Calcium, phosphorus, and vitamin D are important essential nutrients in the dog and the cat. As such, these nutrients are required as a part of a complete and balanced diet. Most commercial diets for dogs and cats provide sufficient amounts of calcium, phosphorus, and vitamin D, but homemade diets may be deficient or unbalanced in these nutrients, which may lead to negative outcomes. Additionally, raw meat diets often show nutritional imbalances. Over-supplementation and deficiencies of nutrients are frequently found, especially regarding calcium, the trace elements copper, zinc and iodine, vitamins A and D and the calcium: phosphorus ratio[1,2].

1. Dicalcium phosphate, Calcium gluconate and vitamin D-3

Calcium, phosphorus, and vitamin D are nutrients that play a key role in maintaining normal organ, cell, and tissue function. Much is known about their role in bone metabolism, but these nutrients are also important in renal health, urinary tract disease, and multiple other organ systems[3,4].

In dogs and cats, the requirements for dietary calcium and phosphorus are increased over maintenance during growth, pregnancy, and lactation. In dogs, the optimal calcium: phosphorus ratio should be ~1.2–1.4:1; however, minimum and maximum ratios by AAFCO are 1:1 to 2.1:1. Less phosphorus is absorbed at the higher ratios, so an appropriate balance of these two minerals is necessary. Also, insufficient supplies of calcium or excess phosphorus decrease calcium absorption and result in irritability, hyperesthesia, and loss of muscle tone, with temporary or permanent paralysis associated with nutritional secondary hyperparathyroidism. Skeletal demineralization, particularly of the pelvis and vertebral bodies, develops with calcium deficiency. By the time there is a pathologic fracture and the condition can be confirmed radiographically, bone demineralization is severe. Often, there is a history of feeding a diet composed almost entirely of meat, liver, fish, or poultry.

Calcium serves two important functions: 1) as a structural component in bones and teeth and 2) as an intracellular second messenger that enables cells to respond to stimuli such as hormones and neurotransmitters. Calcium's two major physiologic functions in bone are to serve as a structural material and as an ion reservoir. When calcium in bone acts as an ion reservoir, it is in equilibrium with serum ionized calcium and under tight homeostatic control. PTH, calcitonin and 1,25-(OH)2-D3 act together to maintain calcium homeostasis in the face of variable dietary intakes and changing calcium requirements during growth, pregnancy and lactation.

Deficiencies and excesses of calcium, as well as calcium-phosphorus imbalances, should be avoided in dogs and cats. A food grossly deficient in calcium, but adequate in phosphorus can cause secondary hyperparathyroidism. Inadequate calcium intake produces hypocalcaemia, which stimulates release of PTH, which in turn stimulates production of 1,25-(OH)2-D3, resulting in a higher fractional absorption of calcium and phosphate, and lower calcium but higher phosphate concentration in urine. PTH acts with vitamin D to promote bone resorption and turnover, which may lead to pathologic fractures. Hypocalcaemia is a common problem in diseased states (chronic or acute renal failure, pancreatitis, eclampsia, etc.), and parenteral supplementation of calcium and/or calcitriol (1,25-(OH)2-D3) is sometimes warranted. Calcium excess is probably more detrimental in rapidly growing animals than in adults, especially large and giant-breed puppies[5,,6].

Phosphorus is a vital participant in a number of tissues and functions. After calcium, phosphorus is the second largest constituent of bone and teeth. Phosphorus is a structural component of RNA and DNA, high-energy phosphate compounds such as ATP and cell

membranes composed largely of phospholipids. As a component of nucleic acids, high-energy phosphate compounds and cell membranes, phosphorus is essential in cell growth and differentiation, energy use and transfer, fatty acid transport and amino acid and protein formation.

About 60 to 70% of phosphorus is absorbed from a typical diet. In general, phosphorus availability is greater from animal-based ingredients than from plant-based ingredients. Phosphorus in meat is found mainly in the organic form, whereas in plants, phosphorus is in the form of phytic acid. Phytate phosphorus is only about one-third available to monogastric animals but availability from different grains can vary markedly. Intestinal phosphorus absorption represents the sum of a saturable, carrier mediated component and a nonsaturable, concentration dependent component. Regulation of total body phosphorus requires the coordinated efforts of the kidneys and intestine.

Under conditions of low dietary phosphorus intake, the intestine increases its absorptive efficiency to maximize phosphorus absorption and the kidneys increase renal phosphorus transport or minimize urinary phosphorus losses. Hormonally, these adaptations result from changes in plasma levels of 1,25- (OH)2-D3 and PTH. Conversely, under conditions of dietary excess, the kidneys increase excretion of minerals. Avoiding excess dietary phosphorus slows progression of kidney disease.

The primary function of vitamin D is to enhance intestinal absorption and mobilization, as well as retention and bone deposition of calcium and phosphorus. This function is manifested through its active form of 1,25-(OH)2-D3 as a hormone that binds to the nuclear 1,25-(OH)2-D3 receptor (VDR) in many types of cells. The active vitamin D3 also has a direct effect on Ca2+ channels located on the plasma membrane.

Vitamin D is absorbed from the small intestine by nonsaturable, passive diffusion, which depends on bile salts. Vitamin D then enters the lymphatic circulation primarily (~90%) in association with chylomicrons; the remainder of vitamin D is associated with an α-globulin fraction. Like other steroids, vitamin D is transported in association with proteins. In most species, the binding protein is vitamin D-binding protein (DBP) or “transcalciferin.” The concentration of DBP greatly exceeds the concentration of vitamin D metabolites in blood. This concentration difference, in conjunction with the binding affinity, results in less than 5% of the available binding sites being occupied by vitamin D compounds. The distribution between bound and free vitamin D compounds greatly favors the bound form. In this fashion, DBP facilitates peripheral distribution of vitamin D from dietary origin and mobilizes endogenously produced vitamin D from the skin.

Vitamin D is distributed relatively evenly among the various tissues where it resides in lipid depots. Vitamin D can be found in adipose, kidneys, liver, lungs, aorta and heart. The primary circulating form of vitamin D is the parent vitamin D (~50%), with the next most abundant form (i.e., 25-OH-D3 [also called calcidiol]) accounting for approximately 20% of the total. In mammals, both vitamin D2 (ergocalciferol) and D3 (cholecalciferol) are not the active form of vitamin D. They are activated in the body by hydroxylation to 25-OH-D3 first in the liver and again to 1,25- (OH)2-D3 (also called calcitriol) in the kidneys. Vitamin D2 is less efficiently used than vitamin D3 in cats[7]. There is a lack of controlled, well-powered studies in dogs, but vitamins D2 and D3 appear to have a similar potency in this species[8].

At normal plasma concentrations, only small amounts of 25- OH-D3 are released from this pool to enter tissues. Thus, circulating levels of 1,25-(OH)2-D3 are a good indicator of vitamin D status.

Several factors tightly regulate the vitamin D endocrine system: 1,25-(OH)2-D3, PTH, calcitonin, several other hormones and circulating levels of calcium and phosphate. The vitamin D-dependent homeostatic system responds to perturbations in calcium concentration. For example, when serum calcium falls below a given level, PTH is secreted by the parathyroid glands, which function to detect hypocalcemia. The kidney responds to PTH, resulting in phosphate diuresis and stimulation of 25-OH-D3 1-hydroxylase. The latter effect increases production of 1,25-(OH)2-D3, which acts to increase enteric absorption of calcium and phosphate. In addition, 1,25-(OH)2-D3 acts jointly with PTH in bone to promote mobilization of calcium and phosphate. The combined result of these responses is to increase plasma concentration of calcium and phosphate. Calcitonin is secreted by the thyroid gland ("C" cells) when circulating concentrations of calcium are increased. Calcitonin suppresses bone mobilization and may increase the renal excretion of calcium and phosphate. In that situation, 25-OH-D3 1-hydroxylase may be inhibited by 1,25-(OH)2-D3, and may actually be converted to 24,25- (OH)2-D3, which may down-regulate the absorption of calcium in dogs[9].

1. Vitamin A

Vitamin A is absorbed almost exclusively as the free alcohol retinol. Within mucosal cells, retinol is re-esterified mostly to palmitate and incorporated into the chylomicrons of the mucosa. Afterwards, it diffuses into lymph. Vitamin A is transported through the lymphatic system with low-density lipoprotein (LDL) to the liver, where it is deposited mainly in hepatocytes and stellate and parenchymal cells.

Some vitamin A derivatives are re-excreted into the intestinal lumen via the bile. This is true for much of retinoic acid and some retinol. The major vitamin A components of bile are vitamin A glucuronides, many of which are reabsorbed. Thus, enterohepatic circulation may provide an important means of conserving vitamin A. Although dogs and cats excrete vitamin A in urine, cats excrete a lesser amount.

When vitamin A is mobilized from the liver, stored vitamin A ester is hydrolyzed before it is released into the bloodstream. Vitamin A retinol is transported to tissues in the bloodstream by a specific transport protein called retinol-binding protein (RBP). RBP is synthesized and secreted by hepatic parenchymal cells.

In contrast to most other species, dogs and cats have a unique way of metabolizing vitamin A. Cats require preformed vitamin A because they lack the oxygenase enzyme necessary for β-carotene cleavage. In addition, studies have shown that cats and dogs do not depend on RBP to transport vitamin A in plasma. Cats and dogs transport vitamin A as retinyl esters (mostly retinyl stearate) bound to LDL and very low-density lipoprotein in amounts 10 to 50 times those of other mammals[10]. This is of interest because free circulating retinyl esters are a sign of hypervitaminosis A in almost all other animal species, including people.
Vitamin A is essential for a number of distinct biologic functions. It is necessary for normal vision, growth, reproduction, immune function and maintenance of healthy epithelial tissue. Vitamin A is also involved in the expression and regulation of many genes[11].

Vitamin E

Vitamin E is a term for a group of compounds with the biologic activity of α-tocopherol. In nature, there are eight isomeric forms of vitamin E, four tocopherols (α, β, γ, δ) and four tocotrienols (α, β, γ, δ). The most biopotent form of vitamin E is α-tocopherol. The relative biopotencies of vitamin E isomers are as follows: α >β >δ >γ. Also, tocopherols are generally more available than tocotrienols [12].

Vitamin E works in conjunction with glutathione peroxidase to protect cells against the adverse effects of reactive oxygen and other free radicals that initiate the oxidation of polyunsaturated membrane phospholipids. Vitamin E in cellular and subcellular membranes is the first line of defense against peroxidation of vital phospholipids.

In addition, vitamin E is important for normal reproduction and is involved in modulating cellular signaling, regulating gene transcription, modulating immune function and inducing apoptosis[13].

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