Effect of anions or foods on absolute bioavailability of calcium from calcium salts in mice by pharmacokinetics

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Abstract: We studied the absolute bioavailability of calcium from calcium L-lactate in mice using pharmacokinetics, and reviewed the absolute bioavailability of calcium from three other calcium salts in mice previously studied: calcium chloride, calcium acetate, and calcium ascorbate. The results showed that calcium metabolism is linear between intravenous administration of 15 mg/kg and 30 mg/kg, and is not affected by anions. Results after oral calcium administration of 150 mg/kg showed that the intestinal absorption process was significantly different among the four calcium salts. The rank of absolute bioavailability of calcium was calcium ascorbate > calcium L-lactate ≥ calcium acetate > calcium chloride. The mean residence time (MRT<sub>ab</sub>) of calcium from calcium ascorbate (32.2 minutes) in the intestinal tract was much longer than that from calcium L-lactate (9.5 minutes), calcium acetate (15.0 minutes) and calcium chloride (13.6 minutes). Furthermore, the foods di-D-fructo-furanose-1,2′,2,3′-dianhydride, sudachi (<i>Citrus sudachi</i>) juice, and moromi-su (a Japanese vinegar) increased the absolute bioavailability of calcium from calcium chloride by 2.46-fold, 2.86-fold, and 1.23-fold, respectively, and prolonged MRT<sub>ab</sub> by 48.5 minutes, 43.1 minutes, and 44.9 minutes, respectively. In conclusion, the prolonged MRT<sub>ab</sub> of calcium in the intestinal tract by anion or food might cause the increased absorbability of calcium.

Keywords: absolute bioavailability of calcium, pharmacokinetics, calcium chloride, calcium L-lactate, DFA III, sudachi juice

Introduction
Calcium is an essential mineral, acting primarily as a component in bones and teeth, as well as playing various physiological roles in cells, even at low levels.1,2 It has been shown that a deficit in calcium causes various diseases, including osteoporosis, hypocalcemia, hypertension, hypercholesterolemia, and cancer.3,4 The intestinal absorption of calcium takes place through both active and passive transport from the gut lumen after food intake in humans and other animals.1 Active transport occurs transcellularly with saturable kinetics and involves the binding of calcium ions by a vitamin D-dependent calcium binding protein in the intestinal mucosa. By contrast, passive transport occurs paracellularly with nonsaturable kinetics, and a constant fraction of calcium is absorbed at high loads. The calcium absorbability from the diet or foods usually has been measured using traditional mass balance techniques involving tracer, urine increment techniques.5 The quantity and retention of calcium are defined by levels in the blood, urine, or body compartments (particularly bone) after multiple administrations or ingestions over several days. These levels are defined...
as absorption, fractional absorption, or nutrient bioavailability of calcium, using the following formulas: 6

\[
\text{Apparent absorption (\%) = } \left(\frac{\text{Intake} - \text{Fecal excretion}}{\text{Intake}}\right) \times 100
\]

(1)

and

\[
\text{Apparent retention (\%) = } \left(\frac{\text{Intake} - \text{Fecal excretion} - \text{Urinary excretion}}{\text{Intake}}\right) \times 100.
\]

(2)

Calcium absorption has been measured in previous studies using mass balance techniques from an oral calcium source intrinsically labeled with a suitable calcium isotope (Table 1). 6-10 The studies showed that calcium absorbability is as low as 20%-40% after calcium salt administration, 6-11 and many modern diets do not provide the recommended levels of calcium (400-1,200 mg/day). 4,8,12 Therefore, calcium supplements are recommended for the prevention of calcium-related diseases, and various calcium salts, including calcium carbonate and calcium lactate, have been examined as calcium supplement sources. 13,14

**Table 1** Calcium absorbability from calcium salts measured by mass balance method

| Calcium salts            | Absorbability (%) | Animals, condition | References |
|--------------------------|-------------------|--------------------|------------|
| **Humans**               |                   |                    |            |
| Calcium carbonate        | 23.5 ± 12.3       | Fast               | Heaney    |
|                          | 39 ± 7            | Human              | Martin    |
|                          | 29.6 ± 5.4        | Diet               | Patrick   |
|                          | 23.5 ± 12.3       | Fast               | Patrick   |
|                          | 39 ± 3            | Human              | Sheikh    |
|                          | 14.7 ± 6.4        | Human              | Uenishi   |
| Calcium citrate          | 24 ± 4.9          | Fast               | Heaney    |
|                          | 24.2 ± 4.9        | Fast               | Patrick   |
|                          | 30 ± 3            | Human              | Sheikh    |
| Calcium citrate malate   | 36.3 ± 7.6        | Diet               | Patrick   |
| Calcium sulfate          | 41 ± 7            | Human              | Martin    |
| Calcium lactate          | 47 ± 8            | Human              | Martin    |
| Calcium oxalate          | 32 ± 4            | Human              | Shekh     |
| Tricalcium phosphate     | 10.2 ± 4.0        | Diet               | Patrick   |
| Calcium acetate          | 25.2 ± 13.0       | Diet               | Patrick   |
| Calcium gluconate        | 32 ± 4            | Human              | Sheikh    |
| **Rats**                 |                   |                    |            |
| Calcium carbonate        | 27.42 ± 3.09      | Rat                | Weaver    |
| Calcium citrate          | 28.69 ± 2.25      | Rat                | Weaver    |
| Calcium citrate malate   | 28.06 ± 1.58      | Rat                | Weaver    |
| Calcium fumarate         | 30.09 ± 1.02      | Rat                | Weaver    |
| Calcium malate fumarate  | 29.13 ± 1.65      | Rat                | Weaver    |

Actual calcium absorption is influenced by both dietary and nondietary factors, such as salts, other foods, or food constituents. 7,15-17 Heaney et al7 showed that even under controlled, chemically defined conditions, absorbability of calcium from food sources is determined mainly by other food components. Wasserman, 15 as well as Buchowski and Miller 16 showed that lactose increases the bioavailability of calcium from a variety of sources, but the magnitude of the effect varies between these sources. Suzuki et al 18 and Tomita et al 19 showed that difructose anhydride III (DFA III; di-D-fructo-furanose-1,2;2′,3′-dianhydride) enhances the absorption and retention of calcium. Such nondigestible diets also have been used as calcium supplement sources. Furthermore, Nii et al 20 showed that sudachi (Citrus sudachi) juice enhances intestinal absorption of calcium from small fishes. Kishi et al 21 showed that dietary vinegar enhances the intestinal absorption of calcium in ovariectomized (OVX) rats. 21

In current medical care, calcium is used as a medicinal element to cure calcium-deficient cases by enteral nutrition or continuous intravenous (IV) infusion. This therapy requires predicted suitable doses using reproducible and precise absorbability of calcium. However, as shown in Table 1, there is no reproducible and precise absorbability of calcium for current drug therapy. All the data are measured using mass balance techniques, in which it is hard to remove the effects of various foods because of the long period of measurement, for example 2 days or more. Pharmacokinetics might be able to determine a more precise bioavailability of calcium after calcium administration using serum concentrations of calcium for several hours. The area under the plasma concentration-time curve (AUC) is a primary function in pharmacokinetics in which the AUC is calculated using the trapezoidal rule from the plasma concentrations measured periodically after dosing. Even though the AUC itself is a relative measure for the extent of absorbability, in pharmacokinetic studies of drugs the absorbability is usually defined using the absolute (F(abs)) or relative (F(rel)) bioavailability. F(abs) was defined as AUCoral after an oral dose of Doral and was normalized with AUCIV after an IV dose of DIV as follows: 22

\[
F_{abs} = \frac{\text{AUC}_{oral}/D_{oral}}{\text{AUC}_{IV}/D_{IV}}.
\]

(3)

F_{rel} is the quantity indicating the equivalency between drugs A and B as follows:

\[
F_{rel} = \frac{\text{AUC}_{A}/D_{B}}{\text{AUC}_{B}/D_{A}}
\]

(4)

where a certain drug (B), dosed D_{B}, is compared with a standard drug (A), dosed D_{A}, and usually the standard
drug (A) has been established by pharmacokinetics. Then, the absolute bioavailability is usually defined as drug absorbability.

However, many studies of calcium have shown a relative measure for the extent of calcium absorbability, even though Tsugawa et al., Cai et al., and Hanzlik et al. indicated the importance of absolute bioavailability. Tsugawa et al. showed that the calcium absorbability from calcium ascorbate is almost comparable to, or higher than, that from calcium chloride, and is significantly higher than that from calcium carbonate. Cai et al. showed that the higher bioavailability of calcium ascorbate was due to a longer transit time in the small intestine compared with calcium ascorbate. Hanzlik et al. showed that calcium formate is clearly superior to calcium carbonate and calcium citrate in the ability to deliver calcium to the bloodstream after oral administration in humans. Thus, no one has examined comparably the absorbability among calcium salts using the absolute bioavailability of calcium by modern pharmacokinetics, and our recent report is the first study to examine supplement sources using the absolute bioavailabilities of calcium from three calcium salts: calcium chloride, calcium acetate, and calcium ascorbate, which are very soluble in water.

As shown in Table 2, the absolute bioavailability of calcium from calcium ascorbate and calcium acetate was 2.6-fold and 1.5-fold, respectively, greater than that of calcium chloride; the calcium absorbability from calcium ascorbate via the intestinal track is significantly higher than that of calcium chloride and calcium acetate. Furthermore, as shown in Table 3, Ueda et al. studied the effects of Hachimi-jo-gan extract on intestinal calcium absorption using pharmacokinetic calculations in an osteoporosis animal model of O VX and sham-operated (SHAM) mice. Hachimi-jo-gan is used clinically and has been shown to be effective in preventing bone loss in O VX rats. Hachimi-jo-gan enhanced the absolute bioavailability of calcium from calcium chloride (5.7%) in O VX (20.2%) and SHAM (19.9%) mice. Hachimi-jo-gan extract potentially improved the intestinal calcium absorption by 1.96-fold and 1.86-fold in O VX and SHAM mice, respectively. Hachimi-jo-gan extract further suppressed the potent stimulation of a receptor activator of the NF-κB ligand-induced osteoclast differentiation in RAW264.7 cells.

In this study, we measured the absolute bioavailability of calcium from calcium L-lactate, and examined the effect of the foods DFA III, sudachi juice, and moromi-su (a type of vinegar and healthy food made from fermenting mash in the production of sake, Japanese liquor) on the absorbability of calcium from calcium chloride. Furthermore, we reviewed, comparatively, the absorbability from three other soluble calcium salts – calcium chloride, calcium acetate, and calcium ascorbate – demonstrating the usefulness of pharmacokinetics in nutrition.

### Table 2 Pharmacokinetic parameters of calcium in mice after IV or oral administration of calcium chloride, calcium acetate, or calcium ascorbate

| Salts     | IV administration | Oral administration |
|-----------|-------------------|----------------------|
| | Dose (mg/kg) | AUC<sub>max</sub> (μg/mL) | MRT<sub>mean</sub> (minutes) | CL<sub>mean</sub> (mL/minute/kg) | V<sub>ss</sub> (mL/kg) 
| CaCl<sub>2</sub> | 15 | 1484.5 ± 41.0 | 29.3 ± 1.3 | 10.1 ± 0.3 | 296.5 ± 8.5 |
| | 30 | 2870.6 ± 90.8 | 33.0 ± 1.1 | 10.5 ± 0.3 | 345.1 ± 15.8 |
| CaAc<sub>2</sub> | 15 | 1507.9 ± 128.4 | 29.1 ± 2.0 | 10.0 ± 0.9 | 289.9 ± 7.4 |
| | 30 | 2637.2 ± 121.6 | 30.0 ± 2.4 | 11.4 ± 0.5 | 340.9 ± 24.7 |
| CaAs<sub>2</sub> | 15 | 1193.9 ± 101.7 | 30.4 ± 1.0 | 12.6 ± 1.1 | 383.6 ± 20.9 |
| | 30 | 2711.3 ± 154.2 | 32.5 ± 1.2 | 11.0 ± 0.6 | 359.2 ± 34.7 |
| CaLc<sub>2</sub> | 15 | 1396.2 ± 104.4 | 28.4 ± 2.0 | 10.8 ± 0.8 | 305.8 ± 29.3 |
| | 30 | 3139.8 ± 123.1 | 31.9 ± 2.1 | 9.6 ± 0.4 | 304.2 ± 10.4 |
| Means | | 30.6 ± 1.7 | 10.8 ± 1.0 | 328.2 ± 33.9 |

Note: Each value represents the mean ± standard deviation (n = 4).

Abbreviations: IV, intravenous; AUC, area under the curve; MRT, mean residence time; CL, plasma clearance; V<sub>ss</sub>, volume of distribution; CaCl<sub>2</sub>, calcium chloride; CaAc<sub>2</sub>, calcium acetate; CaAs<sub>2</sub>, calcium ascorbate; CaLc<sub>2</sub>, calcium L-lactate; T<sub>max</sub>, time to reach the maximum plasma concentration; C<sub>max</sub>, maximum plasma concentration; F<sub>abs</sub>, absolute bioavailability; n, number.
**Table 3** Pharmacokinetic parameters of calcium in female mice after IV or oral administration of calcium

| Mice          | AUC max (μg/mL. minute) | MRT IV (minutes) | CL IV (mL/minute/kg) | V dss (mL/kg) |
|---------------|-------------------------|-------------------|---------------------|--------------|
| IV administration (dose: 30 mg/kg)* |                        |                   |                     |              |
| SHAM         | 2101.0 ± 14.3           | 27.1 ± 3.6        | 14.3 ± 0.9          | 386.0 ± 23.8 |
| OVX          | 2097.0 ± 10.5           | 26.5 ± 1.9        | 14.3 ± 0.7          | 379.0 ± 34.0 |

| Oral administration (dose: 150 mg/kg)* | T max (minutes) | Cmax (μg/mL) | AUC oral (μg/mL. minute) | MRT oral (minutes) | F abs (%) |
|--------------------------------------|-----------------|--------------|--------------------------|--------------------|-----------|
| SHAM                                | 30              | 93.0 ± 2.5   | 1121.0 ± 22.8            | 57.2 ± 4.2         | 10.7 ± 2.8 |
| OVX                                | 30              | 94.0 ± 1.9   | 1086.0 ± 20.1            | 45.3 ± 2.9         | 10.3 ± 2.1 |
| SHAM + Hj                           | 30              | 104.0 ± 3.8  | 2091.0 ± 80.6            | 76.8 ± 2.4         | 19.9 ± 3.1 |
| OVX + Hj                           | 30              | 104.0 ± 2.5  | 2120.0 ± 71.7            | 75.4 ± 5.6         | 20.2 ± 1.7 |

Notes: Each value represents the mean ± standard deviation (n = 5). *Dose refers to a quantity of calcium in the CaCl2 solution; the pharmacokinetic parameters of calcium in male mice (dII strain) were obtained from Ueda and Taira.21

Abbreviations: IV, intravenous; AUC, area under the curve; CL, plasma concentration; V dss, volume of distribution; SHAM, sham-operated mice; OVX, ovariectomized rats; T max, time to reach maximum plasma concentration; Cmax, maximum plasma concentration; F abs, absolute bioavailability; Hj, Hachimi-jio-gan extract.

**Materials and methods**

**Chemicals**

DFA III was purchased from Wako Pure Chemical Industries, Ltd (Osaka, Japan). Calcium L-lactate 5H2O was purchased from Sigma-Aldrich (St Louis, MO, USA). Sudachi juice was prepared by squeezing the juice from fruits of an orange, sudachi, and separating supernatant by centrifugation at 100,000× g for 30 minutes. The moromi-su was purchased from a market store. Other reagents were purchased from commercial sources and were of the highest grade available.

**Animals and pharmacokinetic procedures**

Seven-week-old male ddY mice, weighing 20–30 g, were obtained from SLC Co, Ltd (Shizuoka, Japan). Animals had free access to food (commercial diet, MF pellets; Oriental Yeast Co., Ltd., Tokyo, Japan) and water during the experimental period. Mice were allowed to recover from anesthesia. Solutions of calcium (1% w/v) were prepared for each calcium salt, and either 15 mg or 30 mg calcium/kg of body weight was administered intravenously to the tail vein. The plasma calcium concentrations were measured spectroscopically, as described previously.22 For oral administration, 150 mg calcium/kg of body weight was delivered to the duodenum, and the plasma calcium concentrations were measured. Ten mL/kg of 10% (v/v) of sudachi juice or moromi-su, or 1% (w/v) aqueous solution of DFA III, was administered orally, following oral administration of 150 mg of calcium per kg from calcium chloride, and blood samples were collected. The plasma calcium concentrations were determined. All protocols conformed to the guide for the institutional care and use of animals of Tokushima Bunri University, Tokushima, Japan.

**Pharmacokinetic calculation**

The pharmacokinetic parameters were calculated, as described previously.32 Briefly, the parameters for intestinal absorption, distribution, metabolism, and elimination of calcium – the area under the calcium concentration in the blood-time curve (AUCabs); mean residence time (MRTiv) after IV administration; plasma clearance (CLiv); and apparent volume of distribution (Vdss) at steady-state after IV administration; and AUCoral, maximum plasma concentration (Cmax), and MRToral after oral administration were calculated using the time course of serum calcium concentrations by an iterative nonlinear least-squares method using the MOMENT software program, described by Yamaoka et al.30,31 AUCabs was calculated on the basis of the trapezoidal rule. When MRToral in all compartments was calculated after oral administration, the MRTab in the absorption track as follows:

\[
MRT_{ab} = MRT_{oral} - MRT_{iv}, \quad (5)
\]

**Statistical analysis**

Data are presented as the mean value ± standard deviation. A parameter was considered to be significantly different when the P-values were <0.05 using Student’s t-test.

**Results**

**The absolute bioavailability of calcium from calcium L-lactate**

We studied the pharmacokinetic parameters using time courses of plasma concentrations of calcium in male ddY mice after IV or oral administration of calcium from calcium L-lactate.
The plasma concentrations of calcium from calcium L-lactate in mice for 2 hours after IV administration of 15 mg/kg or 30 mg/kg of calcium were measured as shown in Figure 1A, and the pharmacokinetic parameters of calcium were calculated as summarized in Table 2. The results showed that the pharmacokinetic process is nearly linear owing to a first-order reaction, because mean AUC values increased 2.25-fold, compared with administrations of 15 mg and 30 mg (P < 0.05). Furthermore, MRT, CL, and V_dss did not significantly differ between the two administered doses. The pharmacokinetic behavior of calcium from calcium L-lactate in male mice following oral administration of calcium using time courses of plasma concentrations of calcium (Figure 1B) in mice that were orally administered a dose of 150 mg/kg of calcium, as well as the pharmacokinetic parameters of calcium are summarized in Table 2. The results showed that the blood concentration of calcium reached the C_max of 98.2 µg/mL at the time to reach the maximum plasma concentration (T_max) of 30 minutes. The absolute bioavailability value of calcium L-lactate was 8.9%.

Effects of three foods – DFA III, sudachi juice, and moromi-su – on the absolute bioavailability of calcium from calcium chloride

To examine the enhancing effects of three foods – DFA III, sudachi juice, and moromi-su – on the absolute bioavailability of calcium, 10 mL/kg of 10% (v/v) of sudachi juice or moromi-su, or 1% (w/v) aqueous solution of DFA III, was administered orally, following oral administration of 150 mg of calcium per kg from calcium chloride, and plasma calcium concentrations were measured as shown in Figure 2. The pharmacokinetic parameters were calculated as summarized in Table 4. The result showed that the foods enhance the absorbability of calcium from calcium chloride after oral administration. That is, the foods increased the absolute bioavailability (5.7% ± 1.3%) of calcium from calcium chloride by 14.0% ± 2.1%, 16.3% ± 2.8%, and 7.0% ± 3.1%, respectively.

Discussion

In this study, we examined the pharmacokinetic characterization of calcium from calcium L-lactate, and reviewed the other three calcium salts previously studied – calcium chloride, calcium acetate, and calcium ascorbate – after IV or oral administration in mice. The results for those four calcium salts showed that the corresponding pharmacokinetic parameters (the AUC values) increased 2.04-fold (mean) compared with administrations of 15 mg and 30 mg (P < 0.05); in addition, MRT, CL, and V_dss did not differ significantly between the two administered doses, with mean values of 30.6 ± 1.7 minutes, 10.8 ± 1.0 mL/minute/kg, and 328.2 ± 33.9 mL/kg, respectively. This might indicate that calcium metabolism in animals is linear between those doses, and is not physiologically affected by anions (P < 0.05). However, the results after oral calcium administration of 150 mg/kg of body weight showed that the intestinal absorption process was significantly different among the four calcium salts. That is, the absolute bioavailabilities of calcium from calcium chloride, calcium acetate, calcium ascorbate, and calcium L-lactate were 5.7%, 8.6%, 14.8%, and 8.9%, respectively. The rank of the absolute bioavailability of calcium was calcium ascorbate > calcium chloride > calcium acetate > calcium L-lactate.

Figure 1 Time course of plasma calcium concentrations after intravenous calcium administration of 15 mg/kg or 30 mg/kg of body weight of calcium L-lactate.

Notes: (A) Open circles refer to plasma calcium concentrations after administration of 30 mg/kg of body weight, closed circles refer to calcium administration of 15 mg/kg of body weight, and open squares are the plasma calcium concentrations of the control mice. (B) In total, 150 mg/kg of body weight of calcium L-lactate in 1% solution was orally delivered to the duodenum and blood was collected. Open circles refer to plasma calcium concentrations after oral administration of one of the three calcium salts, and open squares are the plasma calcium concentrations of the control mice. Data points represent the mean ± standard deviation (n = 4).

Abbreviation: n, number.
L-lactate ≥ calcium acetate > calcium chloride, and the rank was consistent with that of the AUC. Thus, the rank also was consistent with the findings of Tsugawa et al\textsuperscript{26} and Cai et al.\textsuperscript{27} Furthermore, the specific magnitude of the greater MRT\textsubscript{ab} of calcium from calcium ascorbate (32.2 minutes) might result in the greater absolute bioavailability of calcium compared with calcium L-lactate (9.5 minutes), calcium acetate (15.0 minutes), and calcium chloride (13.6 minutes). That is, calcium from calcium ascorbate might cross the gut membrane for a longer period of time.

Furthermore, effects of the foods DFA III and sudachi juice significantly increased the absorbability of calcium from calcium chloride 2.46-fold and 2.86-fold, respectively, but moromi-su was less effective (a 1.23-fold increase) compared with other foods. In addition, the foods prolonged MRT\textsubscript{ab} of calcium from calcium chloride in the intestinal tract by 48.5 minutes, 43.1 minutes, and 44.9 minutes, respectively. Thus, DFA III and sudachi juice might be recommended as a supplementary food for promoting the effect of calcium absorption.

In conclusion, the pharmacokinetic calculations showed that calcium metabolism in animals is linear between doses at 15 mg/kg and 30 mg/kg, and is not physiologically affected by anions. However, the intestinal absorption process was

Table 4 Effect of foods on pharmacokinetic parameters of calcium in male mice after oral administration of calcium chloride

| Foods          | $T_{max}$ (minutes) | $C_{max}$ (μg/mL) | AUC\_oral (μg/mL·minute) | MRT\_oral (minute) | $F_{abs}$ (%) |
|----------------|---------------------|-------------------|--------------------------|-------------------|--------------|
| Oral administration (dose: 150 mg/kg) |                     |                   |                          |                   |              |
| DFA III        | 45                  | 94.1 ± 15.3       | 2013.5 ± 20.1            | 81.5 ± 7.9        | 14.0 ± 2.1   |
| Sudachi juice  | 45                  | 101.3 ± 21.1      | 2343.2 ± 22.8            | 76.2 ± 4.2        | 16.3 ± 2.8   |
| Moromi-su      | 45                  | 115.5 ± 32.8      | 9973 ± 80.6              | 78.3 ± 8.4        | 7.0 ± 3.1    |

Note: Each value represents the mean ± standard deviation (n = 4).

Abbreviations: $T_{max}$, time to reach maximum plasma concentration; $C_{max}$, maximum plasma concentration; AUC, area under the curve; MRT, mean residence time; $F_{abs}$, absolute bioavailability; DFA III, di-D-fructo-furanose-1,2′:2,3′-dianhydride; n, number.
significantly different among the four calcium salts after oral calcium administration, and the greater MRT$_b$ of calcium in the intestinal tract might cause higher absorability. Food also might increase MRT$_a$ of calcium in the intestinal tract.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Bronner F. Mechanisms and functional aspects of intestinal calcium absorption. J Exp Zool Part A Comp Exp Biol. 2003;300(1):47–52.
2. Weaver CM, Heaney RP. Calcium in Human Health. Totowa, NJ: Humana Press; 2005.
3. Peacock M. Calcium metabolism in health and disease. Clin J Am Soc Nephrol. 2010;5(Suppl 1):S23–S30.
4. Heaney RP. Calcium intake and disease prevention. Arq Bras Endocrinol Metabol. 2006;50(4):685–693.
5. Heaney RP. Factors influencing the measurement of bioavailability, taking calcium as a model. J Nutr. 2001;131(Suppl 4):1344S–1348S.
6. Sheikh MS, Santa Ana CA, Nicar MJ, Schiller LR, Fordtran JS. Gastrointestinal absorption of calcium from milk and calcium salts. N Engl J Med. 1987;317(9):532–536.
7. Heaney RP, Recker RR, Weaver CM. Absorbability of calcium sources: the limited role of solubility. Calcif Tissue Int. 1990;46(5):300–304.
8. Patrick L. Comparative absorption of calcium sources and calcium citrate malate for the prevention of osteoporosis. Altern Med Rev. 1999;4(2):74–85.
9. Martin BR, Weaver CM, Heaney RP, Puckard PT, Smith DL. Calcium absorption from three salts and CaSO$_4$-fortified bread in premenopausal women. J Agric Food Chem. 2002;50(17):3874–3876.
10. Weaver CM, Martin BR, Costa NM, Saleeb FZ, Huth PJ. Intestinal absorption of calcium fumarate salts is equivalent to other calcium salts when measured in the rat model. J Agric Food Chem. 2002;50(17):4974–4975.
11. Uenishi K, Fujita T, Ishida H, et al. Fractional absorption of active absorbable alcal calcium (AAACA) and calcium carbonate measured by a dual stable-isotope method. Nutrients. 2010;2(7):752–761.
12. Hanzlik RP, Fowler SC, Fisher DH. Relative bioavailability of calcium from calcium fumarate, calcium citrate, and calcium carbonate. J Pharmocol Exp Ther. 2005;313(3):1217–1222.
13. Qin M, Zhang Z, Maki K, Naito M, Morimoto A, Kimura M. The effect of calcium supplement given with a mixture of calcium carbonate and calcium citrate on the mandibular alveolar bone of pubertal rats. J Bone Miner Metab. 1998;16:88–95.
14. Straub DA. Calcium supplementation in clinical practice: a review of forms, doses, and indications. Nutr Clin Pract. 2007;22(3):286–296.
15. Wasserman RH. Lactose-stimulated intestinal absorption of calcium: a theory. Nature. 1964;201:997–999.
16. Buchowski MS, Miller DD. Lactose, calcium source and age affect calcium bioavailability in rats. J Nutr. 1991;121(11):1746–1754.
17. Shigematsu N, Okuhara Y, Shiomi T, Tomita F, Hara H. Effect of difructose anhydride III on calcium absorption in humans. Biosci Biotechnol Biochem. 2004;68(5):1011–1016.
18. Suzuki T, Hara H, Kasai T, Tomita F. Effects of difructose anhydride III on calcium absorption in small and large intestines of rats. Biosci Biotechnol Biochem. 1998;62(5):837–841.
19. Tomita K, Shiomi T, Okuhara Y, Tamura A, Shigematsu N, Hara H. Ingestion of difructose anhydride III enhances absorption and retention of calcium in healthy men. Biosci Biotechnol Biochem. 2007;71(3):681–687.
20. Nii Y, Osawa T, Kunii D, Fukuta K, et al. Effects of citrus fruit (Sudachi) juice on absorption of calcium from whole small fish in healthy young men. Food Science and Technology Research. 2006;12(1):27–30.
21. Kishi M, Fukaya M, Tsukamoto Y, Nagasawa T, Takehana K, Nishizawa N. Enhancing effect of dietary vinegar on the intestinal absorption of calcium in ovariectomized rats. Biosci Biotechnol Biochem. 1999;63(5):905–910.
22. Ueda Y, Taira Z. Pharmacokinetic characterization of calcium from three calcium salts (calcium chloride, calcium acetate and calcium ascorbate) in mice. Journal of Hard Tissue Biology. 2012;21:291–298.
23. Ohtani M, Tsugawa N, Kamao M, Okano T. Absorbability of calcium from a new calcium supplement prepared from bovine marrow-free bone in rats. J Nutr Sci Vitaminol. 1998;44(6):887–895.
24. Heller HJ, Stewart A, Haynes S, Pak CY. Pharmacokinetics of calcium absorption from two commercial calcium supplements. J Clin Pharmacol. 1999;39(11):1151–1154.
25. Heaney RP. Quantifying human calcium absorption using pharmacokinetic methods. J Nutr. 2003;133(4):1224–1226.
26. Tsugawa N, Yamabe T, Takeuchi A, et al. Intestinal absorption of calcium from calcium ascorbate in rats. J Bone Miner Res. 1999;17:30–36.
27. Cai J, Zhang Q, Wastney ME, Weaver CM. Calcium bioavailability and kinetics of calcium ascorbate and calcium acetate in rats. Exp Biol Med (Maywood). 2004;229(1):40–45.
28. Ueda Y, Kanayama M, Yamauchi N, Iio C, Taira Z. Effects of Hachimijio-gan extract on intestinal absorption of calcium in ovariectomized mice and stimulation of RANKL-induced osteoclast differentiation of Raw264.7 cells by lipopolysaccharide. Journal of Hard Tissue Biology. 2012;21:469–476.
29. Hidaka S, Okamoto Y, Nakajima K, Suekawa M, Liu SY. Preventive effects of traditional Chinese (Kampo) medicines on experimental osteoporosis induced by ovariectomy in rats. Calcif Tissue Int. 1997;61(3):239–246.
30. Yamaoka K, Nakagawa T, Uno T. Statistical moments in pharmacokinetics. J Pharmacokin Biopharm. 1978;6(6):547–558.
31. Taira Z, Yabe K, Yamaguchi Y, et al. Effects of Sho-saiko-to and its components, baicalin, baicalein, glycyrrhizin and glycyrrhetic acid, on pharmacokinetic behavior of salicylamide in carbon tetrachloride intoxicated rats. Nature. 1964;201:997–999.