition (GFN) as a means to integrate key aspects of nutritional systems (nutrients, foods, diets, appetites and nutritional homeostatic physiology) and to map the relationship between nutrient intakes, physiology and health outcomes. We set out some of the foundational principles of GFN and discuss its use in a large preclinical study in mice, exploring the impacts of macronutrient balance on appetite, physiology, health and ageing. We then consider the nutritional drivers of liver disease, and propose that GFN offers a framework for the future study of the causes and treatment of non-alcoholic fatty liver disease (NAFLD).

Framing nutrition

Humans, like all animals, require dozens of different nutrient types in appropriate amounts and balance to survive, develop and function optimally. Once ingested, these nutrients interact in complex ways with physiology to impact health. While nutrients provide the basic currencies for health, people do not generally eat pure sources of nutrients – rather, we forage for, cultivate, purchase and consume foods. Foods contain mixtures of nutrients along with other substances, and have physico-chemical properties that are greater than the sum of their nutrient parts: a cake, for example, is not predictable from its nutrient composition alone. As is the case for nutrients, we usually do not eat foods singly either; instead we combine them into meals and, along with snack foods, meals accumulate over time to comprise our habitual diet, which reflects personal and cultural preferences, time constraints, economics, and the nature of the food environment. The integrated intake of these dietary nutrient mixtures ultimately influences physiology and health.[4]

It follows that a nutritionally balanced diet does more than deliver a requisite number of calories; it provides an optimal mix of multiple nutrients and fibre as well as energy to meet the needs and circumstances of the individual. But what is a balanced diet? And what are the consequences of failing to attain dietary balance? Public health advice has emphasised both foods and nutrients. Food-focussed classifications for dietary balance have included food pyramids and health rating schemes, whereas nutrient-based classifications include recommended daily intakes (RDIs) for micro and macronutrients.

The evidence base for determining nutritional guidelines has mainly derived from studies that have considered single nutrients – *e.g.* animal

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Please cite this article in press as: Simpson SJ et al. The nutritional geometry of liver disease including non-alcoholic fatty liver disease (NAFLD). J Hepatol (2017), https://doi.org/10.1016/j.jhep.2017.10.005

Key point

GFN integrates key aspects of nutritional systems to map the relationships between nutrients, physiology and health.

studies in which single dietary constituents have been manipulated in experimental diets, epidemiological association studies between intakes of single nutrients and health outcomes, and single-nutrient clinical trials. This 'single-nutrient approach' is based on there being a one-to-one relationship between nutrients and diseases associated with their deficiency (or, less commonly, excess) and assumes that providing the appropriate dose of the nutrient will either prevent or cure disease.[5] While this approach has had considerable success in dealing with diseases associated with micronutrient deficiencies, it has not been effective when considering chronic diseases associated with over-nutrition.[1]

The fundamental problem with one-nutrient approaches is that they do not consider the interactions that occur between the multiple nutrients and other components that comprise foods and diets and which ultimately interact with physiology.[6] One consequence of taking a single-nutrient approach has been to create artificial divisions between proponents of different single-nutrient explanations for chronic diseases, such as obesity and diabetes: the debate over the roles of fat *vs.* sugar being a notable example.[7,8] This has not only led to confusion among the general public, policy makers and medical practitioners, but also to changes in food processing and marketing that have exacerbated rather than alleviated health problems, such as the widespread replacement of fats with added sugars in processed foods. In response to these failures, there has been pressure to move away from 'reductionist' nutrient-based approaches towards more 'holistic', food-based approaches.[1,5,9]

Rather than abandoning nutrient-based approaches, we have instead proposed an integrative framework that incorporates nutrients, foods and diets within the same model and relates these to physiological and health outcomes across multiple scales.[1] This approach, called the Geometric Framework for Nutrition (GFN), explicitly accounts for the interactions among nutrients within foods and diets, and maps the consequences of different dietary compositions on multiple measures of physiology and health.[4]

Introducing the geometric framework for nutrition

GFN has its origins in the biological sciences, in particular ecological and evolutionary theory.[4,10–12] Taking an explicitly ecological perspective, we have shown that the important question is not whether the emphasis in nutritional science should be placed on either nutrients or foods, but that both need to be combined within a single model. GFN provides such an integrative model by considering how mixtures of nutrients (and other dietary components) determine the nutritional properties of foods and how foods in turn combine into meals, diets, and dietary patterns to influence health and disease by acting across the hierarchy of influences from patterns of gene expression to metabolism, immune function, microbiome, organ function, systems physiology, appetite and behaviour. This multilevel framework can be extended beyond the individual to social groups, populations and ecosystems.[4] It can also be developed to integrate influential aspects of the modern food environment such as economics into the same models.[1]

The basis of GFN models is a graph called a nutrient space, in which each nutrient of interest is included as a dimension. A simple two-nutrient example is shown (Fig. 1), in which the x-axis represents amount of protein eaten (P), and the y-axis intake of non-protein energy (nP, typically carbohydrate and fat combined). This is an example of an 'amounts-based' nutrient space. The alternatives are proportions-based nutrient spaces, in which the axes either represent the concentration of the nutrient within the total diet mixture (*e.g.* grams of protein per gram of diet), or the proportion of energy contributed by the nutrient to the combined total of the nutrients included in the graph (*e.g.* percentage of total energy coming from protein). The latter graphs are called right hand mixture triangles[13] (Fig. 2).

In the amounts-based model shown (Fig. 1), foods are represented within the nutrient space as lines (''food rails'') radiating from the origin at an angle defined by their relative proportions of P and nP. The nutritional requirements of the animal integrated over a given time period are represented as a point on the graph – or as a moving trajectory in a dynamic model. The animal is included in the model as a moving point. When it consumes a given food it moves outwards in the nutrient space parallel to that food rail. A nutritionally balanced food is one that intersects the intake target and allows the animal to move directly to its target, achieving the target intake of P and nP simultaneously, whereupon it can stop eating. A nutritionally imbalanced food, by contrast, contains nutrients in proportions that are not the same as at the target. Because the animal cannot therefore reach the target, it must compromise between undereating some nutrients and over-eating others relative to the intake target. The nature of those compromises and the extent to which different nutrients are prioritised when confined to an imbalanced diet is a key aspect of the nutritional phenotype, as is the animal's post-ingestive capacity to retain limiting nutrients and void excesses.[4]

Although the animal cannot reach its intake target when confined to an imbalanced diet, it can do so if it has access to two or more foods whose rails subtend a region in the nutrient space that includes the target. These are termed complementary foods and the animal can reach its intake

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