Timely Topics in Nutrition

Nutritional epidemiology in small animal practice

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Why is my dog overweight? Is the cat food I'm feeding a possible cause of hyperthyroidism? What type of diet should I feed my growing Great Dane pup? If I change my older cat's diet, is he less likely to develop kidney disease?

Pet owners typically ask their veterinarians these and many other diet-related questions on a daily basis. The veterinary profession has only partial answers to many of these questions at this time. To thoroughly answer these questions, dietary research must be conducted, using epidemiologic methods with complementary laboratory investigation. This area of epidemiologic research is called nutritional epidemiology. The knowledge gained from such nutritional epidemiology studies must then be made available to the profession, and veterinary practitioners must be able to understand the results and apply them wisely.

The purpose of this report is to describe nutritional epidemiology and to illustrate the power of this type of investigative approach. This report is not a comprehensive review, but rather provides examples to highlight past studies and present knowledge about the effects of diet as the cause or treatment of disease. In addition, epidemiologic principles and study designs are outlined herein, to help veterinarians use this information in a clinical setting, and future directions in nutritional epidemiology involving the practitioner are presented. For the purposes of this report, the discussion is limited to dogs and cats. However, many of the principles of nutritional epidemiology presented here can be applied to other species.

Nutritional Epidemiology

The interplay between diet, other environmental and management factors, and genetic susceptibility is complex.[1] Epidemiology provides a set of methods and approaches that allow veterinarians to account for the multifactorial nature of disease and maintenance of health. Through epidemiology, we can examine the causes and distributions of disease and health in free-living populations, with the ultimate goals of controlling and preventing disease.[2] Typically, epidemiologic studies are considered analytic observational or experimental.[2] The analytic observational study designs include cross-sectional, case-control, and cohort studies. Cross-sectional studies provide information about risk factors and disease status at one point in time. Risk factors are potential predisposing variables or exposures of interest, such as type of food fed or amount of a particular nutrient consumed. In case-control studies, risk factors for animals with the disease of interest are compared with those in animals without that disease. In cohort studies, animals with and without a particular risk factor or exposure are evaluated over time, and the disease outcomes in each group are measured. Experimental epidemiologic studies or field experiments are clinical trials in which each animal or group of animals is assigned to 1 of 2 or more treatments.

Nutritional epidemiology is a special focus area in which diet, nutrition, and feeding practices are addressed as they relate to the cause, treatment, or prevention of disease.[1] Understanding the cause of a disease can provide the mechanisms to control or prevent it. Treatment through dietary modification can improve the quality of life, halt the progression of illness or increase the rate of recovery from disease, or cure the condition.

Nutritional epidemiology provides 2 main categories of information. The first is about cause: did something about a particular diet cause this particular health problem? The second pertains to treatment: can some modification or supplementation of the diet be used as an effective treatment for this health problem? These types of information have direct application to daily veterinary practice, client education, and future research directions.

Diet as a Cause of Disease

Diet can cause disease by 3 main mechanisms. The first is a dietary deficiency of specific nutrients or required components. The second is dietary excess, sometimes referred to as overnutrition; however, specifying the particular dietary component in excess, instead of using the nonspecific term, is more useful. Caloric surplus, manifested as obesity, has lately been an area of concern for pet owners and veterinarians.[3] The third category is management factors relating to diet, including frequency of feeding and type of foods (eg, dry or canned, high protein or reduced calorie).

To prove that a dietary factor causes disease, one

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must understand the scientific criteria by which causation is documented; this is an application of epidemiologic principles in nutritional epidemiology. Some of the causal criteria can be fulfilled by epidemiologic studies, whereas others are supported by laboratory experiments. Five criteria are commonly accepted as guidelines to demonstrate causation[2]: proper time sequence (the proposed cause must precede the disease); greater likelihood of animals with the proposed cause having the disease than of animals without the cause (this strength of association is often measured by odds ratios or relative risks); increased likelihood of the disease with higher doses or longer exposure to the cause; biological plausibility of the cause; and supporting evidence from other studies, preferably conducted in different populations and in which different methods were used. In a given situation, however, 1 or more of these criteria may not apply. Decisions about causation are made by the scientific community and the individual scientist (eg, veterinarian), using subject-matter knowledge and scientific evidence, and cannot be made solely on the basis of statistics or by unthinking adherence to certain rules.

An example of dietary deficiency causing disease is taurine deficiency and dilative cardiomyopathy (DCM) in cats.[4,5] The association between taurine deficiency and chronic retinal degeneration in cats was identified in 1975, and this association was critical in initiating the study that led to discovering the link between taurine and DCM.[6] Chronic retinal degeneration had been diagnosed in a cat 1 year before the diagnosis of DCM. Although the cat died, the owner asked her veterinarian whether DCM could be related to the previous taurine deficiency. Knowing that the myocardium and retina had similar taurine content and the lack of effective treatment for DCM led to the initial hypothesis that taurine deficiency caused DCM.[4] Low blood taurine concentrations preceded development of DCM; this was demonstrated indirectly in a 4-year experimental feeding trial[4] in which 2 of 11 previously healthy cats fed low-taurine diets developed DCM. In addition, all privately owned cats with DCM in another study had been fed commercial diets that had been proven to induce low blood taurine concentrations.[4] Data on taurine and heart failure or arrhythmias in other species provided additional plausibility for the association between taurine deficiency and DCM. Carnitine deficiency in human beings and dogs provided an analogous condition.[4] The connections between low taurine intake and low blood concentrations and DCM were carefully established. Although the researchers in this area did not specifically calculate measures of association or use statistical tests, the epidemiologic data clearly indicated that more cats fed low taurine diets and with low blood taurine concentrations developed DCM than did cats with normal taurine intake and blood values.[7]

A cross-sectional study[a] revealed a statistically significant association between consumption of cat foods supplemented with taurine and higher blood taurine concentrations in cats. Studies in which the treatment of DCM was evaluated revealed that the condition of cats with DCM that had their diet supplemented with taurine improved clinically and echocardiographically.[4] Although formal randomized clinical trials of taurine as a treatment for DCM were not done, because DCM had been documented to have a high fatality rate, the improvement found with taurine treatment alone was believed to be strong evidence for taurine as a cause and a cure. Additional evidence was the decrease in frequency of DCM after the reformulation of commercial cat foods to include increased taurine content in 1987.[a]

Some questions about taurine and DCM remain unanswered. Why do some cats develop DCM, chronic retinal degeneration, or both, whereas others fed the same diet develop neither disease? Why are some diets with apparently high taurine content still associated with low blood taurine concentrations?[8] What is an adequate taurine intake for cats? Future directions for nutritional epidemiologic studies include cohort and case-control studies in which possible factors, such as type of diet, main ingredients, or frequency of feeding, that may lead to low blood taurine concentrations are evaluated. From such studies, specific hypotheses about environmental and management factors that influence blood taurine concentrations in cats could be generated and further examined in clinical trials and laboratory experiments.

Dietary surpluses that potentially cause disease include excessive caloric intake and obesity, overnutrition and metabolic bone diseases in dogs, and ash and urinary tract disease in cats. Obesity in dogs and cats has become a growing problem in the United States.[3,9] Obesity is caused by excess energy intake with excess adipose tissue formation,[10] presumably attributable to an imbalance between caloric intake and expenditure. However, simple though that sounds, obesity is usually related to a complex situation involving the owner's needs and perceptions, as well as the nutritional needs of the pet.[10] Studies of obesity, therefore, must include not only objective measurements of body condition and definitions of obesity, but also owners' perceptions and reasons for their behavior. In many cases, the owner must be counseled and encouraged by the veterinarian to restrict the pet's intake as part of the treatment.

The first step in designing epidemiologic studies to examine the potential causes and treatments of obesity must be to learn about the prevalence of the disease. The second step is to begin to understand the effects of factors such as age, breed, sex, and species on the prevalence of obesity. In a cross-sectional study of 8,268 dogs in 11 veterinary practices in the United Kingdom,[11] almost 24% of the dogs were overweight. Labrador Retrievers and spayed dogs were overrepresented in this overweight group. In a cross-sectional study of cats in the United States,[12] the prevalence of different body conditions and the association between age, breed, sex, and various dietary factors (including type of food, feeding frequency, and competing for food with another cat) were estimated. Of the studied cats, 25% were overweight. Apartment dwelling, inactivity, middle age, and being male, neutered, and a nonpurebred were associated with cats being overweight. A longitudinal (cohort) study on the long-term effects of obesity would be a valuable project to document the now-speculative adverse outcomes of long-term obesity on health in pets.

Excessive intake of calories, protein, and specific nutrients has often been suggested as a cause of metabolic bone disease in pups.[9,13] In a widely cited early study,[13] the frequency of osteochondrosis was compared

in dogs fed ad libitum and in dogs fed a restricted diet. Clinically, the ad libitum-fed dogs had more lameness, hyperextension of the carpi, and enlargement of the costochondral junctions and metaphyseal region of the long bones. Bilateral osteochondritis dissecans (OCD) developed in the scapulohumeral joints of 1 ad libitum-fed dog and 2 restricted-fed dogs. However, the amount of food eaten was not adequately determined, and the effects of sex and litter also were not controlled. Because osteochondrosis seems to have a genetic component and is observed more often in males, these are potentially serious shortcomings. A further study[14] in which only increased dietary calcium content was evaluated revealed a greater frequency of skeletal lesions in the high-calcium group. At the conclusion of that 6-month study, the frequency of skeletal lesions had equalized between the high-calcium-intake and control groups. However, food intake differed between the groups, and statistical analyses were inappropriate.

In a more recent study,[15] increased dietary protein content, without a concomitant increase in calories or other nutrients, did not result in osteochondrosis in Great Dane pups. In a case-control study of diet, exercise, and OCD, high dietary calcium content, relative to energy content, also was implicated as a key risk factor for OCD.[16] However, a hypothesis based on the clinical impression that feeding of specialty-type dog foods (available only through pet stores or veterinary clinics) increased the risk of OCD was not substantiated. These studies suggest that high dietary calcium, but not protein content, are critical in the development of OCD in dogs.

Applying these results to pet dogs is difficult, however, because of the limitations in some of the studies. In addition, most pet dogs are fed commercial dog or puppy foods, and owners do not have control over such formulation. The question is still unanswered: should owners of breeds at risk for diseases such as OCD, hypertrophic osteodystrophy, and panosteitis routinely adjust their pups' diet by limiting amounts or types of food?

In a well-designed study,[17] ad libitum consumption of a balanced diet was implicated in hip dysplasia in dogs kept in research colonies. Whether results from dogs intentionally bred for a high incidence of hip dysplasia can be applied to breeds with lower incidence, however, is difficult to determine. In addition, extrapolating data from dogs housed in a laboratory setting to pet dogs in a home setting is difficult. Epidemiologic studies in this area could provide more concrete guidelines for restricting intake of commercially available foods in pet dogs.

Diet was suggested as a potential risk factor or cause of feline urologic syndrome (FUS) in 1925, even before the term FUS was coined.[18] In the 1950s, dietary ash was proposed as a factor in the pathogenesis of lower urinary tract disease (LUTD) in cats. In 1970, the name FUS was created to include a syndrome of dysuria, obstruction, urolithiasis, and hematuria in cats.[19] In a review in 1973,[20] the authors stated that nothing had ever been proven with regard to diet and FUS, but that epidemiologic studies should be conducted, recognizing the power of the epidemiologic approach.[20] During the 1970s and early 1980s, reports of epidemiologic studies in which diet was evaluated as a potential cause of FUS were published.[21] These studies illustrate the typical progression of epidemiologic research, from simple descriptive studies to more complex analytic ones. Initially, reports of case series were published, in which the clinical picture of the disease was detailed and its cause was suggested. The incidence and prevalence of the disease also were estimated through surveys. In later epidemiologic studies, an analytic approach was used and control or comparison groups were included to test specific hypotheses about diet and FUS. One of the earliest case-control studies[22] was conducted in Copenhagen and explicitly compared the type of diet fed to cats with and without FUS. That analysis also accounted for the effect of breed, sex, age, and season on the increased risk of FUS attributable to feeding large quantities of dry cat food. This pivotal study was the first in which an association between consumption of dry cat food and FUS was documented. Other studies suggested that increasing the amount of dry food as a proportion of the diet increased the risk of FUS in a dose-response manner.[22,23,24] The role of dietary magnesium content also was examined in feeding studies.[25]

In the late 1980s and early 1990s, the role of urine pH on struvite crystal formation, independent of dietary magnesium content, was better defined.[18] The clinical utility of considering FUS a single syndrome also was questioned, because the diagnosis of FUS was being used for various clinical signs with distinct treatments and prognoses.[26] Urolithiasis, lower urinary tract infection, and idiopathic cystitis (feline interstitial cystitis) were separated as clinical entities, on the basis of information about diet and other causes, treatment, and prognosis. Most recently, other environmental factors have been suggested as potential causes of interstitial cystitis in cats.[27]

Because of changes in commercial cat foods to prevent FUS, a shift from struvite to calcium oxalate uroliths has been observed.[26] Concern that the acidifying nature of most commercial diets may cause hypokalemia and chronic renal disease also has been expressed.[19] Early experimental studies and clinical trials might have disclosed some of the current problems resulting from the change in diets. Instead, the study of LUTD in cats has generated 2 new questions: one concerning the effects on cats chronically fed low-magnesium, acidifying diets, and the second on other, perhaps related, causes of LUTD that are noninfective and do not lead to urolith formation. Diet and environmental factors such as indoor housing, use of litter pans, and life stresses are being evaluated to further elucidate the causes of and relationships between certain types of LUTD in cats.[28]

Dietary management factors also have been hypothesized to cause disease. Frequency of feeding or ad libitum feeding has been linked to the incidence of FUS.[21] The relative proportions of dry and canned food also have been implicated in hyperthyroidism in cats, with a large proportion of canned food in the diet being linked to increased risk of the disease.[29] The mechanism may include iodine content of the food, or canned food may be a surrogate variable for another true cause of the disease.[30] The increase in frequency of hyperthyroidism in cats has been hypothesized to be attributable to envi-

ronmental factors, especially diet, and is still being investigated.[31]

Diet as a Treatment for Disease

Treatment of disease by diet has 3 main objectives: to control the disease and improve quality of life; to cure the disease; or to improve health and well-being as supportive treatment in conjunction with other treatment modalities. The ideal type of study to evaluate the ability of diet to treat disease is a randomized clinical trial. When feasible, randomly assigning animals to receive the current best treatment or new treatment(s), along with ensuring that the evaluators are unaware of treatment assignments, provides the strongest evidence for efficacy. Use of only a single treatment in the study, without a comparison group, will rarely provide convincing support for diet as an efficacious treatment.

Control of disease or delaying of its progression is a common objective for dietary treatments. Commercial diets have been specially formulated for animals with gastrointestinal disease[32,33]; for example, in 1 case series, the long-term control of exocrine pancreatic insufficiency by diet was documented in dogs.[33] The importance of owner education and of customizing the diet to the individual situation was emphasized.

Dietary management of chronic renal failure in dogs is still a controversial subject,[34,35] in part because of the limited number of clinical trials in dogs with naturally developing chronic renal failure.[35] In 1 clinical trial, 14 client-owned dogs with chronic renal failure that were randomly assigned to be fed commercial canned food, a moderate-protein diet, or a low-protein diet were included.[34] The authors concluded that the moderate-protein diet provided the best quality of life for these dogs. However, they acknowledged the difficulties in assessing efficacy associated with client compliance, the lack of similarity of age of dogs, the lack of uniformity in severity of anemia between treatment groups, and the small sample size. Poor client compliance can be linked to various factors including the dog's response to dietary treatment, perceived palatability of the food, ease of product use and purchase, and understanding of the protocol. All of these factors make randomized clinical trials difficult to design and conduct. However, only clinical trials in client-owned animals can provide answers for questions about optimal diets for the management of chronic renal failure in dogs and cats.

A dietary cure for disease generally must correct a specific nutritional imbalance, such that correction of the imbalance cures the disease. Returning a dog or cat to normal body weight also can be considered as curing disease. A report of the use of a standardized weight-loss program in private veterinary practice illustrated some of the difficulties in conducting studies on the treatment of obesity in pets.[36] Owners were allowed to select a commercially marketed or prescription "light" pet food for their dog or cat, to increase client compliance. A complete program including exercise and recheck visits was prescribed and explained. However, because of the variety in diets chosen, owner compliance, and range of obesity and activity of the pets, the ability of the author to determine the effectiveness of a given diet was limited. Although the overall weight loss induced by the program could be evaluated, determining which factors were responsible for a given owner's success and, therefore, improving the efficacy of the weight-loss program, were not possible.

The role of diet in supportive treatment has been expanding and receiving increasing attention in veterinary medicine.[37] The benefits of dietary modifications in altered metabolic states resulting from illness or trauma have been demonstrated.[37,38] These modifications may include changes in nutrients or methods of administration, including enteral and parenteral routes.[37] Anorexia or cachexia secondary to other diseases such as cancer also can be treated by alternate methods of forced intake.[39,40] Formal epidemiologic studies in which the type of diet and route of administration are compared are still needed to clarify the optimal application of diet as a supportive treatment.

As veterinarians, we include dietary changes as treatments in individual animals for many diseases and reasons. Our knowledge of etiopathogenesis and choice of treatment are based on previous experience with similar populations or groups of animals. Information obtained from populations must be carefully applied to our individual patients. Experiences of other veterinarians and scientists may be accessed by consultation or review of the literature. Articles must be critically evaluated for validity and for applicability to a particular clinical setting. Excellent guidelines have been published to assist with this process, and continuing education programs are beginning to provide workshops in this area.[41,42]

Many nutritionally related questions in the practice of veterinary medicine are still unanswered. Nutritional epidemiology places the emphasis on the importance of the possible effects of diet and nutrition, as alterable environmental factors, in the development and treatment of disease. The veterinary literature is 1 source of information on new studies and results. Some clinical questions can be answered by simple and inexpensive epidemiologic studies conducted in private practices. Veterinarians may wish to consider consulting an epidemiologist or biostatistician on the optimal design for a study in nutritional epidemiology to appropriately answer important questions for their clients.

[a]Pion PD, Skiles ML, Hird DW, et al. Epidemiologic evaluation of taurine deficiency and dilated cardiomyopathy in cats (abstr). *J Vet Intern Med* 1990;4:117.

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