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Parathyroid Hormone-Related Peptide and Vitamin D in Phosphocalcic Metabolism for Dromedary Camel

Review Article

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ABSTRACT

In mammals, phosphocalcic and bone metabolisms are mainly regulated by parathyroïd hormone, parathyroïd hormone-related peptide (PTHrP) and 1α,25-dihydroxyvitamin D or calcitriol. In camels, circulating levels of calcitriol are 10 times higher than those determined in other ruminants and further increase during early lactation. Calcitriol and parathyroïd-related peptide stimulate intestinal absorption of calcium and phosphorus, and phosphocalcic excretion by the mammary glands to maintain breast milk production in the same species. These endocrinian features allow, on one hand to improve the uptake of calcium and phosphorus in the adult, and on the other, to meet the phosphocalcic needs during growth and development of the young calf, in a precarious medium. In camels, the status of vitamin D varies with the season and the postpartum stage. Hypocalcemia and hypophosphatemia due to a deficiency of vitamin D are responsible for many bone disorders which could be corrected by a diet rich in calcium, phosphorus and vitamin D.

KEY WORDS calcium, dromedary camel, PTHrP, vitamin D.

INTRODUCTION

The physiological peculiarities of the camel in relation to its particular mineral metabolism were largely reported by several authors (Faye and Bengoumi, 2000). These peculiarities show clearly the adaptation of the animal to a climatic and nutritional biotope which is marked by scarcity of water, and relatively low nutritional value of pasture resources. On major minerals, calcium (Ca) and phosphorus (P) are particularly essential for bone growth of young and milk production. In camel, milk is the only source of minerals for the calf until weaning which is still very late (up to 12 months) in this species and within the traditional farming. In camels, fundamental and applied investigations were performed on mineral metabolism endocrine regulation that involves among other factors, parathyroid hormone (PTH), PTH-related peptide (PTHrP or parathyroid hormone related peptide) and active vitamin D. The results of the work so far, seem to emphasize again the power of the camel to withstand arid and semi arid areas. This article proposes a synthesis of current knowledge about the camel and discusses them in light of those obtained in other domestic ruminants.

PTH and PTHrP

In mammals, PTH is the major regulator peptide of Ca homeostasis. Produced almost exclusively by the parathyroid cells, PTH stimulates the release of Ca, phosphate and collagen in bone. The kidney responds to PTH by Ca reabsorption, phosphate excretion and synthesis

of 1,25-dihydroxyvitamin D3 [1,25$(OH)_2$D3], the most active metabolite of vitamin D, which stimulates Ca intestinal absorption. PTH is also responsible for the growth and differentiation of cartilage, hypotensive effects and gastrointestinal vasodilatation, and may participate in the regulation of Ca metabolism in the central nervous system (Fitzpatrick *et al.* 1992). According to Kataria and Kataria (2006), the average normal values of serum PTH levels (ng/ml) in male camel, non pregnant female camel and pregnant female camel are 1.81 ± 0.03; 1.90 ± 0.05 and 2.10 ± 0.02, respectively.

A second factor, PTHrP regulates placental Ca transfer and fetal development of the skeleton, by modulating both cell proliferation and differentiation (Manen *et al.* 2000). In bone and kidney, endocrine effects related to PTH and those paracrine/autocrine of PTHrP are mediated by the receptor PTH/PTHrP type 1 (PTH/PTHrPR1) which is coupled to a G protein that recognizes the amino-terminal region of hormone. Activation of this protein leads to the synthesis of cyclic AMP and hydrolysis of phosphatidylinositol 4,5-bisphosphate (Zhang *et al.* 2006). However, expression of PTH/PTHrPR1 is much greater in the kidney, bone and growth plate (Mc Cuaig *et al.* 1994). Found both in man than in the animal in the syndrome humoral hypercalcemia malignancy (Broadus *et al.* 1988), PTHrP is also produced by human osteosarcoma cells "osteoblast-like" in culture (Rodan *et al.* 1989). This peptide is physiologically present in the fetal sheep parathyroid (Abbas *et al.* 1990), the matrix of long bones of fetal rats (Karmali *et al.* 1992), bovine ovarian cells (Watson *et al.* 2001) and milk of human (Budayr *et al.* 1989), cattle (Onda *et al.* 2006) and goat (Ratcliffe *et al.* 1992). In hypercalcemia of malignancy and in the fetus, PTHrP acts according to an endocrine pathway (Rosol and Capen, 1997). The presence of PTHrP in milk, raises the question of its possible role in the regulation of Ca homeostasis in the mammary gland and in the systemic circulation of lactating female, and in the regulation of osteogenesis in her newborn.

Action of PTHrP on mammary transfers of calcium

The PTHrP is present in milk at high concentrations (nanomolar) compared with those measured simultaneously in maternal plasma in the cow, goat, pig and woman (Budayr *et al.* 1989; Ratcliffe *et al.* 1992; Onda *et al.* 2006) (Table 1).

During early lactation, PTHrP could play an important physiological role by modulating the Ca transfer in milk. Indeed, in milk, a significant positive correlation between levels of this peptide and those of Ca has been demonstrated in sheep and cow (Thurston *et al.*, 1990, Law *et al.* 1991; Onda *et al.* 2006). In cow, PTHrP is synthesized and secreted by alveolar epithelial cells with a peak of mRNA expression of the peptide at stage 5 to 6 weeks of lactation, suggesting the physiological importance of PTHrP in the regulation of Ca homeostasis and transport in the mammary epithelial cells (Onda *et al.* 2006). However, Kocabagli *et al.* (1995) reported in sheep, that PTHrP didn't appear essential for maintaining Ca homeostasis during lactation.

Table 1 Circulating levels of parathyroid hormone-related peptide (PTHrP) in mammalian species

Species	PTHrP
Goat	Non pregnant, non lactating : 3.3 ± 1.5 pM (Rong *et al.*1997) Before parturition : 2.9 ± 1.7 pM (Rong *et al.* 1997) At parturition : 4.2 ± 2.4 pM (Rong *et al.*1997) Postparturient : 3.7 ± 2.2 pM (Rong *et al.*1997) Neonate (1st postnatal day) : 6.1 ± 1.7 pM (Rong *et al.*1997) Milk (at parturition) : 8.69 ± 2.95 nM (Ratcliffe *et al.*1992)
Cow	Non pregnant : 0.75 ± 0.33 ng/mL (Filipovic *et al.* 2008) 1st postpartum day : 1.47 ± 0.25 ng/mL (Onda *et al.* 2006) Periparturient : 0.57 pM (Onda *et al.*2006) Milk : 14.900 – 41.200 pM (Onda *et al.*2006)
Woman	1st trimester of pregnancy : 0.81 ± 0.12 pM (Ardawi *et al.*1997) At term : 2.01 ± 0.22 pM (Ardawi *et al.*1997) Postpartum : 2.63 ± 0.15 pM (Ardawi *et al.*1997)

During lactation, the increased needs for Ca can not be covered by the digestive tract of lactating females. In cattles, the Ca balance is negative during the first week of lactation, with a loss of skeletal Ca content by almost 13% (Horst *et al.* 2005). Some studies on mammals have reported that some of PTHrP secreted by the mammary glands may pass into the general circulation and modulate the resorption of the bone to ensure good maternal galactopoiesis and therefore maximize the phosphocalcic nutritional performance of the calf (Barlet *et al.* 1995). The transfer of PTHrP from mammary glands to systemic circulation was highlighted by an arteriovenous difference of PTHrP levels in the mammary glands of goat (Ratcliffe *et al.* 1992). In cattle, the 1st week of lactation are characterized by bone resorption of the maternal skeleton, which appears to be mediated by PTHrP to promote the mammary export of Ca (Filipovic *et al.* 2008). In fact, in the lactating camel (Riad *et al.* 1994) and goat (Barlet *et al.*

1992), intravenous infusion of PTHrP significantly increases the mammary secretion of Ca and P in milk. Moreover, Vanhouten *et al.* (2003) observed in mice, that specific alteration of mammary PTHrP significantly reduces the "bone turnover" and the leakage of bone Ca into milk.

The expression of PTHrP in the mammary glands appears to be regulated by prolactin secretion which is stimulated by milking or suckling (Thiede, 1989). Thus, in goat, the production and the rate of secretion of PTHrP were significantly reduced in the mammary gland treated once a day compared to contra lateral mammary gland treated 4 times per day (Thompson *et al.* 1994). This reduction alters mammary tight-junction (Stelwagen and Callaghan, 2003) which could affect the Ca transfer in milk.

Action of PTHrP on neonatal intestinal reabsorption of calcium

Very high concentrations of PTHrP in colostrum and milk of domestic ruminants such as cow (Onda *et al.* 2006), goat (Ratcliffe *et al.* 1992) and camel (El Khasmi *et al.* 2000a) have been identified, hence the physiological role that could play this peptide in neonatal bone growth are well known. So, in the camel which had been fed with a milk replacer (lacking PTHrP) since its birth, intravenous or oral administration of PTHrP, or ingestion of colostrum of camel (rich in PTHrP), induced a significant increase of intestinal absorption of xylose, compared with the control receiving milk replacer alone (El Khasmi *et al.* 2000a).

On the other hand, in the camel, a study of the kinetics of postprandial calcemia and phosphatemia after an oral administration of milk replacer, in the presence and absence of PTHrP infused intravenously, showed that this peptide induced a significant postprandial hypercalcemia and hyperphosphatemia (Figure 1) without influence of urine volume or renal excretion of Ca (El Khasmi *et al.* 2003b). The stimulatory effect of intestinal absorption by PTHrP might be mediated directly on the enterocyte, or indirectly by increasing the renal synthesis of calcitriol or the activity of calcitriol receptors.

In addition, PTHrP is known to be a potent vasodilatator of smooth muscle cell (SMC) (Philbrick *et al.* 1996) and then could promote an adequate gastrointestinal function (Mok *et al.*, 1989).

According to Gao and Raj (2005), vasodilatation of SMC due to PTHrP appears to be mediated by cyclic adenosine monophosphate (cAMP) which activates a voltage-operated or calcium-dependent potassium channels.

The use of strontium test as a reliable biomarker of intestinal absorption of Ca in camels (El Khasmi *et al.* 2003a), demonstrated in the same species, that PTHrP is able to modulate the intestinal absorption of Ca (El Khasmi *et al.* 2008). The PTHrP seems likely to contribute to accelerated processes of postpartum bone mineralization, first, by stimulating the intestinal absorption of minerals contained in milk (Barlet *et al.* 1995) and secondly, by regulation of division and differentiation of bone cells (Barling *et al.* 2004).

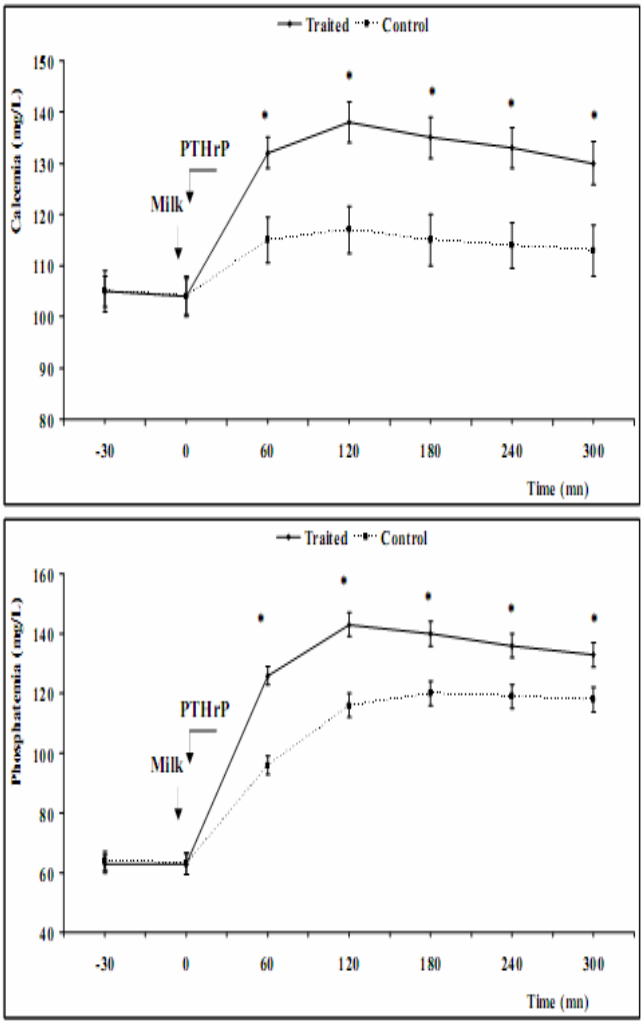

Figure 1 Postprandial calcemia and phosphatemia in two groups of three camel calves. One received an intravenous infusion of a solution of the related peptide parathyroid hormone (PTHrP) (0.175 nmoles) and the other received a saline solution. At the start of the infusion, all animals received an oral load of milk replacer (mean ± SEM, * $p<0.05$; simultaneous comparison between treated and control animals) (El Khasmi *et al.* 2003a)

Vitamin D

In mammals, the physiological control of Ca metabolism and skeletal remodelling is normally under regulation of systemic hormones, especially calcitonin, PTH), and $1,25(OH)_2D3$ (Holick, 2007).

Vitamin D has an exogenous origin (vitamin D2 or ergocalciferol in plant and Vitamin D3 or cholecalciferol in animal tissues and milk), and an endogenous origin (skin

conversion of 7-dehydrocholesterol to vitamin D3 in the presence of sunlight). Vitamin D - synthesized by the skin or obtained by food - is metabolized by the liver into 25-hydroxyvitamin D (25-OH-D), which enters the systemic circulation and then is hydroxylated in the kidney by the enzyme 25-OH-D-1αhydroxylase (encoded by the gene CYP27B1) to the active form $1,25(OH)_2D3$. The actions of $1,25(OH)_2D3$ in multiple target tissues are mediated by the nuclear vitamin D receptor (VDR), a phosphoprotein that binds the hormone with high affinity. Serum 25-OH-D level is the best marker of whole-body vitamin D status (Goff, 2000; Deluca, 2004; Holick 2007). Hypocalcemia induces the secretion of PTH by the parathyroid gland, which reduces the excretion of Ca, inhibits phosphate reabsorption and stimulates the production of $1,25(OH)_2D3$ in the kidneys. Calcitriol will then increase the active phosphate transport in the intestines and stimulate Ca reabsorption in the kidney. The entry of Ca through the luminal membrane and the action of calbindin D9k which facilitates the transfer of cytoplasmic Ca across the basolateral membrane, are the major mediators of intestinal Ca absorption induced by $1,25(OH)_2D3$ (Van Cromphaut *et al.* 2001). The $1,25(OH)_2D3$ also stimulates osteoblast differentiation and gene expression biomarkers of bone turnover such as osteocalcin and osteoponine. When $1,25(OH)_2D3$ is produced in large quantities, osteocytes secrete FGF23 as inhibitor of phosphate reabsorption and calcitriol production in the kidney (Verstuyf *et al.* 2010).

Importance of vitamin D

In camels, the circulating levels of vitamin D are 10 to 15 times higher than those measured in other domestic ruminants (Horst *et al.* 1983; Ross *et al.* 1989; Riad 1995), and further increase during early lactation (El Khasmi *et al.* 2000b) (Table 2). These higher plasma levels seem potentiate the phenomenon of intestinal absorption of camel, which appears higher than that of other ruminants (Riad *et al.* 1994) to meet the phosphocalcic demands of lactation. In domestic ruminants, treatment with vitamin D, 25-OH-D or 1,25 $(OH)_2D3$ at doses often pharmacological, by oral or parenteral way during few days before parturition, increases simultaneously the intestinal reabsorption of Ca and the circulating levels of calcitriol, which could prevent postpartum hypocalcemia secondary to milk production (Braithwaite, 1978; Okura *et al.* 2004; Taylor *et al.* 2008).

Physiological variations of circulating levels of vitamin D

Huge seasonal variations in vitamin D status were observed in all domestic species and humans (Mc Dowell, 1989).

Table 2 Circulating levels of 1,25-dihydroxyvitamin D $[1,25(OH)_2D3]$ in mammalian species

Species	$1,25(OH)_2D3$
Sheep	50 – 60 pg/mL (Ross *et al.* 1989)
Cow	Non pregnant : 10 – 100 pg/mL (Horst *et al.* 1983) Periparturient : 36.8 ± 9.8 pg/mL (Yamagishi *et al.* 2005) 1st postpartum day : 96.6 ± 25.9 pg/mL (Yamagishi *et al.* 2005)
Camel	Non pregnant : 835 ± 45 pg/mL (Riad, 1995) Calf : 1215 ± 248 pg/mL (El Khasmi *et al.* 2000b)
Woman	1st trimester of pregnancy : 69 ± 17 pM (Ardawi *et al.* 1997) At term : 333 ± 83 pM (Ardawi *et al.* 1997)

In llamas and alpacas (Smith and Van Saun, 2001), and camels (Mohamed, 2008), the circulating levels of vitamin D are not influenced by age, but vary depending on the season. In the dromedary, the highest levels were detected during the period from February to July, while lowest levels were observed during the period from August to January (Mohamed, 2008). In the camel, the serum 25-OH-D levels (ng/ml) in summer and winter are 443 ± 96 and 276 ± 13, respectively (Shany *et al.* 1978). The seasonal variations of vitamin D in the blood were also reported in sheep (Smith *et al.* 1987), horse (Maenpaa *et al.* 1988) and humans (Webb *et al.* 1988). These variations are much more pronounced in calves and young camels aged one year (Smith and Van Saun, 2001).

Variations in circulating concentrations of vitamin D in different species of camel, could be explained by the degree of coat color, as is the case of llamas and alpacas (Smith and Van Saun, 2001), and Arabi and Anafi camels (Mohamed, 2008). The month of birth and light intensity (Van Saun *et al.* 1996), physiological status (lactation, neonatal development) (Riad *et al.* 1994; El Khasmi *et al.* 2000b) and dietary supplementation may play a significant role in these variations.

According to Smith *et al.* (1987), the status of vitamin D in the newborn lamb is positively correlated with that of its mother. On the other hand, Kurmann and Indyke (1994) reported that the content of vitamin D in bovine milk, varies during the season, with lower values in winter and higher levels in summer. The status of vitamin D in the newborn sheep is also linked with the consumption of colostrum during the 1st days of lactation (Smith *et al.* 1987; Gay and Besser, 1991).

Action of vitamin D on mammary transfers of calcium

To maintain milk production, the daily requirement of Ca in early lactation is about 100 g in cow (Allen and Samson, 1985), 30 g in goat and 19 g in ewe (Eidgenössische, 1999). During this physiological stage, domestic ruminants respond to an exogenous supply of $1,25(OH)_2D3$ by hypercalcemia, hyperphosphatemia and increase of phosphocalcic excretion by the mammary glands (Naito *et al.* 1989; Okura *et al.* 2004; Yamagishi *et al.* 2005; Namioka *et al.* 2008). Indeed, camels in third lactation that received $1,25(OH)_2D3$ intravenously, showed a significant increase in the concentration and excretion of Ca and P in milk (El Khasmi *et al.* 2001a) (Figure 2).

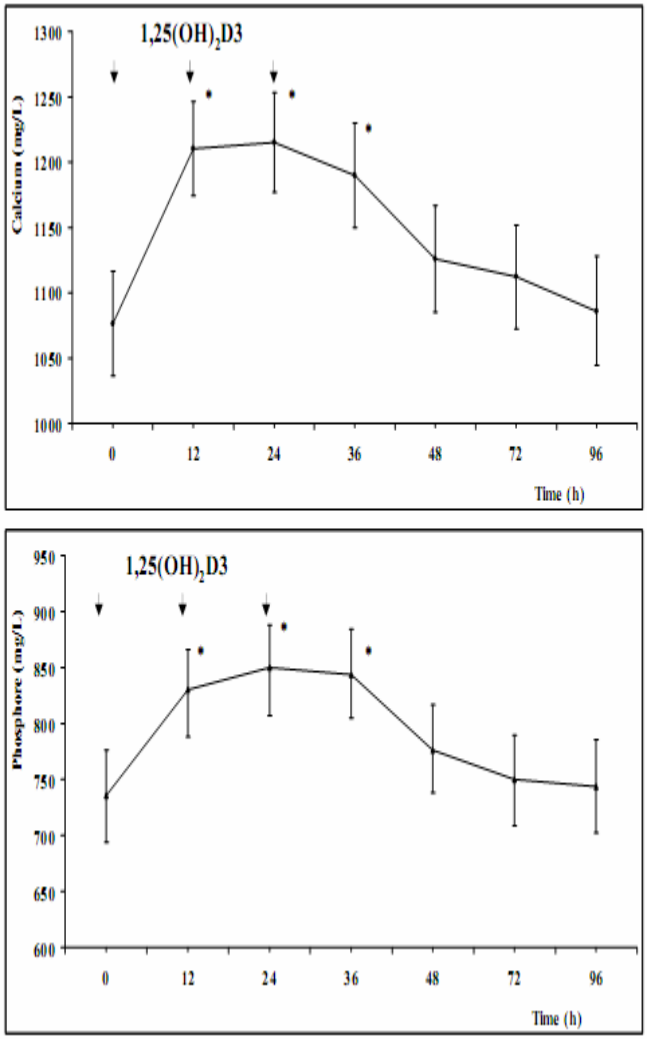

Figure 2 Effect of 1α,25-dihydroxyvitamin D3 (3x0.05µg/kg BW i.v.) on milk levels of calcium and phosphorus in six lactating camels. (mean ± TE ; * P<0.05 ; comparison with respect to stage 0 h) (El Khasmi *et al.* 2001a)

Similarly, according to Riad *et al.* (1994), in lactating camel the intramuscular injection of 1α-hydroxyvitamin D (1α-OH-D) stimulates the secretion of both Ca and Pi in milk. The effects of metabolites of vitamin D observed to maintain milk production in female, could be direct on the mammary gland, and not due to hypercalcemia and hyperphosphatemia consecutive to the treatment. Moreover, in the same species, it was demonstrated that intravenous infusion of Ca gluconate (7 mg Ca / kg BW) for 30 min, has no effect on mammary excretion of Ca and Pi (Riad *et al.*, 1994). On the other hand, in cattle, specific receptors to calcitriol were demonstrated in mammary glands and their number increases dramatically during lactation (Colston *et al.* 1988).

The stimulatory effects of mammary phosphocalcic secretion by active vitamin D in lactating camel are similar to those reported in cattle (Hidiroglou and Proulx, 1982) and goat (Bengoumi *et al.* 1996). Calcitriol could indirectly contribute to milk production by its action of regulating the Ca homeostasis. Indeed, Liesegang *et al.* (2006) reported in goat and sheep that circulating levels of 1,25 $(OH)_2D3$ and osteocalcin become very high in the first postpartum week, indicating an activation of bone remodeling which is able to compensate the Ca transfer from maternal skeleton to milk. This activation could be mediated by several hormones including PTH and calcitriol.

Action of vitamin D on neonatal intestinal reabsorption of calcium

Circulating levels of $1,25(OH)_2D3$ in cattle (Barlet *et al.* 1981; Naito *et al.* 1983; Rajaraman *et al.* 1997) and camel neonates (El Khasmi *et al.* 2000b) increased significantly during the 1st postpartum day, probably as a result of increased biosynthesis of this metabolite in response to active intestinal phosphate absorption in newborn (Steichen *et al.* 1980). Moreover, in newborn calves that received vitamin D (54.00 IU at a rate of 13.500 IU/week), Nonnecke *et al.* (2009) observed a positive correlation between plasma levels of Ca and those of $1,25(OH)_2D3$. On the other hand, the milk of the camel rich in 25-OH-D especially during the colostral phase (El Khasmi *et al.* 2001b), could be a significant source of vitamin D, for the young camel whose long bone growth is important. Increased plasma levels of 1,25 $(OH)_2D3$ on the 1st postpartum days may reflect a degree of early maturation of renal function in the biosynthesis of this active metabolite which appears as a potent stimulator of phosphocalcic assimilation and bone mineralization in newborn camel.

In camel calves aged 4 to 6 months, the use of stable strontuim test for functional exploration of intestinal Ca absorption (El Khasmi *et al.* 2003a) demonstrated that intravenous injection of $1,25(OH)_2D3$, stimulates Ca absorption (Figure 3) and induces a significant postprandial hypercalcemia and hyperphosphatemia (Figure 4) (El Khasmi *et al.* 2003b).

This supports the association of Ca homeostasis in lactating camel, and hypercalcemia in her newborn calf,

with their high levels of 25-OH-D and 1,25(OH)$_2$D3 (El Khasmi *et al.* 2000b).

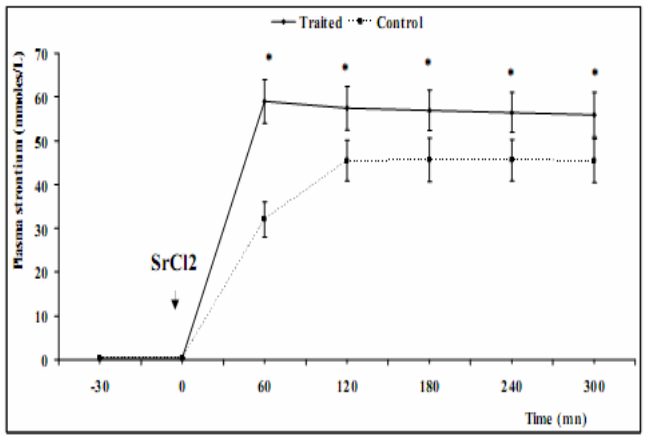

Figure 3 Effect of 1α,25-dihydroxyvitamin D3 (3 x 6.65 µg i.v.) on plasma levels of strontium after oral load of 4,1 nmoles $SrCl_2$ in camel (moyenne ± SEM ; * p<0.05 ; simultaneously comparison between treated and control animals) (El Khasmi *et al.* 2003b)

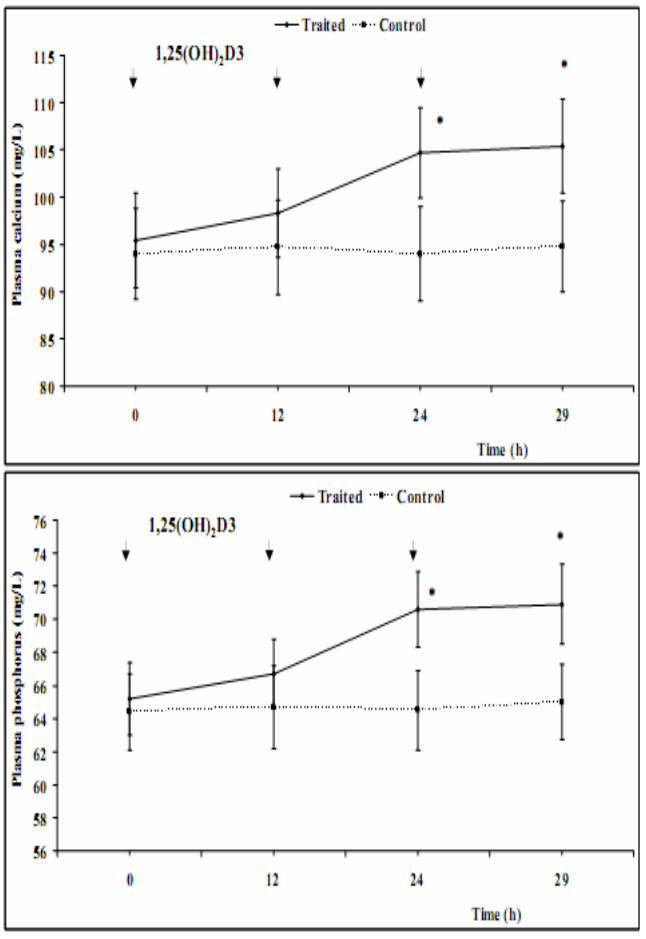

Figure 4 Effect of 1α,25-dihydroxyvitamin D3 (3 x 6.65 µg i.v.) on plasma levels of calcium and phosphorus in camel, after oral loading of 4,1 nmoles $SrCl_2$ (moyenne ± SEM ; * p<0.05 ; simultaneously comparison between traited and control animals) (El Khasmi *et al.* 2003b)

On the other hand, hypercalcemiant and hyperphosphatemiant effects were observed after an intramuscular injection of 1α-OH-D in sheep (Barlet, 1975), cattle (Riad *et al.* 1987) and camel (Riad *et al.* 1994), or following an intravenous injection of 1,25(OH)$_2$D3 in the latter species (El Khasmi *et al.* 2001a, 2003a).

Historically, vitamin D deficiency has been associated with osteomalacia, osteopenia, osteoporosis and muscle weakness, illustrating the crucial role of vitamin D in bone mineralization and Ca absorption. In ovine species and their newborns, the minimum daily intake of vitamin D required to prevent rickets are respectively 5.6 and 6.7 IU/kg birth weight (National Research Council, 1985). However, the dietary vitamin D in camels, had received very little attention compared to other domestic ruminants.

Cases of rickets related to vitamin D deficiency have been reported in the newborn lamb (Van Saun, 2004), sheep (Bonniwell *et al.* 1988) and llamas (Van Saun *et al.* 1996). In the young camel, this vitamin deficiency is the primary cause of rickets consecutive to hypophosphatemia (Kistral-Boneh *et al.* 1999).

In addition, in North Africa, the phosphorus deficiency observed in camel species is responsible for Krafft disease, long described (Kchouk and Durand, 1958) and leading to arthritis and periarticular exostoses, then to musculoskeletal disorders, followed by paralysis (Faye and Bengoumi, 2000).

In addition, decreased bone mineral density is largely associated with a decrease in serum vitamin D and may predispose some alpacas to post traumatic fractures (Parker *et al.* 2002). According to Van Saun *et al.* (1996), the hypophosphatemia and vitamin D deficiency observed in camelids could be corrected by treatment with a supplement of vitamin D.

On the other hand, in cattle, treatment with 1,25(OH)$_2$D3 induced hypercalcemia and hyperphosphatemia, and reduces leakage of inorganic phosphorus in the salivary glands (Riad *et al.* 1987).

The measurement of circulating levels of 25-OH-D is a more reliable biomarker of vitamin D status, so, according to Horst *et al.* (1994), a vitamin D deficiency in bovine species is allowed to circulating rates below 5 ng/mL.

CONCLUSION

The regulation of phosphocalcic and bone metabolisms in mammals, is maintained primarily by PTH, PTHrP and 1,25(OH)$_2$D3. In camels, circulating levels of 1,25(OH)$_2$D3 are 10 to 15 times higher than those determined in other domestic ruminants and further increase in early lactation. Moreover, in camel,

$1,25(OH)_2D3$ and PTHrP stimulate the intestinal absorption of Ca and Pi, and the mammary excretion of these two minerals in milk. This endocrine characteristic improves not only the uptake of Ca and P in the adult camel, but also promotes the growth and development of the young calf. Like most mammals, the vitamin D status of camel, varies with the season and the postpartum stage.

Hypocalcemia and hypophosphatemia due to a deficiency of vitamin D is responsible for many bone disorders observed in this species, which could be corrected by an exogenous supply of Ca, Pi and vitamin D.

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