New findings on vitamins A, D, E, K

Jürgen Zentek

Institute of Animal Nutrition

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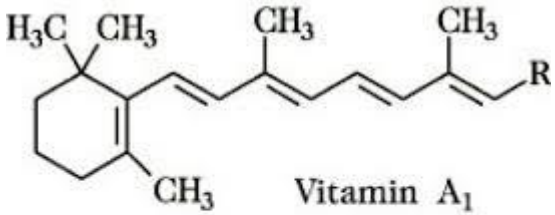


Fat soluble vitamins

Vitamin	Chemical	Active substances
A	Retinol	Retinol (Vitamin-A_1-Alcohole) Retinal (Vitamin-A_1-Aldehyde) Retinoic acid (Vitamin-A_1-Acid) Dehydroretinol (Vitamin A_2) Provitamin A: α-Carotin, β-Carotin,γ-Carotin, Chryptoxanthin
D	Cholecalciferol	Cholecalciferol (Vitamin D_3) Ergocalciferol (Vitamin D_2) 1,25-Dihydroxy-Cholecalciferol
E	α-Tocopherol	α -, β-, γ-, δ-Tocopherol α -, β-, γ-, δ-Tocotrienol
K	Phyllochinon	Phyllochinon (Vitamin K_1), Menachinon (Vitamin K_2) Menadion (Vitamin K_3) Menadiol (Vitamin K_4)

Vitamin A

- Several polyene alcohols with vitamin A activity
  - Epithelial cells (epithelial protection vitamin)
  - Expression of numerous genes and thus the protein synthesis (growth vitamin)
  - Bone growth (maintenance of the osteoclast activity)
  - Visual process
  - Synthesis of mucopolysaccharides



Vitamin A_1

R = CH_2OH : Retinol
R = CHO : Retinal
R = COOH : Retinoinsäure

www.spectrum.de

Vitamin A

- Dogs
  - In contrast to other animal species, vitamin A (retinol) predominantly occurs in the dog as retinyl esters
  - Transported by lipoproteins
- Cats
  - Cats are reported to transport retinyl ester in plasma as we
  - More susceptible to chronic hypervitaminosis A
  - Dependent on preformed vitamin A in the diet

Cats have a very limited capacity to make retinol from β-carotene

Vitamin A

Journal of Feline Medicine and Surgery (2014) **16**, 243–248

CASE REPORT

Hypervitaminosis A-induced hepatic fibrosis in a cat

Juliana M Guerra DVM[1,2]
Alexandre G T Daniel MSc DVM[3]
Thiago R A Aleja

Rationale: The excessive intake of vitamin A in the form of vitamin concentrate, supplement or vitamin-rich liver can result in hypervitaminosis A in man and animals. Although osteopathologies resulting from chronic vitamin A intoxication in cats are well characterized, no information is available concerning feline hypervitaminosis A-induced liver disease.
Clinical summary: We report the first case of hepatic stellate cell lipidosis and hepatic fibrosis in a domestic cat that had been fed a diet based on raw beef liver. Radiographic examination revealed exostoses and ankylosis between vertebrae C1 and T7, compatible with deforming cervical spondylosis. Necropsy showed a slightly enlarged and light yellow to bronze liver. Microscopic and ultrastructural analyses of liver tissues revealed diffuse and sev
hepatic stellate cell hyperplasia and hypertrophy. These cells s
α-smooth muscle actin and desmin markers. The necropsy find
with osteopathology supported the diagnosis of hypervitamino
Practical relevance: As in human hepatology, if there is dietary
of vitamin A, then hypervitaminosis A should be considered in t
liver disease in cats.



d and yellowish, with
ite foci

Nutritional maximum (Fediaf 2016):

33,333 IU/100 g DM in reproduction
40,000 IU/100 g DM adult and growing cats

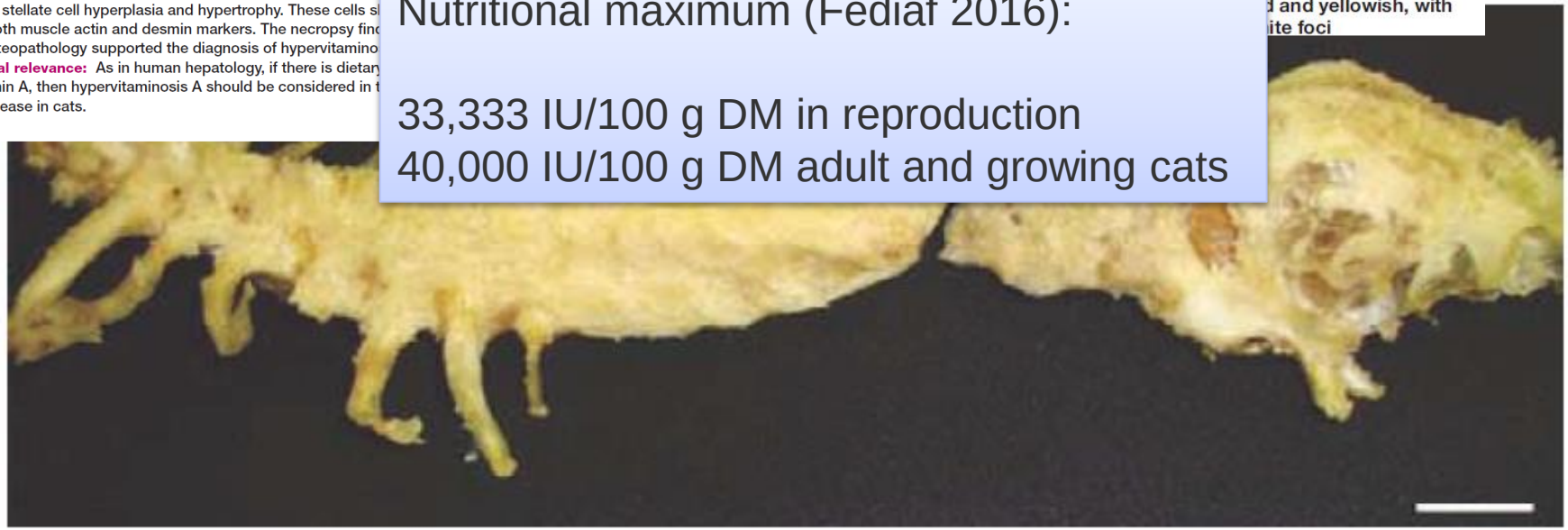


Figure 2 Macerated skeleton showing extensive and diffuse exostoses involving the cervicothoracic vertebrae, and a complete fracture between C1 and C2. Bar = 2 cm

Vitamin A tolerance in dogs

- Dogs are known to have a high tolerance for dietary vitamin A
- Safe upper limit for puppies has not been well derived from experimental data

  - Fediaf (2016): 40,000 IU/100 g DM

Safety evaluation of vitamin A in growing dogs

Penelope J. Morris[1]*, Carina Salt[1], Jens Raila[2], Thomas Brenten[3], Barbara Kohn[4], Florian J. Schweigert[2] and Jürgen Zentek[5]

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(Submitted 4 August 2011 – Final revision received 20 December 2011 – Accepted 6 January 2012 – First published online 1 March 2012)

Abstract

The safe upper limit for inclusion of vitamin A in complete diets for growing dogs is uncertain, with the result that current recommendations range from 5·24 to 104·80 μmol retinol (5000 to 100 000 IU vitamin A)/4184 kJ (1000 kcal) metabolisable energy (ME). The aim of the present study was to determine the effect of feeding four concentrations of vitamin A to puppies from weaning until 1 year of age. A total of forty-nine puppies, of two breeds, Labrador Retriever and Miniature Schnauzer, were randomly assigned to one of four treatment groups. Following weaning at 8 weeks of age, puppies were fed a complete food supplemented with retinyl acetate diluted in vegetable oil and fed at 1 ml oil/100 g diet to achieve an intake of 5·24, 13·10, 78·60 and 104·80 μmol retinol (5000, 12 500, 75 000 and 100 000 IU vitamin A)/4184 kJ (1000 kcal) ME. Fasted blood and urine samples were collected at 8, 10, 12, 14, 16, 20, 26, 36 and 52 weeks of age and analysed for markers of vitamin A metabolism and markers of safety including haematological and biochemical variables, bone-specific alkaline phosphatase, cross-linked carboxyterminal telopeptides of type I collagen and dual-energy X-ray absorptiometry. Clinical examinations were conducted every 4 weeks. Data were analysed by means of a mixed model analysis with Bonferroni corrections for multiple endpoints. There was no effect of vitamin A concentration on any of the parameters, with the exception of total serum retinyl esters, and no effect of dose on the number, type and duration of adverse events. We therefore propose that 104·80 μmol retinol (100 000 IU vitamin A)/4184 kJ (1000 kcal) is a suitable safe upper limit for use in the formulation of diets designed for puppy growth.

Key words: **Puppies: Dogs: Retinol: Retinyl esters: Vitamin A**

British Journal of Nutrition

Hypothesis and objectives

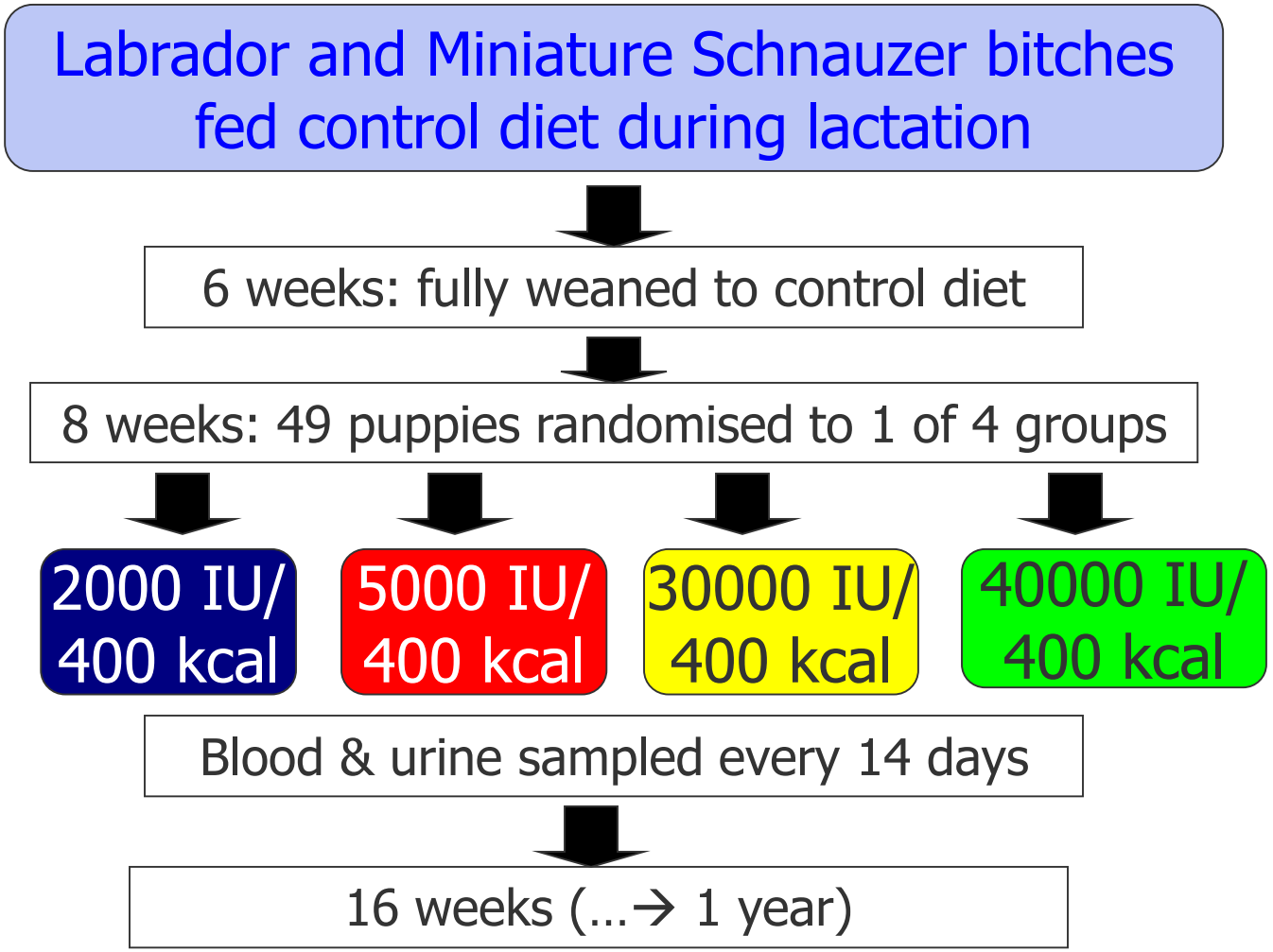
- Hypothesis:

  - Puppies do not differ in vitamin A metabolism compared to adult dogs

- Objective:

  - to investigate the impact of a broad spectrum of dietary vitamin A intakes in puppies up to the age of 16 weeks

Design


Labrador and Miniature Schnauzer bitches fed control diet during lactation
6 weeks: fully weaned to control diet
8 weeks: 49 puppies randomised to 1 of 4 groups
2000 IU/ 400 kcal
5000 IU/ 400 kcal
30000 IU/ 400 kcal
40000 IU/ 400 kcal
Blood & urine sampled every 14 days
16 weeks (…→ 1 year)

Diet

	per 400 kcal
Proximates	
Crude protein (g)	30
Crude fat (g)	17
Crude ash (g)	7
Crude Fibre (g)	2
Nitrogen free extract (g)	37
Minerals	
Calcium (g)	1.3
Phosphorous (g)	0.9
Zinc (mg)	13.1
Vitamins	
Vitamin A (IU)	1975
Vitamin D (IU)	161

Traits

- Bone growth
- Urine (Free Catch)
  - Retinol, Retinyl Esters
  - Retinol Binding Protein
  - Tamm-Horsfall Protein
- Blood
  - Haematology
  - Clinical Chemistry
  - Retinol, Retinyl Esters
  - Bone ALP (bone formation)
  - Cross Laps



Vitamin A intakes

	Group			
	A	B	C	D
/	Vitamin A, IU			
400 kcal	2093	4902	30547	40133
kg BW	736	1839	11312	15125
kg $BW^{0.75}$	1123	2776	17340	23402

Serum retinol

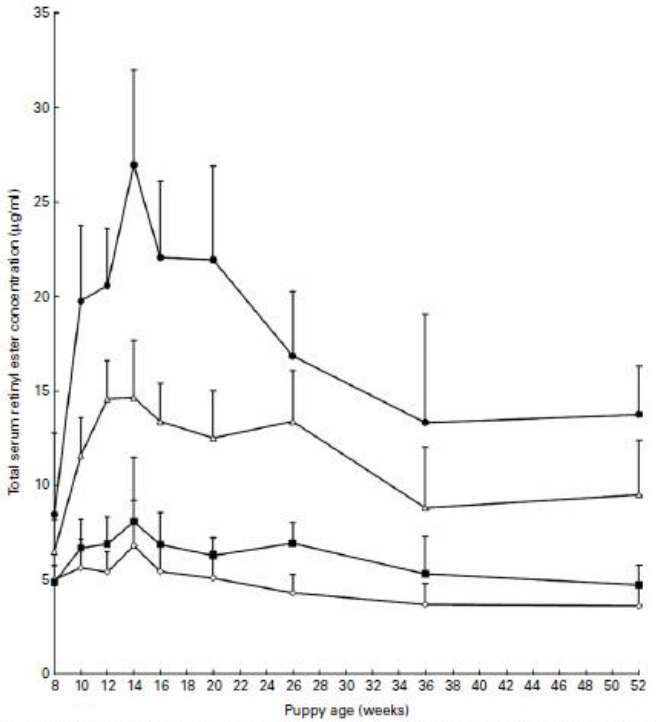


Fig. 3. Change in total serum retinyl ester concentrations with age in growing puppies. Values are means, with 95% CI represented by vertical bars. Mean values were significantly different between the groups ($P<0{\cdot}05$). Group A (—◇—), 5.24 µmol retinol (5000 IU vitamin A)/4184 kJ (1000 kcal) metabolisable energy (ME); group B (—■—), 13.10 µmol retinol (12 500 IU vitamin A)/4184 kJ (1000 kcal) ME; group C (—△—), 78.60 µmol retinol (75 000 IU vitamin A)/4184 kJ (1000 kcal) ME; group D (—●—), 104.80 µmol retinol (100 000 IU vitamin A)/4184 kJ (1000 kcal) ME.

Serum retinyl esters

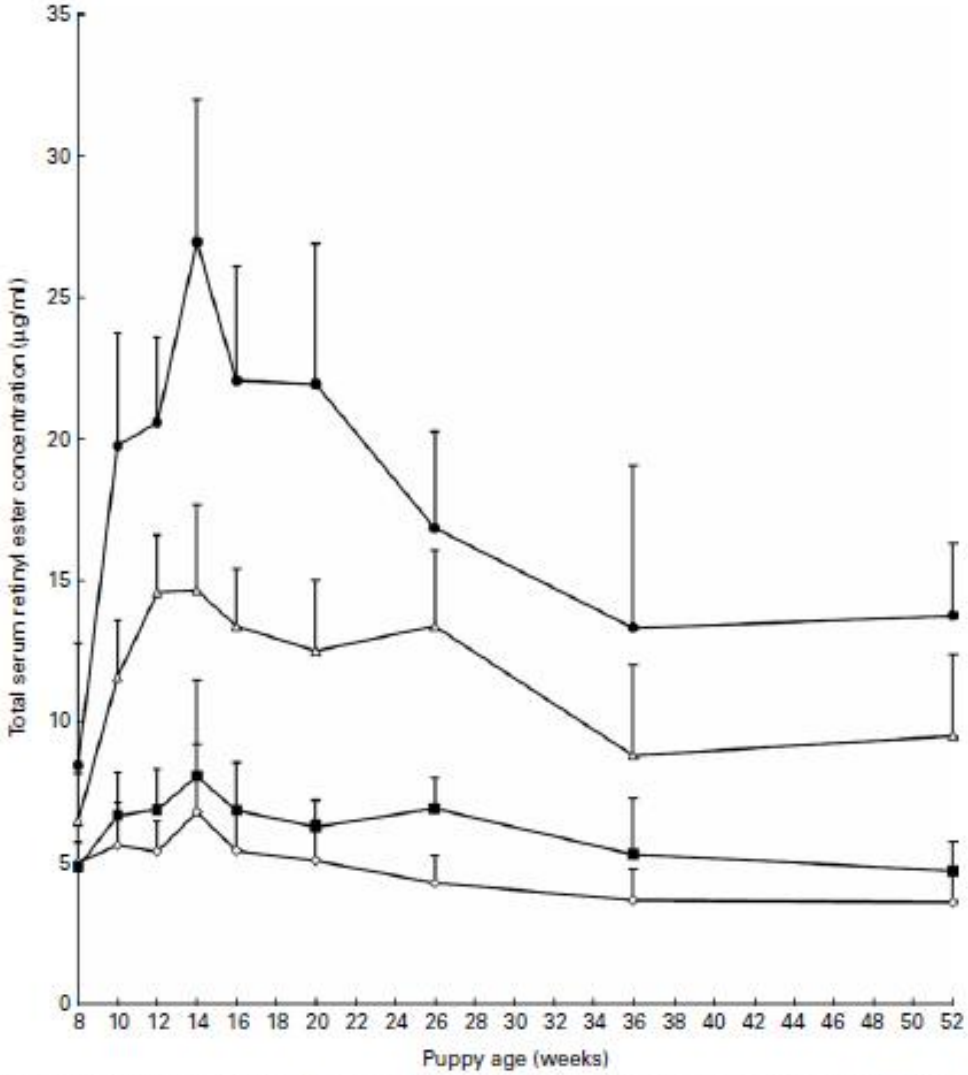


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Retinyl ester levels in urine

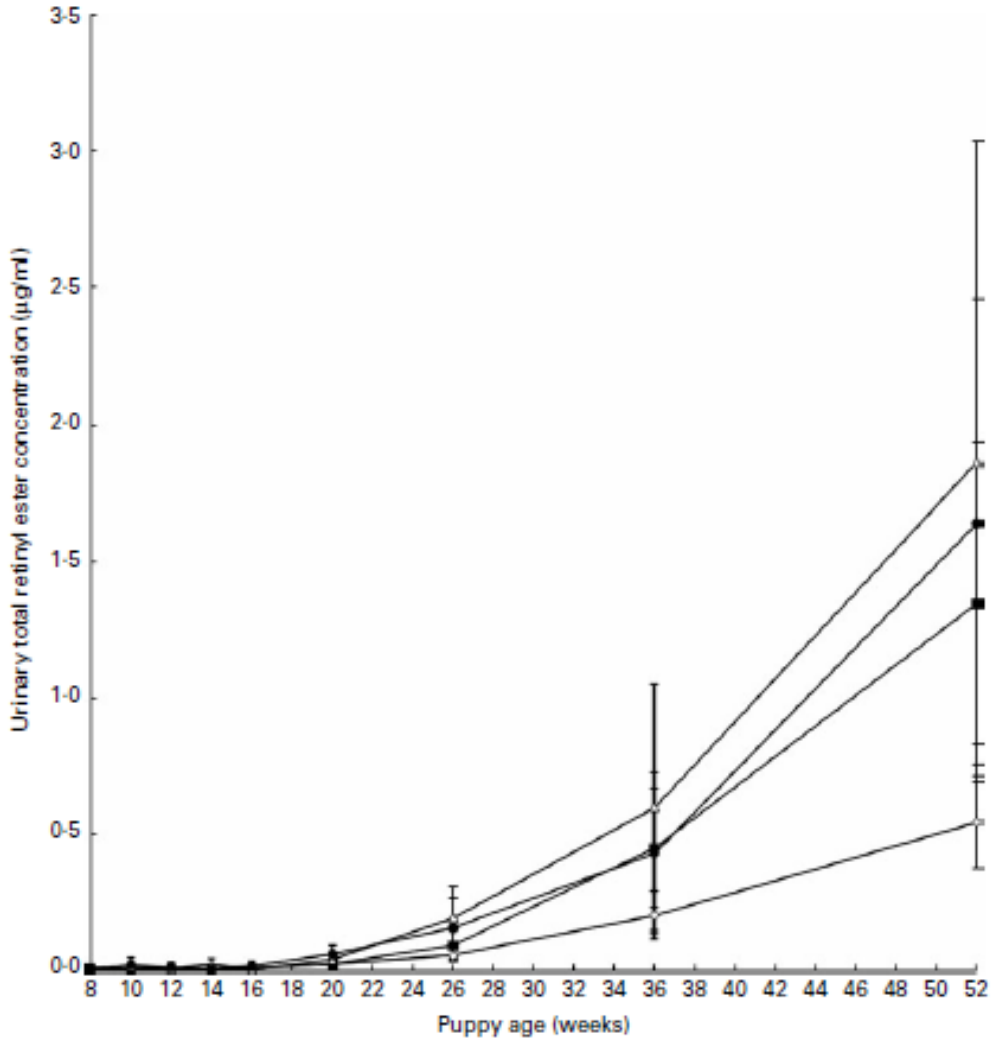


Fig. 4. Total urinary retinyl ester excretion. Values are means, with 95 % CI represented by vertical bars. Mean values were significantly different between the groups ($P < 0{\cdot}05$). Group A (—◇—), 5.24 µmol retinol (5000 IU vitamin A)/4184 kJ (1000 kcal) metabolisable energy (ME); group B (—■—), 13.10 µmol retinol (12 500 IU vitamin A)/4184 kJ (1000 kcal) ME; group C (—△—), 78.60 µmol retinol (75 000 IU vitamin A)/4184 kJ (1000 kcal) ME; group D (—●—), 104.80 µmol retinol (100 000 IU vitamin A)/4184 kJ (1000 kcal) ME.

Conclusions

- Vitamin A intakes induced significant differences in plasma retinyl ester levels
- The urina ol and retinyl esters se on existent”?)
- No clinica l signs of a detriment n A could be observed up to 40.000 IU/400 kcal

FEDIAF (2016):

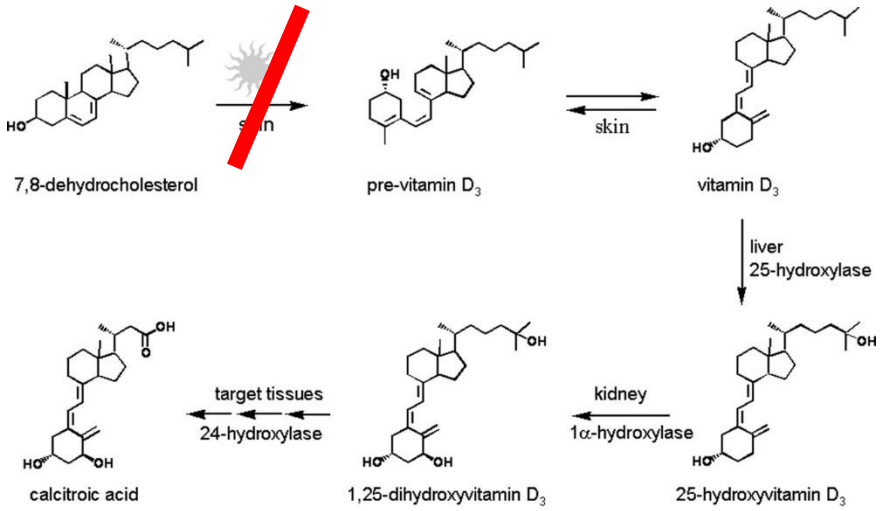
Dogs: 500 - 606 IU/100 g DM

Cats: 333 – 900 IU/100 g DM

No indications of health problems

Vitamin D

- Various substances with vitamin D activity
- Cholecalciferol (vitamin D_3) and ergocalciferol (vitamin D_2)
- Ca and P absorption in the intestine



http://ajprenal.physiology.org/content/ajprenal/289/1/F8/F1.large.jpg

Vitamin D

- Suboptimal vitamin D supply
  - Inadequate mineralization of the skeleton – depending on Ca and P
  - Chronic inflammatory bowel diseases can also affect the vitamin D status of dogs

- Excess
  - Excessive Ca and P concentrations in the blood
  - Calcification of vessels, organs
  - In general, the vitamin D intake should not exceed 10 times the normal requirement (even with therapeutic measures)

Vitamin D

- Rickets with diets with no supplemental vitamin D

- Normal growth rates and skeletal development in dogs fed diets containing compliant vitamin D levels (Tryfonidou et al, 2002)

- Impaired endochondral ossification in puppies fed a diet containing extremely high levels of vitamin D (Tryfonidou et al., 2003)

Vitamin D

- Dietary 135-fold cholecalciferol supplementation severely disturbs the endochondral ossification in growing dogs

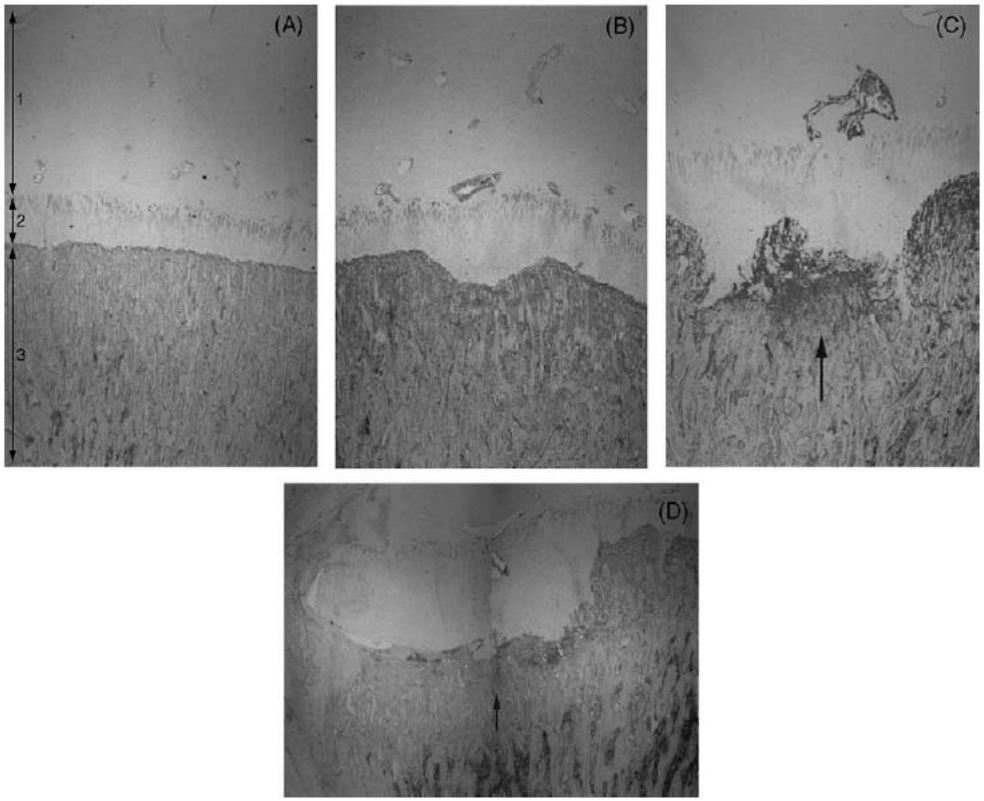


Fig. 3. Physeal growth plate of the 9th rib of Great Danes at 21 weeks of age raised on balanced food with 11.4 µg Vitamin D_3/kg according to the recommendations of the NRC [28] (*CVitD* group; A) and 1350 µg Vitamin D_3/kg (*HVitD* group; B–D). Dogs of the *HVitD* group had irregular growth plates with variable severity due to focal disorders of endochondral ossification characterized by arrest of chondrocyte apoptosis, retarded formation of primary spongiosa and protrusion of the growing cartilage in the metaphyseal area with necrosis in the most severe cases (arrow). 1, cartilage; 2, growth plate; 3, metaphyseal area.

Tryfonidou et al. 2003

Vitamin D intoxication caused by ingestion of commercial cat food in three kittens

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sagepub.co.uk/journalsPermissions.nav
DOI: 10.1177/109[illegible]
jfms.com
SAGE

Astrid Wehner[1], Julia Katzenberger[1], Anna Groth[2], Roswitha Dorsch[1], Petra Koelle[1], Katrin Hartmann[1] and Karin Weber[1]

	Vitamin D_3-declared* (IU/kg)	Vitamin D_3-measured** (IU/kg)
Food 1: wet food (Almo Nature Kitten with chicken)	OS: 1500 DM: 6466	OS: 46,900 DM: 202,155

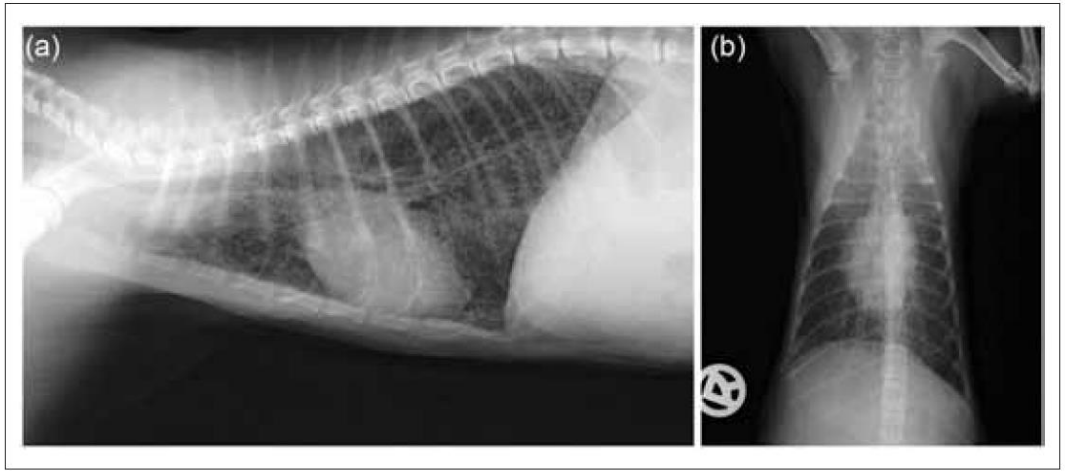


Figure 1 Thorax, right lateral (a) and dorsoventral (b) view of cat 1 at presentation. The lungs were well inflated and the diaphragm flattened, which may represent dyspnoea. There was evidence of a generalised miliary interstitial pattern and peribronchial cuffing throughout the lungs, and a curvilinear, interrupted, mineral opacity line superimposed on the cardiac silhouette in the area of the ascending aorta and the left ventricular outflow tract, as well as evidence of bronchial mineralisation. Differential diagnosis for the generalised interstitial pattern included interstitial mineralisation secondary to hypercalcaemia, bronchopneumonia and, less likely, neoplasia secondary to a round cell tumour. Fungal pneumonia, metastatic neoplasia or uraemic pneumonitis were considered unlikely

PLOS ONE

RESEARCH ARTICLE

Impact of Increasing Dietary Calcium Levels on Calcium Excretion and Vitamin D Metabolites in the Blood of Healthy Adult Cats

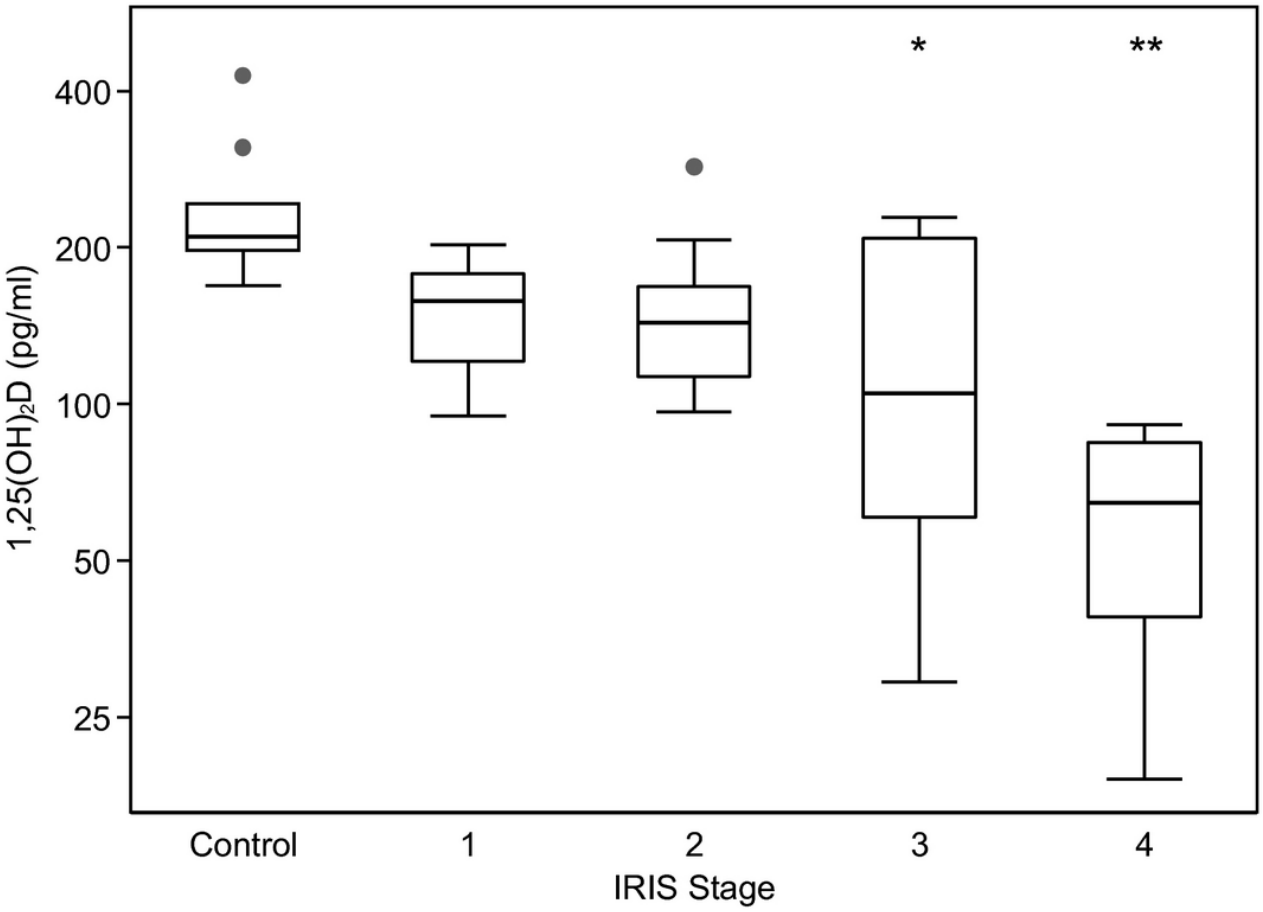
Nadine Paßlack[1]*, Bettina Schmiedchen[2], Jens Raila[2], Florian J. Schweigert[2], Friederike Stumpff[3], Barbara Kohn[4], Konrad Neumann[5], Jürgen Zentek[1]

1 Institute of Animal Nutrition, Department of Veterinary Medicine, Freie Universität Berlin, Königin-Luise-Str. 49, 14195, Berlin, Germany, **2** Institute of Nutritional Science, University of Potsdam, Arthur-Scheunert-Allee

Results

Urinary Ca concentrations remained unaffected, but faecal Ca concentrations increased ($P < 0.001$) with increasing dietary Ca levels. No effect on whole and intact parathyroid hormone levels, fibroblast growth factor 23 and calcitriol concentrations in the blood of the cats were observed. However, the calcitriol precursors 25(OH)D_2 and 25(OH)D_3, which are considered the most useful indicators for the vitamin D status, decreased with higher dietary Ca levels ($P = 0.013$ and $P = 0.033$). Increasing dietary levels of dicalcium phosphate revealed an acidifying effect on urinary fasting pH (6.02) and postprandial pH (6.01) ($P < 0.001$), possibly mediated by an increase of urinary phosphorus (P) concentrations ($P < 0.001$).

Association of Vitamin D Metabolites in Dogs with Various Stages of Chronic Kidney Disease



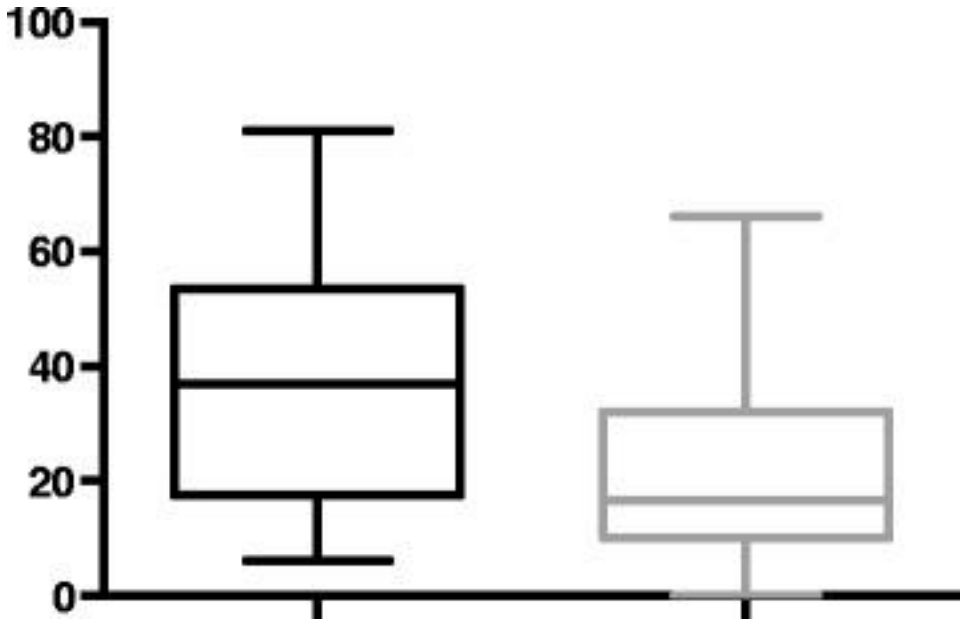
Journal of Veterinary Internal Medicine
10 FEB 2017 DOI: 10.1111/jvim.14653
http://onlinelibrary.wiley.com/doi/10.1111/jvim.14653/full#jvim14653-fig-0002

Parker et al. 2017

Vitamin D in dogs with PLE

Hypovitaminosis D is associated with negative outcome in dogs with protein losing enteropathy: a retrospective study of 43 cases

Box and *Whisker plots* representing 25(OH) D serum concentrations between PLE dogs in the poor outcome versus good outcome groups. (25(OH) D serum concentration in poor outcome group: median 16.5 nmol/L, range 0–66 nmol/L; good outcome group: median 37 nmol/L, range 6–81 nmol/L, $p = 0.017$)



Allenspach et al. 2017

Vitamin D

- Recommended allowances

  - FEDIAF (2016) recommendation for dogs and cats:

    - 227 IU/100 g DM
    - Legal vs. nutritional maximum
    - Cats seem to be more tolerant to high vitamin D diets

Dietary antioxidants

- Vitamin E
  - Chemically closely related substances (tocopherols)
  - α-tocopherol with the highest activity
  - Difference to other tocopherols

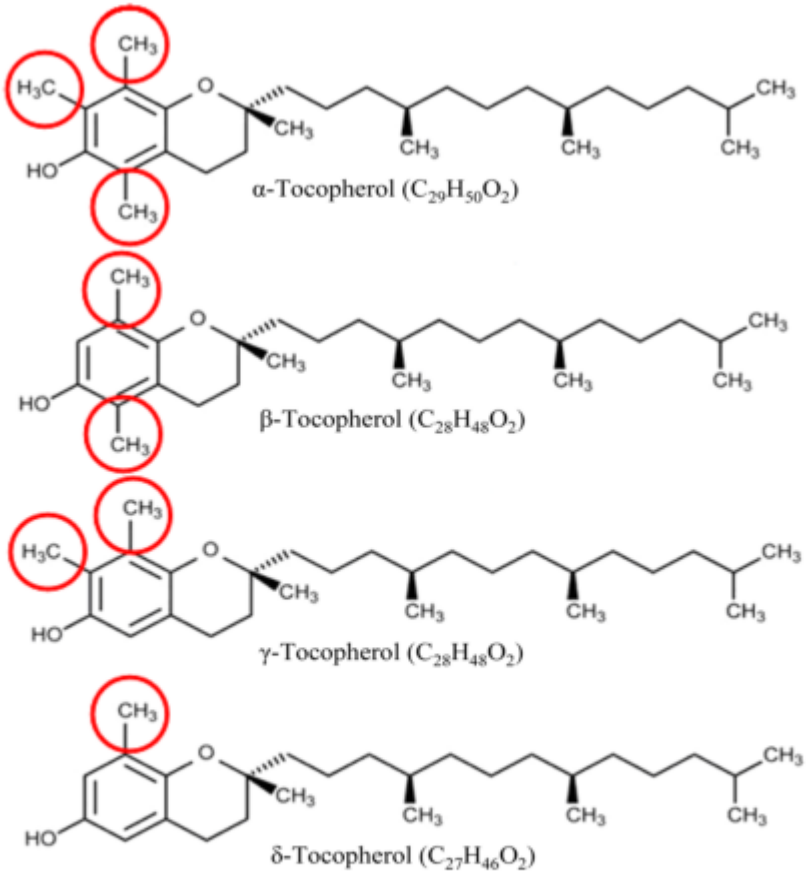


Figure 2. Chemical structures of tocopherol homologues showing differences only in the number and position of methyl substituents on the aromatic ring of chromanol head circled in red.

Hussain et al. 2013

Dietary antioxidants

- Vitamin E deficiency

  - Growth disorders
  - Damage to the skeletal and cardiac muscle
  - Central nervous system disorders
  - Retinopathies
  - Discoloration of body fat (yellow fat disease)

Dietary antioxidants

- Vitamin E

  - Preserves lipid-rich membranes from damage by peroxidation
  - Importance for the respiratory chain as well as in the synthesis of long-chain fatty acids, vitamin C, or deoxyribonucleic acids

Dietary antioxidants

- Vitamin E

  - Tocopherols are stored to some extent in liver and body fat
  - Recommended allowance (FEDIAF 2016):

    - 3.6-5 IU/100 g DM dogs
    - 3.8 IU/100 g DM cats

Oxidative stress

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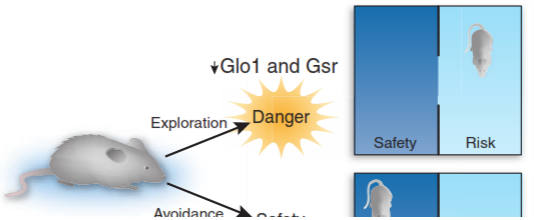
Oxidative stress is the new stress

Jay A Gingrich

Emotional stress may increase anxiety, but in mice, a different kind of stress—oxidative stress—to anxious behavior.

Anxiety and fear are useful when the situation warrants. The stress of an upcoming exam prods the student to master the test material to allay anxiety. Fear, and the self-preserving actions it elicits, is adaptive when an organism is faced with life-threatening situations.

A brief stint in a psychiatrist's consulting room, however, will demonstrate that not all fears and anxieties are useful. Many people



Beyond oxidative stress: an immunologist's guide to reactive oxygen species

Carl Nathan[1,2] and Amy Cunningham-Bussel[1,2]

Abstract | Reactive oxygen species (ROS) react preferentially with certain atoms to modulate functions ranging from cell homeostasis to cell death. Molecular actions include both inhibition and activation of proteins, mutagenesis of DNA and activation of gene transcription. Cellular actions include promotion or suppression of inflammation, immunity and carcinogenesis. ROS help the host to compete against microorganisms and are also involved in intermicrobial competition. ROS chemistry and their pleiotropy make them difficult to localize, to quantify and to manipulate — challenges we must overcome to translate ROS biology into medical advances.

Modulation of oxidative stress as an anticancer strategy

Chiara Gorrini[1], Isaac S. Harris[1,2*] and Tak W. Mak[1]*

Abstract | The regulation of oxidative stress is an important factor in both tumour development and responses to anticancer therapies. Many signalling pathways that are linked to tumorigenesis can also regulate the metabolism of reactive oxygen species (ROS) through direct or indirect mechanisms. High ROS levels are generally detrimental to cells, and the redox status of cancer cells usually differs from that of normal cells. Because of metabolic and signalling aberrations, cancer cells exhibit elevated ROS levels. The observation that this is balanced by an increased antioxidant capacity suggests that high ROS levels may constitute a barrier to tumorigenesis. However, ROS can also promote tumour formation by inducing DNA mutations and pro-oncogenic signalling pathways. These contradictory effects have important implications for potential anticancer strategies that aim to modulate levels of ROS. In this Review, we address the controversial role of ROS in tumour development and in responses to anticancer therapies, and elaborate on the idea that targeting the antioxidant capacity of tumour cells can have a positive therapeutic impact.

Beyond oxidative stress: an immunologist's guide to reactive oxygen species

Carl Nathan[1,2] and Amy Cunningham-Bussel[1,2]

Abstract | Reactive oxygen species (ROS) react preferentially with certain atoms to modulate functions ranging from cell homeostasis to cell death. Molecular actions include both inhibition and activation of proteins, mutagenesis of DNA and activation of gene transcription. Cellular actions include promotion or suppression of inflammation, immunity and carcinogenesis. ROS help the host to compete against microorganisms and are also involved in intermicrobial competition. ROS chemistry and their pleiotropy make them difficult to localize, to quantify and to manipulate — challenges we must overcome to translate ROS biology into medical advances.

Sources: Nature

Benefits vs. harm

- Free radicals
  - Useful…
    - when they are produced in the right amount, at the right place, at the right time
  - Detrimental…
    - when imbalanced, lipid peroxidation, cell death, genetic damage
  - Result of the extremely reactive nature of free radicals

Heaton et al. 2002

Dietary antioxidants

- Vitamins E, C, combination with dietary fish oil

  - increased bactericidal activity

Veterinary Immunology and Immunopathology 139 (2011) 217–228

Contents lists available at ScienceDirect

Veterinary Immunology and Immunopathology

journal homepage: www.elsevier.com/locate/vetimm



Research paper

Influence of dietary antioxidants and fatty acids on neutrophil mediated bacterial killing and gene expression in healthy Beagles

Jean A. Hall[a,*], Rachel M. Chinn[a], William R. Vorachek[a], M. Elena Gorman[a], Joe L. Greitl[b], Dinesh K. Joshi[b], Dennis E. Jewell[b]

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[b] Pet Nutrition Center, Hill's Pet Nutrition, Inc., 1035 NE 43rd Street, Topeka, KS 66617-1587, United States

Dietary antioxidants

- α-tocopherol acetate, β-carotene, lutein in sled dogs

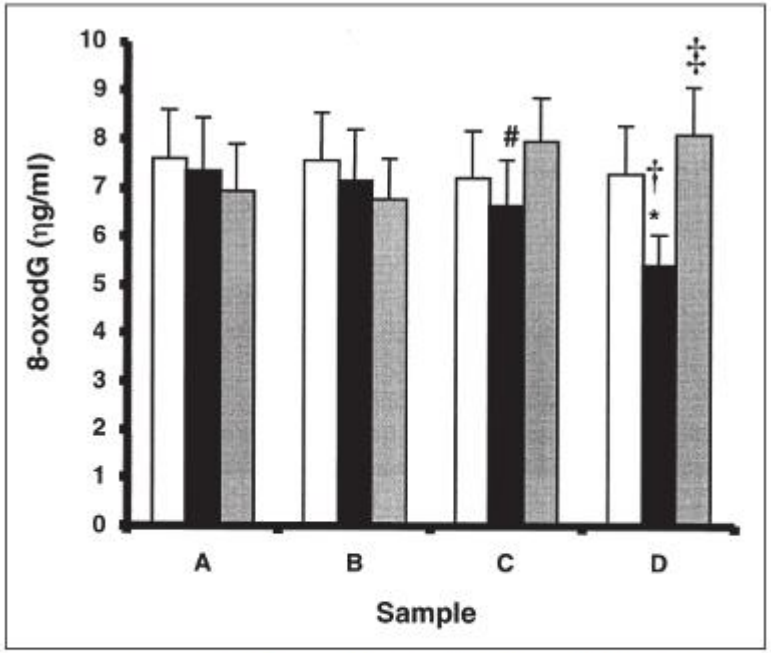


Figure 3—Mean (± SD) plasma concentrations of 7,8 dihydro-8-oxo-2'deoxyguanosine (8-oxodG) in sedentary nonsupplemented dogs, exercising supplemented dogs, and exercising nonsupplemented dogs. *Significantly ($P < 0.01$) different, compared with values for other 2 groups. #Significantly ($P < 0.05$) different, compared with value for exercising nonsupplemented group. †Significantly ($P < 0.05$) different from values for same group determined at times A, B, and C. ‡Significantly ($P < 0.05$) different from value for same group determined at time B. *See* Figure 1 for key.

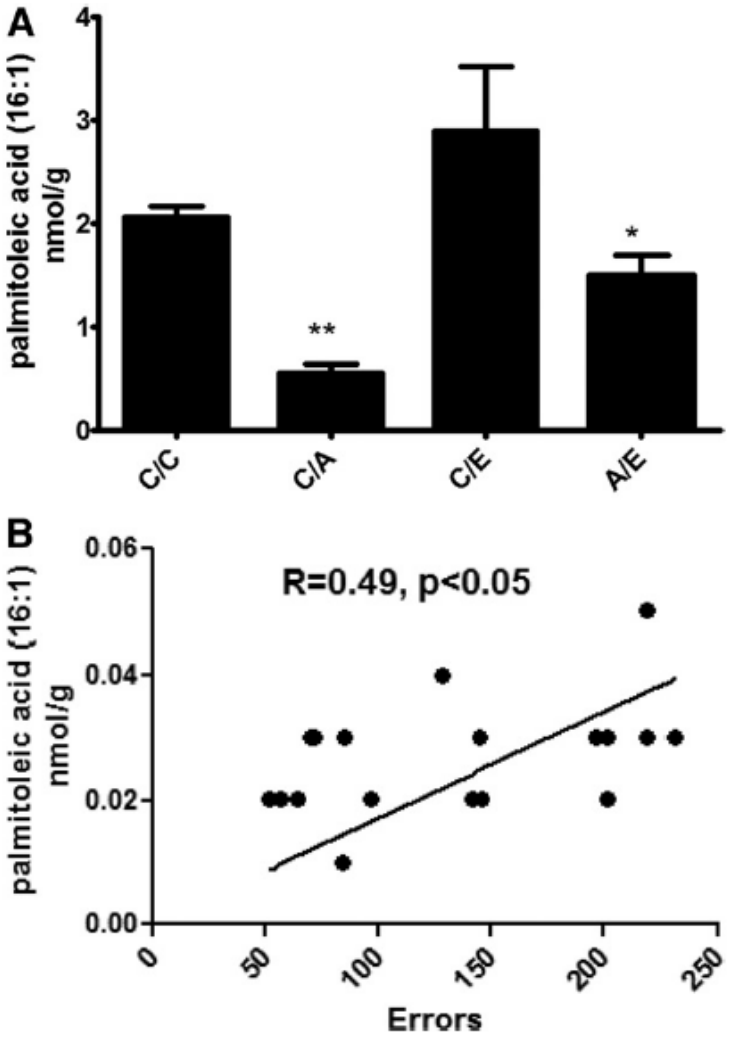
Less oxidation products

Baskin et al. 2000

Behaviour

- α-tocopherol, L-carnitine, α-lipoic acid, ascorbic acid, spinach flakes, tomato pomace, grape pomace, carrot granules, and citrus pulp

Snigdha et al. 2012



Cancer

- Cancer patients

  - Antioxidants are among the most commonly used supplements
  - Potential benefits for cancer patients
  - They also may have detrimental effects

Freeman 2009

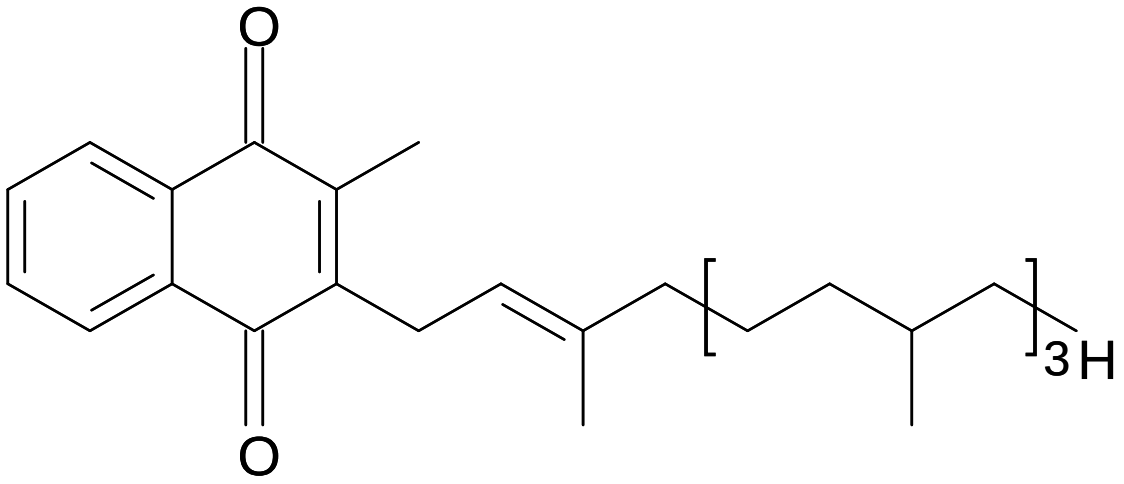
Other applications

- Potential for antioxidants

  - Inflammatory or degenerative diseases
  - Cardiovascular diseases
  - Cataracts
  - Mycotoxins

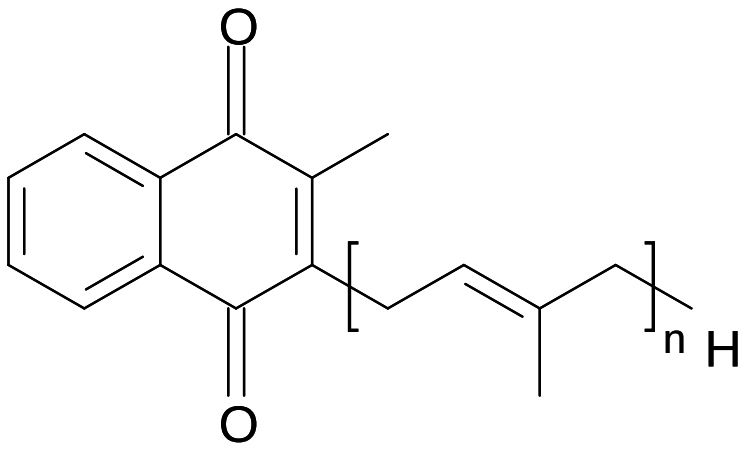
Vitamin K_1 –Phylloquinone (PK)-

- Green leafy plants and several vegetable oils
- PK consists of a naphthoquinone ring with a methyl group attached at the 2nd position and a phytyl group at the 3rd position
- 2-methyl-3-phytyl-1,4-naphthoquinone



Vitamin K_2 –Menaquinone (MK)-

- Produced by the intestinal microbiota of mammals and birds
- 2-methyl-3-multiprenyl-1,4-napthoquinone
- Isoprenoid side chain of variable length at the 3rd position
- MK-n → n representing the number of isoprenoids



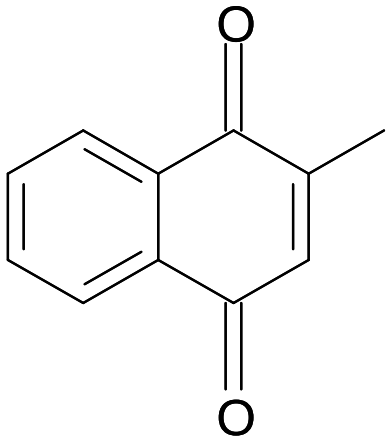
➢ Menaquinones produced by intestinal bacteria

Vitamin K_2 –Menaquinone (MK)-

	MK-4	MK-5	MK-6	MK-7	MK-8	MK-9	MK-10	MK-11
Bacteroides spp.			X	(X)	X	X	X	X
Enterobacteria				(X)	X			
Veillonella spp.			(X)	X	(X)			
Eubacterium lentum			X					
Wolinella spp.			X					

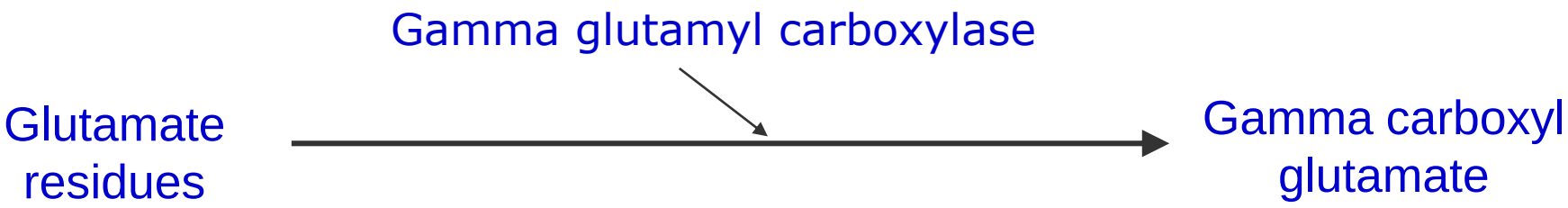
Vitamin K_3 –Menadione-

- Synthetic origin
- 2-methyl-1,4-naphthoquinone
- Four authorized compounds in Europe



Vitamin K –Biological functions-

- Co-substrate for carboxylation of the vitamin K-dependent proteins
- Vitamin K-gamma glutamyl carboxylase → modifying enzyme



→Higher Ca-binding capacity

→ Higher activity of vitamin K-dependent proteins

Vitamin K –Biological functions-

- Vitamin K-dependent proteins
  - Coagulation proteins: clotting factors II, VII, IX and X, protein C, protein S
  - Protein Z (unknown function)
  - Bone-related proteins: osteocalcin, matrix Gla protein
  - Growth arrest-specific gene 6
  - Plaque Gla protein, nephrocalcin, prolin-rich Gla proteins 1 and 2 (unknown function)

Vitamin K –Hypovitaminosis-

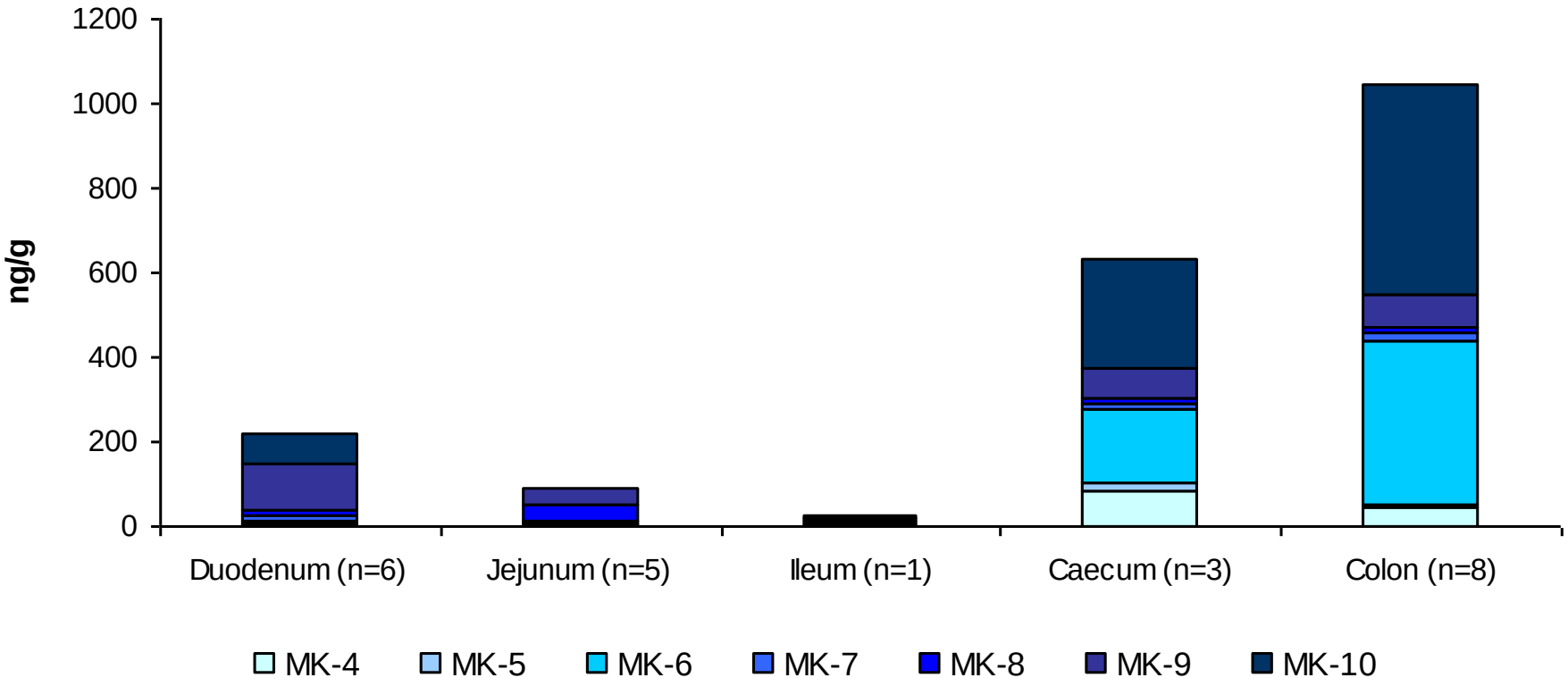
- Primary deficiency
  - Not described in dogs
- Secondary deficiency
  - Intake of vitamin K antagonists :
    cumarin, phenylindandion, other anticoagulant rodenticides, antibiotics (with thiotetrazole side chain)
  - Modification of the intestinal microflora (intake of antibiotics)
  - Intestinal disorders

Vitamin K –Toxicity-

- PK and MK
  - No toxic symptoms or adverse effects after ingestion of high amounts
- Menadione
  - High intake (> 1000-fold the recommendations) induced formation of Heinz bodies
    → haemolytic anaemia

Results –Digesta-

- Highest concentration of MK in colon and caecum
- Predominant were MK-10 and -6, followed by MK-9 and MK-4



Conclusion

- Production of MK takes place in the intestinal tract of dogs
- Amount of intestinal MK might contribute to the requirements of vitamin K
- Further investigations about the mechanism of absorption and the biological activity are needed

10 µg/100 g DM in cat food

Conclusion

- Vitamins have lots of benefits for the health of dogs and cats
- It is important to watch the vitamin supply in the light of new feeding practices
- Probably, oversupply is more important than deficiencies, but changing dietary habits (…in Europe)