Minimal and Optimal Fatty Acid Nutrition: The Quest for Omega-3 Nirvana

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Abstract

Marine oils and their related omega-3 rich nutrients are one of the most broadly researched dietary ingredients in modern nutrition. Numerous studies in both human and veterinary species have been conducted resulting in a fertile arena for marketing such products. Establishing an omega-3 dietary minimum, however, has been confounded by several factors including the metabolic relationships among polyunsaturated fatty acids. To address this question, it is necessary to consider quantifiable physiological measurements linking omega-3 fatty acids to some essential biological function and stage of life. Optimal nutritional strategies beyond minimal requirements for omega-3 fats in veterinary species show benefits that likely exceed such minima.

Glossary of Abbreviations
DHA: Docosahexaenoic Acid
DM: Dry Matter
DPA: Docosapentaenoic Acid
EPA: Eicosapentaenoic Acid
ERG: Electroretinogram

Introduction

Discovery of what constitutes an adequate diet was unraveled by the studies of many pioneers in the field of nutrition. Although numerous medical observers of the time recognized that certain diseases were related to diet, nutrition scientists and chemists were limited by the techniques of chemical analyses available. Early studies used biological assays of the more common foodstuffs along with carefully planned feeding experiments. In this way, several nutrient requisites were revealed. These findings led to the prevention or treatment of frank deficiencies and diseases when the specific food or food extract containing that particular nutrient was added to the diet.

An essential nutrient is one that is needed by the body and that cannot be made from other substances or intermediates in adequate amounts. Some nutrients may be conditionally essential because under certain conditions they are indispensable. Marketing claims oftentimes are made regarding some dietary essentials that lead to unnecessary recommendations for routine supplementation when none may be necessary (daily vitamins anyone?).

How Is an Essential Nutrient Determined?

Traditional approaches to methods used to determine essentiality include several techniques (Table 1). There are advantages and disadvantages to each of them. Their selection depends on various assumptions and limitations and must be considered when designing studies. Requirements for different nutrients sometimes have to be measured according to different criteria. For example, with dogs and cats it has been impossible to perform some dietary deficiency experiments due to humane considerations. Values established by

Table 1. Classical Techniques Used to Determine Essential Nutrients

Method	Limitation
Maximum growth	Used in production animals, may not provide optimal health and longevity data
Amount suckled is sufficient	Varies among populations, may not be ideal
Prevent/cure disease	May allow subclinical deficiency
Tissue saturation	Some nutrients may accumulate in specific tissues not measured
Balance studies	Requires appropriate pool size, assumes higher levels are not optimum though they may provide additional benefit
Changes in secondary metabolite	Does not take into account other determinants affecting the metabolite
Amount typically consumed	At best provides adequate intake estimate

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scientific deduction are preferred and are far better than any alternative that comes to mind.

Modern nutrition science has extended the question of minimal and optimal nutrition to also include purposeful ingredients involved in alimentary health such as phytonutrients, fibers and various fatty acids. Hence, it is necessary to embrace new standards for evaluating them either physiologically or at the molecular and cellular levels. Recognition of frank deficiency diseases appears less commonplace today, especially when Western-type diets are consumed. However, more sophisticated physiological and molecular techniques presently available allow enumeration of the cellular functions of many dietary essentials. In this way new benchmarks can be advanced to characterize a nutrient's essential nature. The definition of "minimum requirement" now includes not only recognition of clinical deficiencies but also those at the cellular level. Cellular deficiencies may exist long before any clinical syndrome is observed. At the other end of this spectrum, the phrase "optimized nutrition" may also be advocated as cellular processes responsible for how incremental amounts of a nutrient beyond some minimum can augment health and development and potentially delay progressive pathologies. Going forward, one remaining frontier for the nutritional sciences lies in the appreciation of how complex nutrient interactions of actual foodstuffs consumed provide overall wellness. This latter notion remains an added challenge for our generation as well as a topic for another time.

Brief Chronology of Dietary Polyunsaturated Fatty Acid Studies

Beyond the pioneering work of Burr and Burr in 1929 on the essential nature of fatty acids,[1] widespread characterization of the unsaturated fatty acids by lipid chemists awaited the expansion and utilization of the packed column gas liquid chromatograph. Earlier models in the 1940s and 1950s were available, but the introduction of a unit called the Aerograph allowed many labs to utilize this technology.[2] Compared to today's equipment these instruments required more effort tweaking them for best results, and packing columns by hand was sometimes difficult to do reliably. It also should be noted that most chromatographers back then turned their instruments off after linoleic acid was resolved, and arachidonate often eluted as a broad-based "bump" rather than a sharp peak. Poor resolution and long retention times were needed to elute longer chain fatty acids (like the omega-3s), and most peaks, thereafter, were also broad, poorly defined and difficult to quantify.

At roughly the same time, omega-6s were found to be cholesterol lowering in rats, humans and other animals, and the food industry capitalized on this observation. Given the ubiquitous nature of linoleic acid in vegetable oils like soy and corn, along with hydrogenization and transesterification of oils to provide organoleptic properties for the margarine industry, the focus on omega-6 fats continued.

It was not until the later 1970s when Ralph Holman recommended a change in total parenteral nutrition to include α-linolenic acid, an omega-3 fatty acid, that interest was stimulated in human nutrition.[3] In this case the patient developed neurological signs that disappeared when α-linolenic acid was included in the parenteral emulsion.

Since these early observations, omega-3 fatty acids, such as eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3), have been found to have important health benefits including cardioprotective, inflammatory and neurological outcomes. Additional benefits have been reported for hypertension, renal diseases, arthritis, autoimmune disorders, gastrointestinal diseases, and, to some degree, cancer (reviewed in 4).

Benefits of Fish Oils in Dogs: When More Is Better

In dogs, studies using various dietary amounts of fish oils for skin, cardiovascular, renal, lipid, joint, and metabolic disorders have been published. Recommended supplemental amounts of EPA+DHA using fish oils have recently been reviewed.[4] Dosages using metabolic body weight adjusted by means of multiplication factors ranging from 115 to 310 have been recommended (Table 2). Studies relating to cognitive function and perhaps cancer are ongoing and were not included at that time. It should be noted, however, that therapeutic amounts indicated in Table 2 do not necessarily define an omega-3 requirement but rather offer pharmacological dosages. Whether increased amounts of fish oil omega-3 in otherwise clinically normal animals would either optimize general health or be preventive for such disorders is

Table 2. Therapeutic fish oil dosages using factors (A) of metabolic body weight in adult dogs (dosage = [A] * $[\text{Wt kg}]^{0.75}$). Resultant dosages refer to the amount of combined EPA+DHA in mg recommended for each disorder listed based on published studies. Adapted from reference 4.

Clinical Disorder	Metabolic Body Weight Factor (A)
Idiopathic hyperlipidemia	120
Kidney disease	140
Cardiovascular disorders	115
Osteoarthritis	310
Inflammatory or immunologic (atopy or IBD	125
NRC recommended allowance	30
NRC safe upper limit	370

Dosages may be increased up to the National Research Council's safe upper limit, depending on the severity and chronicity of the disorder,[5] and should be used under veterinary supervision.

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unknown. However, recommended intakes and safe upper limits of combined EPA and DHA for healthy animals have been proposed[5] (Table 2). A minimal requirement may be inferred from the recommended intake amount but awaits further verification.

Is There a Basis for Omega-3 Essentiality?

It is widely accepted that linoleic acid, an omega-6 fat, is a dietary essential in dogs. Hansen, et al. and Hansen and Weise showed retarded growth and skin lesions in dogs when fed fat-deficient diets.[6,7] Had the early lipid nutritionists also reported on the omega-3 fatty acid α-linolenate, it, too, may have been regarded as essential. Both structural and metabolic differences between these two fatty acids are apparent. First, neither are structurally transformable into the other fatty acid type. Second, dogs readily convert linoleate to arachidonate and related eicosanoids while conversion of α-linolenate to EPA is inefficient and to DHA even less efficient.[8] Whether this limited conversion is adequate for any roles that the longer chain omega-3s play depends upon demonstrating the importance of the physiological and cellular functions of the longer chain acids and whether practical amounts of dietary α-linolenate substrate will support their synthesis. Thus, at issue is whether longer chain omega-3 must be provided. Furthermore, should dietary long-chain omega-3s be needed for a particular life stage then a conditional requirement may exist. For example, arachidonic acid may be conditionally essential for reproduction in cats.[9]

Essential Functions of Long-Chain Omega-3

There is a growing consensus that omega-3 fatty acids are essential nutrients. However, the extent to which important cell functions ascribed to long-chain omega-3s is under investigation. To date, much of the evidence for omega-3 essentiality has been based on physiological measurements such as neurological development and visual acuity. However, it is equally important to establish whether there is a biochemical basis for essentiality. DHA, rather than EPA, is more likely to be essential for dogs because EPA synthesis from α-linolenate may be sufficient for health maintenance under normal conditions while DHA conversion may not be.

It is well known that EPA can be converted to several eicosanoids including prostaglandins, leukotrienes and thromboxanes, as well as various resolvins and protectins, many of which have roles in cardiovascular, inflammatory and other cell processes.[10] However, no essential role for these EPA-metabolites has been reported and tissue concentrations are typically low.[8] The reported anti-inflammatory effects of EPA have been shown using higher dietary amounts. Such therapeutic effects may thus be a pharmacological one rather than an essential cell function.

The scientific basis for considering DHA as essential is more persuasive. DHA is reasonably abundant in many tissues and present in large amounts in the brain and retina implying a structural role. DHA also is needed for normal development of the nervous system and optimum visual acuity suggesting a functional role (for a review see 11). In the retina, there is evidence that DHA is highly conserved by being recycled, providing a reliable supply of this fatty acid to the rod outer segment.[12] DHA also interacts with rhodopsin and plays a key role in the control of visual function.[13] In the absence of dietary omega-3, the body compensates by replacing it with docosapentaenoic acid (DPA n-6), an omega-6 fatty acid that is not functionally similar[14] but may instead be a cellular attempt to provide some structural support. Based on these findings, DHA is involved in several important cellular and physiological functions that may only be met by dietary inclusion rather than by limiting its conversion from shorter chain precursors.

Physiological Responses and Potential Minimal and Optimal Dietary DHA Concentrations for Dogs: Studies on Puppy Development

Feeding studies in which puppy development have been evaluated using fish oil omega-3 fatty acids have revealed some interesting findings related to possible requirements for these nutrients, particularly DHA. One study in puppies (and adults) investigated diet mixtures containing low and high omega-3 fats including α-linolenate and long-chain forms.[15] Retinas from the high omega-3 group increased in both DPA n-3 and DHA but not EPA or α-linolenate.[15]

Our laboratory fed pregnant dogs moderate and high dietary amounts of DHA using fish oil from the time of breeding through gestation and lactation.[16,17] A third diet contained 12 times more α-linolenate on a weight basis compared to DHA,[16,17] and a control group was fed minimal omega-3 amounts. Milk from dams fed the high α-linolenate diet was markedly enriched in α-linolenate, and puppies suckling showed significant DHA accumulation.[16,17] However, the puppies appeared to lose their ability to convert α-linolenate to DHA after weaning[16] similar to our findings in adult dogs.[8] Given the high dietary concentration of α-linolenate, it is unknown what minimal amount of this nutrient may be required in milk to support this conversion. In addition, visual development and performance using electroretinogram (ERG) responses of 12-week-old puppies from the above study revealed a significant improvement in visual function for animals in the high fish oil group compared to the other groups.[17]

Zicker, et al. also evaluated ERG responses and cognitive assessments of puppies fed DHA-enriched diets.[18] In this case, DHA-enriched diets also containing some α-linolenate were fed beginning with weaning. A strong correlation between the

DHA content of the diets and improved ERG-assessed visual functions was seen. Cognitive function tests showed puppies fed diets containing DHA had fewer T-maze errors for reversal tasks as well as other significant cognitive function test differences compared to controls.[18]

These studies support using low yet reasonable concentrations of omega-3 for reproduction and/or puppy development. It should be noted that the control diets in these studies did not reveal any clinical deficiency signs. Thus, using their omega-3 content as a point of reference, support for feeding 6- to 8-week old puppies 0.016-0.022% DHA dry matter (DM), 0.08-0.14 % α-linolenate DM, and 1.1-2.2 % LA DM can be advocated. By contrast, where optimal neurological development of puppies is concerned, 0.2 % DHA DM provided significant retinal and cognitive improvements over controls. While these latter studies included at least some amount of α-linolenate, it should be recalled that conversion of α-linolenate to DHA after weaning (approximately 6 weeks) is minimal. These dietary recommendations serve as a useful point of embarkation in designing future studies to assess omega-3 requisites at this time.

Conclusion

A conditionally essential role for DHA in puppies appears reasonable chiefly because of its various roles in brain function and in view of low DHA conversion from omega-3 precursors after weaning. Although visual functions and cognition are improved at higher dietary omega-3 content, control diets with only small amounts of omega-3 fats showed no clinical impairments. Thus, it is difficult to unquestionably conclude that the lower omega-3 diets used in studies to date are "deficient." Nonetheless, data supporting optimal puppy development is an important milestone in fatty acid nutrition. Provision of dietary DHA may also be important for that subset of adult dogs that cannot synthesize enough DHA from precursors. Because the extent of this question is unknown, a global recommendation for DHA may be preferred for all life stages. Finally, because α-linolenate plays a supportive role in omega-3 metabolism by providing essential fatty acid balance, contributing to skin health, converting to EPA, and synthesizing eicosanoid, practical dietary amounts of α-linolenate are also advised at this time.

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