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Review of Ca Metabolic Studies and a Model for Optimizing Gastrointestinal Ca Absorption and Peak Bone Mass in Adolescents

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Abstract

Purpose: The objective of this study is to review researches regarding factors that potentially affect adolescent calcium (Ca) metabolism, and to suggest a potential modeling approach for optimizing gastrointestinal Ca absorption and peak bone mass. **Background:** Optimal gastrointestinal Ca absorption is a key to maximizing peak bone mass in adolescents. Urine Ca excretion in adolescents rises only after bone accretion is saturated, indicating that higher intestinal Ca absorption and bone retention is necessary to ensure maximum bone accretion. Hence, maximizing peak bone mass is possible by controlling the factors influencing gastrointestinal Ca absorption and bone accretion. However, a mechanism that explains the unique adolescent Ca metabolism has not yet been elucidated. **Review:** Dietary factors that enhance gastrointestinal Ca absorption may increase the available Ca pool usable for bone accretion, and a specific hormone may direct optimal Ca utilization to maximize peak bone mass. IGF-1 is an endocrine hormone whose levels peak during adolescence and increase fractional Ca absorption and bone Ca accretion. Prebiotics, generally obtained from dietary sources, have been reported to exert a beneficial effect on Ca absorption via microbiota activity. We selected and reviewed three candidates that could be used to propose a comprehensive Ca metabolic model for optimal Ca absorption and peak bone mass in adolescents. **Modeling:** Modeling has been used to investigate Ca metabolism and its regulators. Herein, we reviewed previous Ca modeling studies. Based on this review, we proposed a method for developing a comprehensive model that includes regulatory effectors of IGF-1 and prebiotics.

Keywords: Calcium metabolism, Dietary protein, IGF-1, Mathematical modeling, Prebiotics

Introduction

Osteoporosis is a highly prevalent disease, characterized by loss of bone mass over time after achieving peak bone mass at adolescence, resulting in an increased fracture incidence. Recent reports have shown that about 10 million people in the US are affected by osteoporosis (Russo et al., 2009) and healthcare costs are estimated to reach $25.3 billion by 2025 (National Osteoporosis Foundation, [2006]). Maximizing peak bone mass during pubertal growth is a key strategy to prevent osteoporosis. A fundamental way to maximize peak bone mass is to increase bone calcium (Ca) accretion, possibly via high gastrointestinal Ca absorption. Since peak bone mass can be modified by lifestyle choices during adolescence, the nutrient function of bioactive components (e.g., prebiotics) and dietary proteins with respect to adolescent Ca metabolism is currently emphasized.

Adolescent Ca metabolism is characterized by high Ca absorption and bone balance to achieve the maximum peak bone mass. A previous kinetic modeling study (Wastney et al., 1996) estimated 15% higher fractional Ca absorption and 75% higher absorbed Ca in adolescents than in adults. This study also reported that bone balance was highly positive (282±269 mg/d) in adolescents, while young women showed negative balance (-41±165 mg/d). In addition, other studies have shown that adolescent

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urine Ca excretion remains constant and increases only after bone accretion via absorbed Ca is saturated (Matkovic et al., 1990; Matkovic and Ilich, 1993; Jackman et al., 1997, Heaney et al., 2000). These reports collectively suggest that adolescents have high Ca absorption and retain absorbed Ca for bone accretion rather than excrete Ca in urine. Consequently, Ca is more effectively absorbed and metabolized to optimize peak bone mass in adolescents than in adults. However, a mechanism for this unique adolescent Ca metabolism has not been elucidated.

As Ca in the body is derived from dietary intake, gastrointestinal function is a key determinant of effective Ca utilization to maximize peak bone mass. To be absorbed in the intestine, Ca must be present in an available form (Awumey and Bukoski, 2006) and the absorptive mechanism needs to be stimulated to guarantee high Ca absorption. A potential factor that leads to maximum peak bone mass by increasing intestinal Ca absorption is insulin-like growth factor-I (IGF-1) (Fatayerji et al., 2000).

IGF-1 levels are highest during the period when peak bone mass is achieved (Mitchell et al., 1990). In addition, they are reported as the largest predictor of Ca retention in adolescents, while other regulators, parathyroid hormone (PTH) and vitamin D, are not effective in predicting bone Ca retention in adolescents (Hill et al., 2008). Some nutrients such as dietary fibers (Martin et al., 2010; Weaver et al., 2010) and proteins (Vatanparast et al., 2007) are reported as functional food components that improve gastrointestinal Ca absorption and bone health. Dietary protein has shown Ca intake-dependent action on bone health (Dawson-Hughes and Harris, 2002; Engelmann et al., 1975). Because the beneficial effect of dietary protein is mediated by the anabolic effect of increased IGF-I, dietary protein may improve the absorption of Ca in the gastrointestinal tract as well as the bone formation. Furthermore, increased consumption of prebiotics is often correlated with the increase in the growth of bacteria that are beneficial to the host (Kleerebezem and Vaughan, 2009; Rastall et al., 2005). The microbial community along the gastrointestinal tract facilitates mineral absorption through the fermentation of non-digestible foods (Bik et al., 2006; Egert et al., 2006). In particular, microbiota in the lower gastrointestinal tract play a role in the modification of the environment, e.g., pH decreases during the fermentation of fibers. These modifications can affect calcium solubility, thus increasing its absorption. Consequently, the body is able to retain a large Ca pool available for bone formation (Chonan and Watanuki, 1995; Chonan et al., 2001). However, the relationship between diet and the promotion of human bone health is unknown.

A model that is consistent with available experimental data can be used to simulate conditions that that may be difficult to replicate in experiments. Such a model offers a cost-effective way to test various scenarios and obtain informative data before experimental design (Galvanin et al., 2007). To explain how rates of Ca metabolism change in response to regulatory factors, dynamic models have been proposed for various species including rats (Perault-Staub et al., 1992; Tracqui et al., 1992), chickens (Hurwitz et al., 1987), and dairy cows (El-Samad et al., 2002). A comprehensive model of Ca homeostasis that includes the main organs and regulatory branches (PTH and vitamin D) has been developed and applied to simulate the response of Ca homeostasis with respect to clinically interesting situations (Raposo et al., 2002). Another dynamic model was designed to predict changes in serum Ca in response to PTH action caused by citrate infusion, mimicking perturbations in space flight (Wastney et al., 2005). The short-term dynamics of PTH in response to acute changes in serum Ca (Shrestha et al., 2010), and a physiology-based model integrating Ca homeostasis and bone remodeling (Peterson and Riggs, 2010) have also been reported. Recently, modeling to simulate Ca dynamics as a result of system perturbations has been used to aid in the design and interpretation of studies (Lee et al., 2011). Detailed reviews of Ca modeling have been reported (Lee and Cho, 2012; 2013).

Still, little is known about the connection between gastrointestinal absorption and bone accretion during adolescence. To provide insight for future research, the objectives of this study were two-fold: 1) to review previous studies of IGF-1 modulated by dietary protein and prebiotics beneficial to gastrointestinal Ca absorption, and 2) to suggest a modeling approach that can be used to optimize gastrointestinal Ca absorption and peak bone mass.

Review

IGF-1 in Ca metabolism

IGF-1 is a modulator associated with both pubertal growth and Ca/bone metabolism. The effect of IGF-1 and IGF binding protein 3 (IGF-BP3) in adolescents was discovered in a controlled feeding study (Hill et al., 2008).

In this study, a non-linear equation that explained Ca retention as a function of IGF-1 levels was developed. Compared to PTH and the active form of vitamin D, $1,25(OH)_2D$, IGF-1 explained the largest proportion of variation of 11.5% ($P = 0.0051$), suggesting its role as a potential regulator that differentiates between adolescent and adult Ca metabolism. Plasma IGF-1 levels parallel the growth spurt at puberty, peak in adolescence, and decrease thereafter with age (Mitchell et al., 1990). The effect of IGF-1 on Ca absorption has not been directly studied; however, increased IGF-1 levels were associated with increased $1,25(OH)_2D$ in normal men (Wright et al., 1997), and Ca absorption was increased by stimulating 1,α-hydroxylase, which activates vitamin D metabolites (Nesbitt and Drezner, 1993). In addition, IGF-1 modulates bone metabolism. Ca accretion, resulting in a larger pool of exchangeable Ca in adolescents than in young adults is largely regulated by endocrine IGF-1 (Mitchell et al., 1990). However, autocrine/paracrine IGF-1 action stimulates bone cell activity and consequently increases bone formation (Yakar and Rosen, 2003). Mouse strains with higher IFG-1 levels have higher BMD and cortical thickness (Yakar et al., 2010). Protein restriction in rats reduces serum IGF-1 and impairs cortical bone formation (Bourrin et al., 2000). A recent study investigated the correlation between Ca absorption, skeletal growth, and plasma IGF-1 (Zhang et al., 2011). Plasma IGF-I levels, body weight, and various bone parameters (e.g., whole body bone mineral density, and femoral and vertebra bone mineral content [BMC] and density) were monitored, and body weight and bone parameters were examined with respect to age. The results demonstrated that the IGF-1/IGF-BP3-treated group (35%) had 14% higher Ca absorption than the control group for pubertal rats (21%), but not for young adult rats. The femoral Ca content was higher in the IGF-1/IGF-BP3-treated group (31%) than the control group (24%). This result suggests that IGF-1 can increase Ca absorption and bone Ca accretion during puberty, but IGF-I/IGFBP3 is no longer effective after rapid growth, and higher doses are required to produce a significant effect.

Dietary protein modulating IGF-1

Recently, dietary protein has been shown to modulate serum IGF-1. Increasing the protein content from 10% to 20% in the diet resulted in a 27% increase in serum IGF-I in postmenopausal women (Hunt et al., 2009). Protein supplementation increased IGF-I levels in hip fracture patients (Schurch et al., 1998) and the intake of 3 daily servings of milk for a 12-week duration increased serum IGF-I levels by 10% in healthy adults (Heaney et al., 1999). Dietary protein also increases IGF-I levels during growth, as milk supplementation increased serum IGF-I levels in adolescent girls (Cadogan et al., 1997). Serum IGF-I was positively associated with dietary protein in 8-year-old boys (Budek et al., 2007). Historically, dietary protein was thought to have a negative effect on Ca balance and bone mass. In Asian pre-pubertal girls consuming a diet containing high protein (1.67 ± 0.58 g×kg/d) and low Ca (433 ± 70 mg/d), protein intake was negatively related to 5-year BMC accretion for the total body and proximal and distal femur (Zhang et al., 2010). However, in another meta-analysis, no evidence of a relationship between protein and calcium accretion was found (Fenton et al., 2008). Thus, the increased loss of Ca in the urine owing to high-protein diets is perhaps offset by the increased Ca absorption or decreased endogenous secretion in humans (Hunt et al., 2009; Kerstetter et al., 2005; Spence et al., 2005) and rats (Engelmann et al., 1975), rather than by decreased bone resorption. In addition, the influence of protein on Ca retention and bone mass is thought to depend on Ca intake in adults (Dawson-Hughes and Harris, 2002; Engelmann et al., 1975). Protein intake positively predicted total body gain and adult BMC/BMD (bone mineral density) in 133 Canadian girls whose Ca intakes were >1000 mg/d at the age of 23 (Vatanparast et al., 2007). Importantly, none of the other nutrients examined positively predicted bone mass gain.

The effect of dietary protein is still controversial, suggesting that its interaction with Ca intake in mediating bone mass during puberty is not well understood. Based on this review, it is expected that the effect of protein on Ca retention depends on Ca intake in adolescents, as it does in adults. In other words, for a high Ca intake, Ca retention increases with protein consumption, while dietary protein reduces Ca retention for low Ca intake. Alternatively, dietary protein may increase Ca retention via Ca intake. Furthermore, we expect high protein intakes to enhance gastrointestinal Ca absorption and bone formation rates, proposing a possible mechanism for modulating IGF-1 via dietary means.

Prebiotics in Ca metabolism

The bioactive effect of prebiotics such as dietary fibers through the action of microbiota along the gastrointestinal

tract on Ca metabolism is considered beneficial. Several human studies have reported that prebiotics (e.g., galacto-oligosaccharides, GOS) exert a positive effect by increasing the numbers of beneficial bacterial communities in the gut (Bouhnik et al., 2004), cecal epithelial cells related to the effective surface available for absorption (Scheppach et al., 1992), and transcription of genes linked to transcellular and paracellular Ca absorption processes (Raschka and Daniel, 2005). Increased consumption of prebiotics is often correlated with an increase in the members of certain bacterial genera associated with health (e.g., *Bifidobacterium* spp.). Their precise role however is still unknown, although a number of hypotheses have been put forward. Chonan et al. (1995) reported that Ca absorption was increased by 10–20% after GOS consumption in rats. The production of short-chain fatty acid (SCFA) by bacterial fermentation of GOS may lead to a decrease in gastrointestinal pH and increase in Ca solubility, thereby enhancing its absorption and improving health (Chonan and Watanuki, 1995; Chonan et al., 2001).

A beneficial effect of prebiotics was investigated by GOS supplementation to improve bone Ca content (Perez-Conesa et al., 2007) and bone ash weight (Chonan and Watanuki, 1996). Weaver et al. (2010) compared the effect of eight fibers on SCFA production, calcium absorption, mineral retention, bone content, and bone density and strength in a weanling rat model. This study reported that femur ^{45}Ca uptake was 23% higher in dietary fiber-fed rats (fructooligosaccharide/inulin) than in the control group. Recently, the effect of dietary supplementation of prebiotics (GOS) on various Ca kinetic indexes (Ca balance and bone parameters) and microbiota has been demonstrated based on changes in mechanistic variables (total weight, content weight, and gut microbiota community) in growing rats (Weaver et al., 2011). This study investigated the dose response of GOS on rat skeletal health; Ca absorption and retention were increased by 13% and 12 mg/d for treatment with 8% GOS compared to the control group, and they were correlated with increases in bifidobacteria. A recent review reported benefits of various fibers and prebiotics on human health including Ca metabolism (Slavin, 2013).

However, the fundamental role of microbiota in promoting human Ca metabolism is still unknown. It is a potential avenue for dietary manipulation as a means to increase bone health. To accurately evaluate the effect of prebiotics on Ca and bone metabolism via microbial activity, it is necessary to characterize the contribution of the gut microbial community and diet composition to Ca metabolism; modeling may enable us to systemically integrate diverse factors.

Modeling Reviews and Suggestions

One hypothesis is that modulating IGF-1 levels can explain the difference in Ca metabolism between adolescents and adults. As dietary intake is the first step in Ca utilization, gastrointestinal function is a key determinant of effective Ca utilization to maximize peak bone mass. As reviewed, nutrients such as dietary fibers and proteins beneficially affect Ca absorption and consequently affect the bone quality, but their correlation is unclear. Therefore, it can be postulated that prebiotics and dietary protein mediate microbial dynamics and IGF-1 levels, respectively, to promote bone Ca mass via enhanced gastrointestinal Ca absorption in adolescents.

Mathematical modeling is a popular method for testing hypotheses and elucidating unknown biological mechanisms. Although plenty of experiments have been conducted, a dynamic model may help close gaps between physiological phenomena and mechanistic traits. Hence, we propose a methodology, namely, a dynamic model of the regulatory effectors of Ca/bone metabolism, to explain differences between Ca metabolism in adolescents and adults by inserting dynamic functions into an established kinetic model. The developed model can be used to test various scenarios with respect to age (adolescent/adult) and dietary components (prebiotics/protein), and can be used to develop prospective experimental designs to predict peak bone mass in adolescents. A stepwise bottom-up modeling procedure is applied by inserting dynamic functions of Ca metabolism into previously published kinetic models, and is then linked to regulatory branches interconnecting IGF-1 and the microbial community to examine Ca dynamics. A detailed description of the approach follows.

Develop a dynamic Ca metabolic model

Previous modeling and available kinetic studies were first reviewed (Table 1). Some Ca kinetic data is available for adolescents accounting for the effects of subject characteristics (e.g., age, race, and weight) (Bryant et al., 2003; Wastney et al., 1996; Weaver et al., 1995; Weaver et

Table 1. Available models and data for Ca metabolism

Reference	Subject	Age	Property	Target system / Regulators
Raposo et al., 2002	Human	Adults	Dynamics	Ca-P homeostasis/ PTH & vit D
Wastney et al., 2005	Human	Adults	Dynamics	Ca homeostasis/ PTH & citrate
Shrestha et al., 2010	Human	Adults	Dynamics	PTH metabolism / Serum Ca
Doty & Seagrave, 2000	Human	Adults	Dynamics	Water, sodium & Ca regulation/PTH & vit D
Abraham et al., 2009	Human/Rat	Adults	PBPK/PD	Ca homeostasis/ PTH
Hill et al., 2008	Human	Adolescents	Kinetics	Ca retention / Ca intake & IGF-1
Sheikh et al., 1990	Human	Adults	Kinetics	Ca absorption data

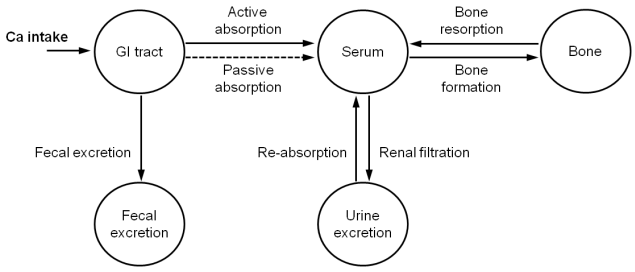

Figure 1. Model schematic of calcium metabolism with dynamic pathways to be formulated. Dynamic functions for individual Ca metabolism will be integrated through an intermediate variable (serum Ca). Note: endogenous excretion will be represented by a constant loss function (not shown), and bone may be modeled by more than one pool, as in Lee et al. (2010).

al., 1997), Ca intake (Braun et al., 2006; Hill et al., 2008; Jackman et al., 1997; Park et al., 2010; Wu et al., 2010), vitamin D (Park et al., 2010), and nutrients (e.g., sodium and fiber) (Braun et al., 2007; Wigertz et al., 2005). Then, an initial model can be designed based on published Ca kinetics models as a backbone for inserting dynamic functions (Lee et al., 2011; Wastney et al., 2005; Wastney et al., 1996) (Figure 1). Dynamic functions will be formulated based on previous studies that mathematically modeled Ca metabolism.

The Michaelis-Menten (M-M) equation (Equation 1) is a simple way to describe active Ca absorption in the gastrointestinal tract (Bronner et al., 1986; Raposo et al., 2002). We can separate the small and large intestine (shown as the GI tract in Figure 1) to represent large intestinal fermentation by microbes, which will be added later. The model will be developed for adults, and then expanded to fit adolescents.

$$\text{Ca absorption} = \frac{V^{I}_{Max} \cdot \text{Ca load}}{\text{K}^{\text{I}}_{\text{M}} + \text{Ca load}} + k_i \cdot (Ca \text{ load} - \text{Serum Ca}) \quad (1)$$

where V^{I}_{Max} = maximum Ca absorption, K^{I}_{M} = M-M constant, and k_i = passive Ca constant.

Doty and Seagrave (2000) assumed constant urine excretion, while Raposo et al. (2002) added dynamic functions to model Ca flows in urine, combining the M-M equation and a polynomial function to set the Ca threshold in renal Ca excretion (Equation 2).

$$\text{Urine Ca excretion} = \frac{V^{K}_{Max} \cdot Serum \text{ Ca}}{\text{K}^{\text{K}}_{\text{M}} + Serum \text{ Ca}} \times \left[A \cdot \left(\frac{Serum \text{ Ca}}{Ca_{thr}} \right)^2 + B \cdot \left(\frac{Serum \text{ Ca}}{Ca_{thr}} \right) + C \right] \quad (2)$$

where V^{K}_{Max} = maximum Ca excretion, K^{K}_{M} = M-M constant, Ca_{thr} = renal threshold for Ca, and A, B, and C are constants.

An alternative dynamic function using the glomerular filtration rate (GFR) can be applied to model urine Ca excretion, as GFR represents the amount of filtered Ca in the kidney. Consequently, urine Ca excretion can be formulated as the amount of filtered Ca minus re-absorbed Ca in the kidney, represented by the M-M equation (Equation 3).

$$Urine \ Ca \ excretion = GFR \cdot Serum \ ionized \ Ca - \frac{V^{K}_{Max} \cdot filtered \ Ca}{K^{K}_{M} + filtered \ Ca} \quad (3)$$

Bone Ca accretion was modeled as a function of Ca intake and IGF-1 in Hill et al. (2008). Raposo et al. (2002) used the M-M equation to examine bone resorption, but a simple linear equation for bone formation. Alternatively, bone formation and resorption were modeled as a function of cortisol (Doty and Seagrave, 2000) (Equation 4).

$$\begin{aligned} Bone \ formation &= K_1 \cdot Serum \, Ca \cdot (-A_1 \cdot C + A_2), \\ Bone \ resorption &= K_2 \cdot (A_3 \cdot C + A_4) \end{aligned} \quad (4)$$

where K and A are constants, and C is cortisol.

The dynamic model that was developed is composed of complex functions; therefore, routine computational software is required to solve the model. WinSAAM (Window version of the Simulation, Analysis and Modeling Software, NIH) is a free but powerful tool for Ca kinetic modeling (Lee et al., 2011; Wastney et al., 1999). Since MATLAB (Mathwork™, Natick, MA, USA) is suitable for solving differential equations and enables easy coding due to internal functions and useful toolboxes, it was used to solve the model for the short-term dynamics of PTH in response to acute changes in serum Ca (Shrestha et al., 2010). Furthermore, alternative software developed for solving large-scale differential equations such as Berkeley Madonna, developed at the University of California at Berkeley, and Hummod (Biological Simulators, Inc.) for physiological models are available (Peterson and Riggs, 2010; Raposo et al., 2002).

Integrating the effect of IGF-1 and Ca metabolism to fit adolescent Ca metabolism

IGF-1 increases Ca absorption and bone formation, and is therefore implemented to upregulate Ca absorption and bone formation via the interaction between IGF and BP3 (Figure 2). PTH secretion/action has been previously modeled as a function of serum Ca using the sigmoidal function (Raposo et al., 2002; Shrestha et al., 2010; Wastney et al., 2005) (Equation 5).

$$\text{PTH secretion} = \frac{\text{A} - B}{1 + \left(\frac{Serum\ \text{Ca}}{S} \right)^{m}} + B \tag{5}$$

where A and B are the maximum and minimum levels of PTH, respectively. S is serum Ca at half of A+B, and m is secretion/action sensitivity, which is a function of plasma Ca.

The developed model should be fit to adolescent Ca metabolism using published Ca balance data (Hill et al., 2008). Unknown parameters will be determined by applying the model to determine values that result in accepted metabolic behavior. Finally, the model is able to simulate adolescent Ca metabolism and differentiate it from adult Ca metabolism based on the variables related to IGF-1 action.

Incorporate dietary effects of prebiotics or protein into Ca metabolism to maximize peak bone mass

To incorporate the dietary effects of prebiotics or proteins into the developed model, it is first necessary to collect data regarding prebiotics and microbial community composition dynamics. There are available data reporting the effects of dietary treatment on human intestinal microbial community composition (Whisner et al., 2014; Whisner et al., 2013) and high-throughput pyrosequencing data regarding

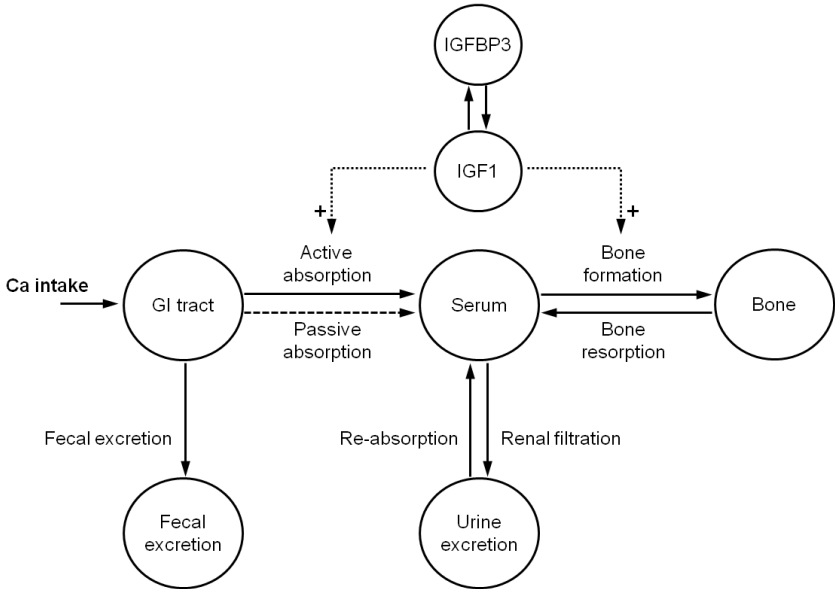

Figure 2. Expanded model of IGF-1 regulatory system on Ca metabolism. IGF-1 will be designed to enhance active Ca absorption and bone formation. IGF-1 pool size will vary between adults and adolescents based on literature estimates. The IGF1 pool will include input and loss pathways (not shown).

the effects of the addition of prebiotics to the diet on the microbial community composition in adolescents and adults (Margulies et al., 2005). These data can be useful additions to the model for identifying microbes involved in the fermentation of prebiotics.

Using the available data, the correlation between prebiotic consumption and microbial community composition can be translated into the model (Kleerebezem and Vaughan, 2009; Rastall et al., 2005), resulting in an equation that describes the increased Ca pool in the gastrointestinal tract, caused by bacterial fermentation. If we can quantify the relationship between dietary protein and serum IGF-1 levels, its connective function can be inserted into the model. Unfortunately, we cannot currently determine the link between IGF-1 and microbes. However, since there is a relationship between IGF-1 and diet, the model will be able to show changes in microbial community composition depending on the diet and IGF-1 levels (Figure 3). The completed model will be used to maximize peak bone mass (i.e., the size of the 'bone' pool, Figure 3) through increased gastrointestinal Ca absorption in response to a change in the microbial community and IGF-1 levels. Based on the optimization, we can suggest experimental designs to test prebiotics and/or dietary protein that may enhance peak bone mass.

As a short final comment on the modeling proposal, it is necessary to verify the model with unused data sets. A set of experiments and literature reviews may be necessary to determine realistic parameter values and mechanistic variables. Otherwise, for unknown parameters, a reverse approach is feasible to optimize parameter values that exhibit the desired behavior and match available experimental results.

Once the model is complete, it will be possible to quantitatively estimate Ca metabolism and to predict optimal Ca utilization for maximizing peak bone mass as a function of IGF-1 and dietary components. This may enable the design of cost-effective experiments to unveil the unique mechanism in adolescent Ca metabolism.

However, there are a few obstacles. First, we are short of available data necessary to define dynamic functions. Second, Ca metabolism varies significantly depending on gender, pubertal state, and race, limiting the applications of the model. Additionally, the model becomes quite complex as numerous parameters and variables are included, requiring sophisticated modeling techniques and a high computational load.

Conclusion

This study aims at proposing a model-based analysis for simulating Ca metabolism in response to IGF-1 and dietary inputs, i.e., prebiotics and protein, to maximize peak bone mass via optimal Ca utilization. To systemically achieve the objective, various studies regarding the effect

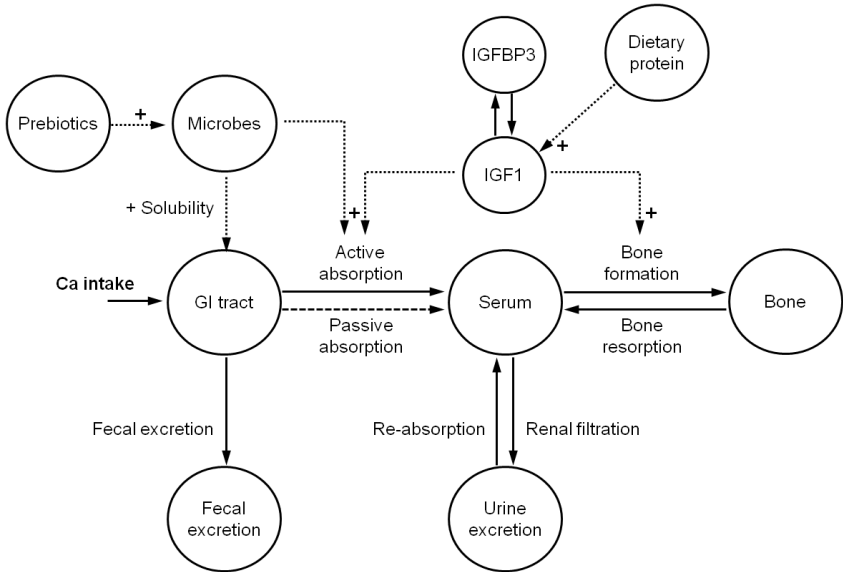

Figure 3. Complete model schematic including IGF-1 action, microbial community, and dietary effect (prebiotics and proteins). As microbes increase Ca solubility in the gastrointestinal tract, the Ca pool in gastrointestinal tract will be designed to change in response to the microbe pool size. In addition to the pathways shown in this figure, the effect of dietary protein on urine Ca excretion may be added to the model.

of IGF-1, prebiotics, and dietary protein on Ca metabolism as well as previous Ca models were reviewed. Then, an approach for constructing a comprehensive model was proposed to explain the unique Ca utilization in adolescents through dietary manipulation. Completion of this modeling will be a breakthrough because no study has explained the differences in Ca metabolism between adolescents and adults in the light of regulatory mechanisms. It will also provide a model-based test for microbial community composition dynamics with respect to diet and IGF-1.

Conflict of Interest

The authors declare no conflict of interest.

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