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

M. El Khasmi and B. Faye

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)2D3], 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/PTHrP1) 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/PTHrP1 is much greater in the kidney, bone and growth plate (Mc Cuig 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), cow (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.

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<th>Species</th>
<th>PTHrP</th>
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<tr>
<td>Goat</td>
<td>Non pregnant, non lactating : 3.3 ± 1.5 pM (Rong et al. 1997)</td>
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<td></td>
<td>Before parturition : 2.9 ± 1.7 pM (Rong et al. 1997)</td>
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<td>At parturition : 4.2 ± 2.4 pM (Rong et al. 1997)</td>
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<td>Postparturient : 3.7 ± 2.2 pM (Rong et al. 1997)</td>
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<td>Neonate (1st postnatal day) : 6.1 ± 1.7 pM (Rong et al. 1997)</td>
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<td></td>
<td>Milk (at parturition) : 8.69 ± 2.95 nM (Ratliffe et al. 1992)</td>
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<td>Cow</td>
<td>Non pregnant : 0.75 ± 0.33 ng/mL (Filipovic et al. 2008)</td>
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<td>1st postpartum day : 1.47 ± 0.25 ng/mL (Onda et al. 2006)</td>
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<td></td>
<td>Periparturient : 0.57 pM (Onda et al. 2006)</td>
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<tr>
<td></td>
<td>Milk : 14.900 – 41.200 pM (Onda et al. 2006)</td>
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<tr>
<td>Woman</td>
<td>1st trimester of pregnancy : 0.81 ± 0.12 pM (Ardawi et al. 1997)</td>
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<td>At term : 2.01 ± 0.22 pM (Ardawi et al. 1997)</td>
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<td>Postpartum : 2.63 ± 0.15 pM (Ardawi et al. 1997)</td>
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During lactation, the increased needs for Ca can not be covered by the digestive tract of lactating females. In cattle, 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. 2005). 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 (Ratliffe 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 (Ri et al. 1994) and goat (Barlet et al. 1995).
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 vasodilator 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).

### 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-1α-hydroxylase (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).

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<tr>
<th>Species</th>
<th>1,25(OH)2D3</th>
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<tr>
<td>Sheep</td>
<td>50 – 60 pg/mL (Ross et al. 1989)</td>
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<tr>
<td>Cow</td>
<td>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)</td>
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<tr>
<td>Camel</td>
<td>Non pregnant : 835 ± 45 pg/mL (Riad, 1995) Calf : 1215 ± 248 pg/mL (El Khasmi et al. 2000b)</td>
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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 ofcolostrum 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](image-url)

**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 consequent 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 strontium 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).

On the other hand, hypercalcemic and hyperphosphatemian 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 Krafitt 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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