

Sports Medicine

 (Review article)

**PHYSICAL ACTIVITY AND EXERCISE AFFECT INTESTINAL CALCIUM
ABSORPTION: A PERSPECTIVE REVIEW**

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ABSTRACT

Moderate endurance exercise and physical activity have a positive effect on calcium metabolism and bone by increasing bone mineral density and reducing urinary calcium loss, whereas immobilization has the opposite effects. However, little is known regarding effects of exercise on the intestinal calcium absorption, which is the sole source of calcium for bone formation. Intestinal calcium absorption affects bone mass and bone strength both of which directly contribute to exercise performance. Previous investigations in humans and rats suggested that endurance exercise stimulated intestinal calcium absorption *in vivo*; however, the underlying mechanisms remain controversial. On the other hand, immobilization decreased the intestinal calcium absorption partly by reducing the serum level of 1,25-dihydroxyvitamin D₃, one of the major calcium-regulating hormones, and the expression of several calcium transporter genes. Further studies deserve to demonstrate in depth the molecular mechanisms of enhanced calcium absorption following different modes of exercise training, such as swimming and running, in different sex and/or age groups. The obtained knowledge would help sport scientists and physicians to design appropriate calcium supplementation and exercise training regime for athletes.

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Key words: calcium; duodenum; endurance exercise; paracellular transport;
strenuous exercise; transcellular transport

Introduction

In human, the net intestinal uptake of calcium is approximately 175 mg/day. Ninety-nine percent of calcium is stored in bone as hydroxyapatite crystal, while 1% is present as an ionized calcium in the intracellular (ICF) and extracellular fluid (ECF). Total plasma calcium concentration is normally maintained within a narrow range of 2.4-2.5 mM, whereas free-ionized calcium concentration ranges between 1.25-1.3 mM. Effective calcium homeostasis is essential for most of the biological processes, including bone metabolism, cell proliferation, blood coagulation, hormonal signaling transduction, and neuromuscular functions.

Calcium balance is maintained by concerted functions of three major organs, i.e., the gastrointestinal tract, bone, and kidneys. Adult humans daily ingest about 500-1200 mg calcium, ~30% of which is absorbed in the small intestine by a mechanism that is controlled primarily by the calcitropic hormones, i.e., 1,25-dihydroxyvitamin D₃ (1,25-(OH)₂D₃) and parathyroid hormone (PTH). To maintain the calcium balance, the kidney must excrete the same amount of calcium that the small intestine absorbs. Bone not only serves a structural function but also provides the calcium exchange system for minute-to-minute adjustment of calcium level in plasma and ECF (1, 2).

Effects of exercise on calcium metabolism

Changes in calcium metabolism during exercise are dependent on the exercise intensity. Moderate endurance exercise increases serum 1,25(OH)₂D₃ level (3, 4), but decreases serum PTH (4). Despite decreased level of PTH, urinary calcium excretion is decreased (4). Plasma ionized calcium may be normal or slightly increased (4, 5). In bone, endurance exercise increases bone mineral density (BMD), bone strength (6) and bone formation rate (7). Thus, moderate endurance exercise seems to induce positive calcium balance, and has a beneficial effect on bone metabolism. In addition, a combination of moderate-impact exercise and adequate calcium intake can increase bone strength during childhood (8). Interestingly, modes of exercise, such as running (weight-bearing exercise) and swimming (non-weight-bearing exercise) can affect bone calcium metabolism in a different way. Huang and co-workers (6) reported that the tibial BMD of running male rats was higher than that of the swimming rats. However, tibiae of the swimming rats exhibited a significantly higher water content ratio, which was linked to mechanical properties of bone

(6). Under certain pathological condition, e.g., osteoporosis, endurance swimming may have a greater benefit than running as it increases femoral BMD with minimal injury from physical impact (7).

On the other hand, strenuous exercise leads to detrimental effects on calcium metabolism. It increases serum PTH concentration, thereby resulting in decreased BMD and low bone mass (9, 10). Urinary calcium excretion is increased, and serum ionized calcium concentration is also slightly decreased (10). However, serum 1,25-(OH)₂D₃ concentration is not affected (10).

Immobilization, in contrast to endurance exercise, leads to increased urinary calcium excretion in humans (11, 12). Bone resorption and progressive bone loss are also accelerated (11–13), while serum PTH and 1,25-(OH)₂D₃ are suppressed (14). Therefore, immobilization, either by paraplegia or weightlessness, induces severe negative calcium balance in both human and animal models.

Although changes in bone calcium metabolism are currently under active investigations, little has been known regarding the effects of exercise on intestinal calcium absorption, perhaps due to an incomplete and/or controversial model of calcium absorption. However, intestinal calcium absorption is the sole mechanism to supply calcium to the body, therefore, beneficial effects of exercise cannot occur without enhanced calcium absorption.

Novel concept of intestinal calcium absorption

In general, calcium transport in the intestine is mediated by a complex array of transporting processes that are regulated by a number of hormones. Among various calcitropic hormones, 1,25-(OH)₂D₃ and PTH are important in controlling calcium absorption (15). Other hormones, such as glucocorticoids, prolactin, and estrogen, may be regulators of calcium absorption in the small intestine (16–19). Intestinal calcium absorption takes place largely along the entire length of the small intestine by both active and passive mechanisms. Active calcium transport is mainly confined to the duodenum and proximal jejunum, whereas passive calcium transport occurs in all segments. The large intestine also has a capability to absorb calcium, but its physiological significance is still controversial (20). Duodenum is the most efficient site of calcium absorption, since it can extract calcium from a very low-calcium diet by an active mechanism (21). This segment also has all components of calcium transport through both transcellular and paracellular pathways, therefore, several

investigators have studied calcium absorption in the duodenum. The duodenal calcium transport includes the following components (Figure 1):

A. Transcellular calcium transport

Transcellular transport a metabolically energized calcium movement consisting of 3 steps, i.e., (i) apical calcium entry, (ii) cytoplasmic calcium translocation in calbindin- D_{9k} -bound form, and (iii) basolateral calcium extrusion. Luminal calcium traverses the brush-border membrane via the transient receptor potential vanilloid family calcium channel (TRPV) 5 and 6 (15, 22). The plasma membrane Ca^{2+} -ATPase (PMCA_{1b}) located at the basolateral membrane finally extrudes cytoplasmic calcium to plasma (15). In addition, cytoplasmic calcium can also be extruded by another transporter, named Na^+/Ca^{2+} exchanger 1 (NCX1). However, the transport capacity of the NCX1 is only 20% compared to 80% of the PMCA_{1b} (15, 21). Under physiological condition, ~20% of the total active intestinal calcium is transported via the transcellular pathway. It becomes more important when calcium demand is increased, e.g., during pregnancy and lactation. Transcellular active transport is directly under $1,25-(OH)_2D_3$ stimulation (15, 23).

B. Paracellular calcium transport

Paracellular transport results from both active (cellular energy dependent) and passive (calcium gradient dependent) mechanisms. There are three components of the paracellular calcium transport, namely passive paracellular, solvent-drag induced, and voltage-dependent transport. The passive paracellular transport is energized by a free energy generated by the transepithelial calcium gradient, i.e., ~5 mM on the luminal side and 1.25 mM on the plasma side. Thus, it is predominant in the presence of high luminal calcium concentration, such as during high-calcium intake or calcium supplementation (24, 25).

In contrast, the solvent drag-induced and voltage-dependent transport are active processes. They depend on the activity of Na^+/K^+ -ATPase which generates the paracellular hyperosmotic environment for solvent drag and transepithelial potential difference (voltage). The paracellular hyperosmotic environment induces osmotic water flow (solvent drag) which drags dissolved ionized calcium through the paracellular space. Under physiological condition, the solvent drag-induced paracellular calcium transport is the most significant component accounting for approximately 80% of the total active calcium transport (26).

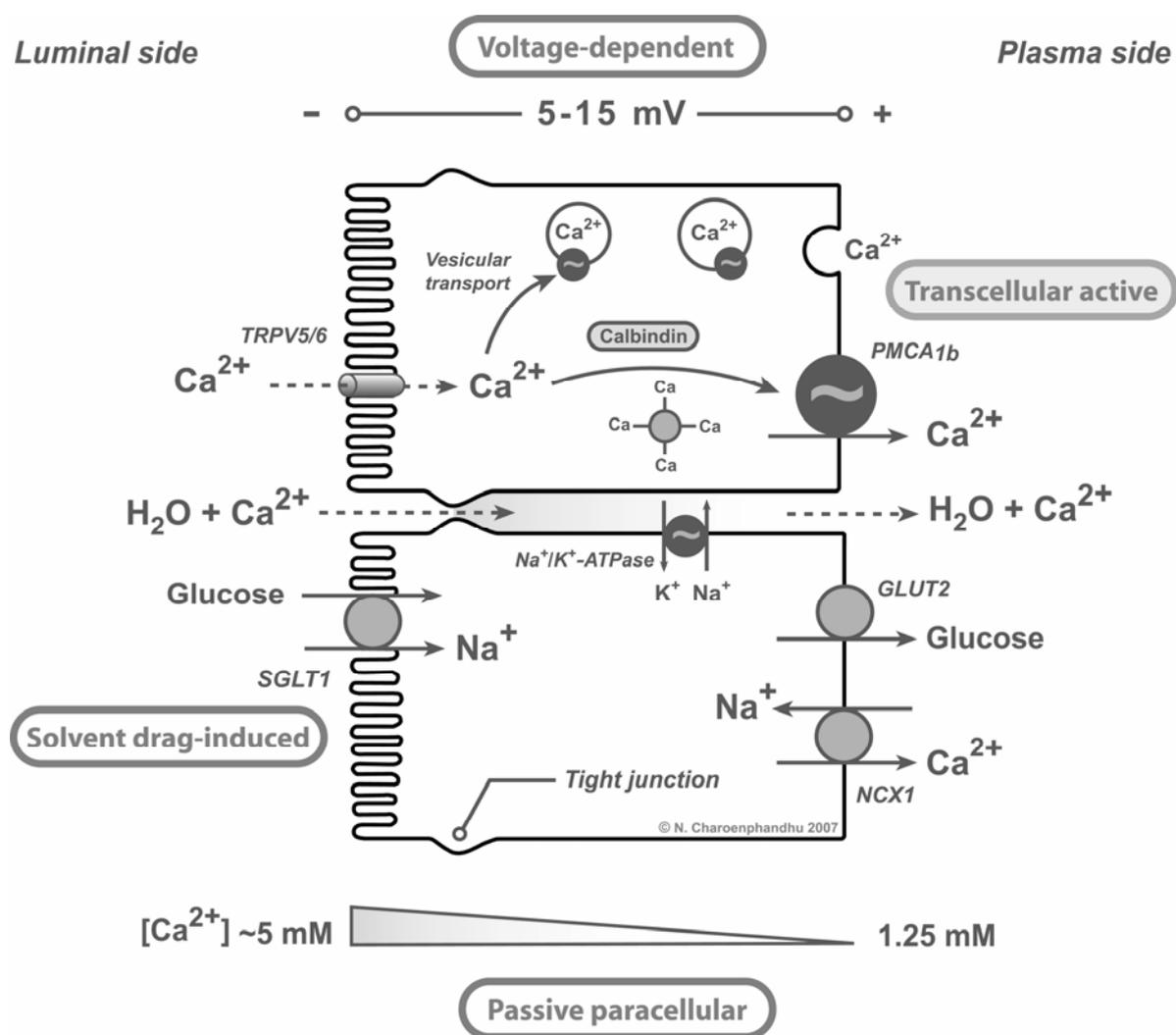


Figure 1: Schematic diagram of the duodenal calcium transport in rats. Calcium moves across the epithelium by either transcellular or paracellular mechanism. Paracellular transport is dependent on the active sodium transport which creates the osmotic gradient within the paracellular space (shown as graded black areas) and transepithelial potential difference (PD) across the epithelial sheet. Sodium mainly enters the absorptive cells with glucose via the sodium-dependent glucose transporter 1 (SGLT1). The PD is approximately 5 mV with the mucosal side being negative with respect to the serosal side. Transcellular active calcium transport, on the other hand, commences with the apical passive calcium entry through the transient receptor potential vanilloid family calcium channel (TRPV). Calcium is then translocated across the cytoplasm, mostly in calbindin- $\text{D}_{9\text{K}}$ -bound form, to the basolateral membrane where it is finally extruded from the cells by Na^+/K^+ -ATPase and $\text{Na}^+/\text{Ca}^{2+}$ exchanger (NCX1).

Recently, several investigators have shown that paracellular transport of ions was somewhat regulated by tight junction proteins of the claudin family (27). Until now, 24 members of claudin family have been identified (27, 28). Claudins possess charged amino acids on their extracellular loops which control the paracellular ion movement in a channel-like manner (27). In the thick ascending limb of the loop of Henle, claudin-16 (also known as paracellin-1) regulates tubular calcium and magnesium reabsorption (29). Although calcium-specific claudins have never been identified in the small intestine, some intestinal claudins, such as claudin-3, have been shown to be $1,25\text{-(OH)}_2\text{D}_3$ -dependent, and some claudin expressions are associated with enhanced intestinal calcium absorption (30).

Effects of exercise on intestinal calcium absorption

As previously mentioned, effects of exercise on intestinal calcium absorption have received scant attention, although it is the sole source of calcium supply for bone formation. Nevertheless, enhanced calcium absorption has been anticipated since endurance exercise was known to increase plasma $1,25\text{-(OH)}_2\text{D}_3$, a potent stimulating hormone for intestinal calcium transport. Although exercise may directly increase BMD and bone formation, exercise may also indirectly enhance skeletal integrity by stimulating the calcium absorption, which ultimately leads to increased bone strength and exercise performance (6). Recently, Armbrecht and colleagues in 2002 (31) demonstrated that mice with high bone mass (C3H/He strain) had a higher rate of duodenal calcium absorption as well as higher expression level of PMCA_{1b} mRNA than those with low bone mass (C57BL/6). This evidence indicates a direct relationship between high intestinal calcium absorption and high peak bone density or bone strength (31).

By using a flat-bed treadmill exercise, Yeh and co-workers found that the endurance exercise trained female Sprague-Dawley rats had higher duodenal active, but not passive, calcium absorption than the control (4). In well trained male athletes orally administered with stable strontium as a marker of calcium absorption, Zittermann and colleagues demonstrated increases in the fractional calcium absorption as well as the serum $1,25\text{-(OH)}_2\text{D}_3$ level after a short-term moderate exercise bout (32). Another study by Zittermann and colleagues in male athletes with a minimum of 8 hours per week of endurance sport activities confirmed that fractional strontium absorption was 4% greater in the athlete group than in the age-matched sedentary group (33). Interestingly, increased fractional strontium

absorption was significantly correlated with serum 1,25-(OH)₂D₃ level (32, 33). Although exercise-enhanced intestinal calcium absorption is likely mediated by an increase in serum 1,25-(OH)₂D₃ level, exercise may also stimulate calcium absorption by changing intestinal motility and epithelial permeability (34, 35). However, effects of strenuous and isometric exercise on the intestinal calcium transport have never been reported. Moreover, the molecular mechanisms of exercise-enhanced calcium absorption are still unknown.

On the other hand, immobilization by bilateral sciatic denervation in female rats led to a decrease in the duodenal calcium absorption, especially the passive components (4). In paraplegic patients, fecal calcium and phosphorus were increased, presumably by a decrease in the intestinal absorption of these elements (36). At the molecular level, immobilization decreased mRNA expressions of TRPV5, TRPV6, Calbindin-D_{9K}, but not PMCA_{1b} in the duodenum of rats (14). Interestingly, this condition also downregulated the renal mRNA expression of 1 α -hydroxylase which synthesized 1,25-(OH)₂D₃, but upregulated mRNA expression of 24-hydroxylase which degraded 1,25-(OH)₂D₃, suggesting that low expression of duodenal calcium transporters was due to a decrease in circulating 1,25-(OH)₂D₃ level (14). 1,25-(OH)₂D₃ supplement has been shown to restore expression of duodenal calcium transporters, but not the expression of the two renal enzymes (14).

Conclusion

It has been known that exercise, especially endurance type with moderate intensity, has several beneficial effects on calcium and bone metabolism. Normally, endurance exercise leads to positive calcium balance and net bone gain, whereas strenuous exercise may produce some adverse effects, e.g., increased renal calcium excretion. Interestingly, endurance exercise also stimulates intestinal calcium absorption in both humans and rats, thereby contributing to the exercise-increased bone mass and BMD. Immobilization however, has detrimental effects on bone since it induces low BMD, and it causes a progressive bone loss.

However, effects of different modes of exercise on the intestinal calcium absorption are largely unknown. For example, effects of swimming on calcium absorption in different age group have never been studied. Swimming, as a type of non-impact, non-weight-bearing exercise, is of special interest because it is recommended for patients with metabolic bone diseases, e.g., osteoporosis, and patients with some cardiovascular diseases. In addition,

although exercise is believed to increase calcium absorption by elevating serum 1,25-(OH)₂D₃ level, the cellular and molecular mechanisms of these changes remain enigmatic.

Moreover, it is important to note that most previous studies on exercise-enhanced calcium absorption focused on the transcellular active calcium transport which was predominantly 1,25-(OH)₂D₃-dependent. Nothing is known regarding the paracellular transport, especially the solvent drag-induced and passive calcium transport, which together contribute up to ~80-90% of the total calcium transport under physiological condition. Effects of exercise on the expression and distribution of claudins, which are regulators of the paracellular transport, are also unclear. Since the high dietary calcium is mainly absorbed by the paracellular mode of transport, the understanding of exercise-stimulated paracellular calcium absorption is important for maximizing the beneficial effect of calcium supplementation in athletes, which should match their bone calcium status as well as modes and intensity of exercise.

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