Calcium and Vitamin D Status During Pregnancy

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Calcium represents the major building block of the mineralized phase of bone. It follows that an adequate calcium availability is as critical for allowing proper skeletal growth in utero as it is important postnataally for obtaining an optimal increase in bone mass and its maintenance later in life.

Of major consideration is the skeleton's dual role as a mechanical support and as a mineral reservoir for homeostasis. Indeed, it is of utmost importance for several major physiologic functions, such as blood coagulation, cell membrane permeability, nerve conduction, and hormonal action (1), that the extracellular concentration of calcium remain stable within narrow limits (2.4–2.6 mmol/liter). This homeostatic role has prevalence on the mechanical function of the skeleton. Thus in all circumstances in which calcium availability is inadequate (insufficient intake postnataally, inadequate transfer from the mother prenataally), reduced bone growth or bone loss will result. Although calcium homeostasis may be maintained without deleterious effect on the skeleton in the short term, it will be sustained at the cost of a decrease in bone mass in the long term.

CALCIUM HOMEOSTASIS

As illustrated in Fig. 1, the organism relies on three organs (bone, kidney, and intestine) and two hormones (vitamin D and parathyroid hormone) to maintain, at all times, a stable extracellular calcium concentration (2). One other peptide, calcitonin (CT), has also been proposed as part of this regulatory system. Although it is likely the case in fish and lower mammals (3), at the present time, a definite physiological role for CT in the control of calcium homeostasis in humans is doubtful. For that reason, its interaction
FIG. 1. Schematic representation of the calcium homeostatic pathway. The broken lines represent contributions that are either marginal or are still subjects of controversy.

has been indicated by the dotted line in Fig. 1 and is not discussed further in this chapter.

As depicted in Fig. 1, the sensors for extracellular calcium concentration are the parathyroid glands. They react rapidly to a decrease in extracellular calcium concentration by secreting parathyroid hormone (PTH) (2). This 34-amino acid peptide acts at the kidney level, where it stimulates the synthesis of 1α,25-dihydroxyvitamin D [1,25-(OH)₂D] (4). This metabolite can be considered a true hormone because its synthesis is tightly regulated and its action is at a site distal from its site of synthesis. The main target organs for 1,25-(OH)₂D are the intestine (5) and bone (6). In the intestinal mucosa cell, the metabolite combines with a cytosol receptor. This complex then interacts with the cell nucleus, where it induces protein synthesis (7). The current concept is that these newly synthesized proteins stimulate calcium transport at the luminal pole of the cell. The intracellular calcium translocation is then regulated by a cascade of events, of which the calcium messenger system is an integral part (8,9). Reaching the basolateral membrane, the calcium is pumped out of the cell by a sodium-dependent process and released into the extracellular space. This overall process depends heavily on the presence of calcium in the intestinal lumen, which itself depends on the feeding cycle. Thus a more stable source of calcium is necessary to allow for the minute-to-minute adjustment of extracellular calcium. This source is the skeleton, where more than 99% of body calcium is stored. To promote calcium release at that level, both PTH and 1,25-(OH)₂D are re-
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quired (10). The exact cellular mechanisms are, however, not yet fully understood. They involve both calcium extrusion from the bone fluid compartment (a rapid response) and the breakdown of the mineralized matrix whereby calcium already incorporated into bone will be returned to the circulation (a slower response). The ensuing increase in extracellular calcium will turn off PTH secretion and thus return the homeostatic mechanism to equilibrium.

The control of calcium flux from the extracellular compartment toward the bone is still a matter of controversy. Indirect evidence seems to favor the hypothesis of a positive effect of 1,25-(OH)₂D on osteoid mineralization (11). A similar role was proposed for another dihydroxylated metabolite of vitamin D, 24r,25-dihydroxyvitamin D [24,25-(OH)₂D] (indicated by dotted lines in Fig. 1), but the hypothesis has now completely lost momentum.

VITAMIN D METABOLISM

Two major forms of vitamin D exist in nature: vitamin D₂ (ergocalciferol), produced by irradiation of the plant sterol, ergosterol, and vitamin D₃ (cholecalciferol), synthesized in animal skin by irradiation of 7-dehydrocholesterol. Since the two compounds have a similar biologic activity in humans, both are used therapeutically and are not further differentiated. The antirachitic factor, vitamin D, can be considered as a vitamin only because in many parts of the world, characteristics of human life style and environment have made skin ultraviolet (UV) irradiation from sunlight insufficient.

The biosynthetic pathway of vitamin D is depicted in Fig. 2. When present

![Diagram showing the main metabolic pathway of vitamin D. Vitamin D₂ (ergocalciferol) is produced by UV irradiation of the plant sterol, ergosterol. Vitamin D₃ (cholecalciferol) is produced in the skin by irradiation of 7-dehydrocholesterol; (IC flux) intracellular flux; (EC) extracellular fluid.](image-url)
in the diet, the fat-soluble vitamin D is efficiently absorbed with the neutral lipids in the small intestine, transferred in the lymphatic system as chylomicrons. When formed in the skin, by UV irradiation of 7-dehydrocholesterol, vitamin D is transported in the blood, bound to an α-globulin. The compound is rapidly cleared from the blood by the liver, where it undergoes a first hydroxylation at the carbon in position 25 to yield 25-hydroxyvitamin D \([25-(OH)D]\), the major circulating form of the vitamin. As in humans, this step is not tightly regulated, the circulating levels of 25-(OH)D can be assumed to be a good reflection of the vitamin D pool size (12). Thus its measurement has become a standard part of any patient’s evaluation in the field.

In the mitochondria of renal proximal tubular cells, further hydroxylation of 25-(OH)D at either carbon C1 or C24 will yield the dihydroxylated metabolites 1,25-(OH)\(_2\)D and 24,25-(OH)\(_2\)D. The former is considered the form of vitamin D directly active on its target organs (13). Its synthesis is tightly regulated by extracellular calcium, PTH, and the intracellular phosphate concentration. Indeed, phosphate deprivation of healthy human subjects is a potent stimulator of 1,25-(OH)\(_2\)D synthesis (14). Although a significant decrease in body phosphate pool is not common in normal individuals because of the ample dietary supply, such a situation is frequent in preterm babies fed human milk, since the latter is noticeably inadequate to supply the required phosphate for a rapidly expanding pool (15).

The observation that nephrectomy resulted in the disappearance of 1,25-(OH)\(_2\)D from plasma led investigators to propose the kidney as the unique site of its synthesis. A recent report has challenged that view by demonstrating the synthesis of this metabolite by calvarial cells in culture (16). Furthermore, during pregnancy, cells from human decidua are also able to hydroxylate 25-(OH)D in the 1α position (17). The physiologic importance of such extrarenal 1,25-(OH)\(_2\)D synthesis will require further investigation.

**FETOMATERNAL RELATIONSHIP**

Fetal skeletal growth depends totally on the net transfer of mineral, mainly calcium, from the mother to the fetus. This function is regulated by active transport systems that will efficiently drain the maternal pool in order to meet fetal needs. The placenta is the site of these critical exchanges (Fig. 3). The fact that extracellular concentrations of both calcium and phosphate are higher in fetal than in maternal circulation (18) gives evidence that mineral exchange depends on active, energy-dependent mechanisms. With regard to vitamin D metabolites, 25-(OH)D appears to cross the placenta easily. A direct close relationship between plasma concentrations of 25-(OH)D in the two pools has been reported (19). Because levels are lower in venous cord blood than in maternal serum, it is believed that the transfer occurs by
passive diffusion (20). Because the fetal pool depends on the maternal supply, it ensues that hypovitaminosis D of the mother will provoke a deficiency in the fetus with likely adverse consequences on the adaptation of the newborn to extrauterine life and early buildup of bone mass. Conversely, the fetus will not be well protected against excessive levels of maternal 25-(OH)D in subjects treated with pharmacologic doses of vitamin D for conditions such as hypoparathyroidism and vitamin D-resistant osteomalacia.

By contrast, there is no direct relationship between maternal and fetal levels of 1,25-(OH)$_2$D (20). Each compartment appears to be autonomous. Concentration of 1,25-(OH)$_2$D in the fetal circulation is usually lower than that of the mother's and seems to depend mostly on endogenous renal synthesis. Indeed, it has been observed that in infants affected by the Potter syndrome and born with renal agenesis, cord levels of 1,25-(OH)$_2$D were only 30% of the normal values (21). Thus, the residual circulating 1,25-(OH)$_2$D probably derives from extrarenal sites, including placental cells (17). The exact role of 1,25-(OH)$_2$D in fetal mineral economy still awaits clarification. Current hypotheses focus on control of the calcium transfer through the placenta and, at least in part, regulation of skeletal mineralization.

PREGNANCY

Maternal total serum calcium decreases throughout the pregnancy, particularly during the last trimester; however, this change parallels that of serum albumin levels so that, in effect, ionized calcium remains constant (22). As mentioned earlier, vitamin D status and hence serum levels of 25-(OH)D will vary in function of the dietary supply and exposure to sunlight. Thus, seasonal effects are evident, especially in European and North American countries, where exposure to sunlight is usually insufficient to allow adequate endogenous synthesis of vitamin D. In such circumstances, pregnant women are dependent on dietary supplies. These are low in European
countries, because milk and dairy products are not fortified with vitamin D, as they are in North America. As a consequence, circulating levels of 25-(OH)D in numerous European women are between one-third to one-half of what they are in American mothers (20). The strong positive correlation between serum 25-(OH)D and 1,25-(OH)₂D levels in unsupplemented mothers, at time of delivery, supports the hypothesis that they are relatively vitamin D deficient (23). This correlation is common in vitamin D-deficient osteomalacia but not in vitamin D-replete subjects (24). It thus appears that in those conditions, synthesis of 1,25(OH)₂D is to some extent substrate dependent. This will affect the efficiency of intestinal calcium absorption in mothers with possible deleterious consequences for the fetus.

Serum 1,25(OH)₂D levels increase during pregnancy (23). This could be due to a moderate degree of hyperparathyroidism, as suggested by higher PTH bioactivity observed during late gestation (25). These higher levels of 1,25-(OH)₂D are critical for optimizing intestinal calcium absorption, particularly during the last trimester of pregnancy when most fetal skeleton mineralization takes place.

Thus, vitamin D supplementation during pregnancy is essential to allow maximal transfer of calcium from the mother to the fetus. It has also been shown to be important for facilitating early adaptation to extrauterine life. Indeed, newborns from supplemented mothers sustain a less frequent and less severe episode of hypocalcemia during the first week of life (23). It is also likely, but not established, that systematic supplementation during pregnancy will prevent the possible occurrence of rickets in newborns.

SPECIFIC CONSIDERATIONS

Diabetes

Frazer et al. (26) have reported on the decrease in cortical bone mass in young insulin-dependent diabetic patients. They have also observed a significant decrease in the circulating levels of 1,25-(OH)₂D. These observations suggest that insulin deficiency may interfere with the metabolism and action of vitamin D. It follows that infants born from diabetic mothers may be in a precarious situation in the neonatal period. This risk could be enhanced in unsupplemented women. Indeed, the incidence and severity of early neonatal hypocalcemia is as high in those infants at term as it is in premature infants (27).

Anticonvulsant Drug Therapy

Biochemical, radiologic, and clinical evidence of rickets and osteomalacia have been described in patients under chronic anticonvulsant drug therapy
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(28,29). This has been attributed to the fact that diphenylhydantoin and, particularly, phenobarbital cause excessive activation of the liver oxidative mechanisms, thereby increasing the rate of degradation of vitamin D and its metabolites (30). This increased turnover may therefore create a state of vitamin D deficiency that will probably be more pronounced in unsupplemented women. It follows that such subjects should be closely monitored during pregnancy and systematically receive supplements of vitamin D or 25-(OH)D.

Pharmacologic Administration of Vitamin D

Subjects affected with severe tubulopathies, pseudohypoparathyroidism, or idiopathic hypoparathyroidism receive high doses of vitamin D on a chronic basis. They present with extremely high circulating levels of 25-(OH)D. Because this metabolite readily crosses the placenta, there is the potential risk of intoxication of the fetus. The recent availability of 1,25-(OH)_{2}D has made it the therapeutic agent of choice in such conditions, since it does not cross the placental barrier easily and therefore represents a lesser risk for the fetus. Furthermore, it has been shown in hypoparathyroidism that even if 1,25-(OH)_{2}D requirements progressively increase during pregnancy, newborns are not affected, even though in some cases there might have been a transient postnatal suppression of renal 1α-hydroxylase activity (31).

CONCLUSION

The substantial strain imposed on maternal mineral stores during pregnancy has to be carefully monitored with regard to adequate vitamin D and calcium supply. In areas where relative vitamin D deficiency is endemic, systematic supplementation bringing daily availability of vitamin D to approximately 1,000 IU is to be encouraged. At the same time, evaluation of calcium intake should be made and supplementation initiated to allow intake of at least 1,500 g/day throughout pregnancy and lactation. Pregnant women who present with specific disturbances of calcium metabolism should receive additional attention in order to maintain adequate homeostasis equilibrium throughout pregnancy.

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