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Guest Editorial

It's not just bones anymore: The new and exciting world of vitamin D

In the 1st and 2nd centuries AD, Roman physicians made the first probable descriptions of rickets, a skeletal disease thought to be due to poor hygiene (Rajakumar, 2003). The first scientific descriptions were given by Daniel Whistler (1619–1684) and then Francis Glisson (1597–1677) in the 17th century. Glisson considered low socioeconomic status and 'stupefaction of the spirits' were the likely causes of the disease (Rajakumar, 2003). Anecdotally, cod liver oil and sunlight had long been known to both treat and prevent rickets and, in the 20th century, vitamin D was found to be the active compound (Pettifor, 2005; Holick, 2006). Since then, there has been substantial research into vitamin D, its mechanisms, metabolism and effects on calcium homeostasis and bone health.

Classically, 1,25-dihydroxvitamin D (1,25-D) is regarded as the active form of vitamin D. When 1,25-D is bound to the vitamin D receptor-retinoid X receptor complex, the complex binds to DNA and alters the transcription of vitamin D-responsive genes (Dittmer and Thompson, 2011). This leads to the well known effects of vitamin D on calcium and phosphorus metabolism, including increased absorption of these minerals from the intestinal tract, their increased resorption from bone and, in conjunction with parathyroid hormone, increased resorption of calcium in the kidneys (Dittmer and Thompson, 2011).

Despite intensive research on vitamin D over the last century, there is still controversy as to the recommended daily intake of vitamin D and the serum concentration of vitamin D that can be classified as indicating 'deficiency' (Holick, 2003). It has been suggested that a further category of 'insufficiency' should be created but, again, opinions on the appropriate level vary (Hanley and Davison, 2005).

The discussion on vitamin D requirements becomes more important given that recent research has suggested that, in addition to the classical effects on calcium metabolism, vitamin D appears to have other functions in the body. One area that has received considerable attention in human medicine in recent years is the effect of vitamin D on the immune system (Cantorna et al., 2004; White, 2008). This is an area of great potential, but has received little attention in veterinary medicine, so the review on vitamin D and the immune system by Dr Maura O'Brien, of the University of Illinois-Urbana Champaign and Dr Mark Jackson, of the University of Glasgow, published in this issue of *The Veterinary Journal*, is timely (O'Brien and Jackson, 2012). The review summarises what is known about the actions of vitamin D on the innate and adaptive immune responses in humans and the little that is known about its non-classical effects in veterinary species.

There are substantial differences among veterinary species in their metabolism of vitamin D and susceptibility to rickets. Therefore, research will need to be carried out in the species of interest, rather than in mouse or rat models. Sheep and alpacas are relatively susceptible to vitamin D deficiency-induced rickets, whereas rickets is rare in cats and dogs (Dittmer and Thompson, 2011). Horses have very low serum 1,25-D and 25-hydroxy-vitamin D concentrations; levels are those that would be associated with rickets in other species (Harmeyer and Schlumbohm, 2004). When exposed to ultraviolet light, the skin of cats and dogs shows no significant increase in dermal vitamin D_3 concentrations, while the same treatment of rat skin results in a 40-fold increase in dermal vitamin D_3 concentrations (How et al., 1995). What effect do these species differences have on the interaction of vitamin D with the immune system?

A potential confounding factor in investigations on vitamin D and its actions is the effect of calcium on the immune system and the need to separate its effects from those of vitamin D (Cantorna et al., 2004). We have studied sheep with inherited rickets and a mutation in the dentin matrix protein 1 (*DMP1*) gene that have persistent hypocalcaemia, but normal to increased serum 1,25-D_3 concentrations (Zhao et al., 2011). In unpublished research on these sheep, immune system defects have been identified, including lymphopenia, decreased absolute $CD4^+$ and $CD8^+$ lymphocyte counts, an increased $CD4^+$:$CD8^+$ lymphocyte ratio, lower lymphocyte proliferation rate and lower interferon-γ concentration in stimulated lymphocytes compared to normal sheep; the sheep had normal serum cortisol concentrations.

Mice with calcium deficiency have decreased thymic weights and decreased $CD4^+$ and $CD8^+$ thymocytes, the concentrations of which were not altered by 1,25-D_3 treatment (Mohamed et al., 1996). However, in humans with 22q11.2 deletion syndrome, there is no significant association between T cell subset changes and hypocalcaemia (Kanaya et al., 2006). Furthermore, in propionic acidaemia of humans, patients are hypocalcaemic but have normal T lymphocyte numbers and reduced numbers of circulating B cells (Griffin et al., 1996). With normal vitamin D concentrations, could the immune system defects in sheep with inherited rickets be due to chronic hypocalcaemia or to some other but unknown cause?

Not only does vitamin D have an important role in immune system function but, as discussed by O'Brien and Jackson (2012), research has also shown possible roles for vitamin D in neoplasia, psychiatric disease, cardiovascular disease, hypertension and diabetes mellitus (Holick, 2005). The issue with many published epidemiological studies linking these conditions to vitamin D status is that, for many, they are only 'associated' with low vitamin D status and there are many confounding factors that may be involved.

Canine mast cell tumours express vitamin D receptors and 1,25-D has been shown to potentiate the anti-proliferative effects of chemotherapeutic drugs in the treatment of mast cell tumours (Malone et al., 2010). With neoplasia and diabetes mellitus increasing in incidence in the more obese and aged companion animal population, we need to ask what is the role of vitamin D in these conditions.

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Conversely, vitamin D may also be toxic. Cholecalciferol toxicity results in hypercalcaemia, hyperphosphataemia and widespread tissue calcification (Murphy, 2002). In the study by Malone et al. (2010) on the effects of calcitriol on canine mast cell tumours, most dogs exhibited the effects of toxicity and treatment was discontinued. Care and regular monitoring of serum calcium and phosphate concentrations will be required when designing studies looking at the effects of vitamin D treatment on medical conditions.

Vitamin D is an important hormone and there is still much to learn about its effects on different body systems, not just bone. It is a field that perhaps has been neglected in the past but, with the burgeoning interest in vitamin D in humans, it is likely that this interest will overflow into veterinary species and is a subject into which further research should be directed.

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