The effect of Calcium and Sodium Intake on Bone Health

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Abstract. Bone health gets more and more attention in the younger population since the peak bone mass will be achieved during one’s childhood and adolescence. Bone mineral density (BMD), an important indicator, is commonly used to indicate overall bone health. The development of BMD is critical during the growth period, which could contribute to less incidence of osteoporosis as people get old. Osteoporosis is one of the most common bone diseases, which could lead to other health complications. In addition to other factors affecting bone health such as physical activity and hormones, nutrition is the most important factor of bone health. Calcium (Ca) and vitamin D (VD) act hand in hand. The absorption of dietary calcium is highly affected by VD. Different hormones regulate Ca homeostasis and balance in the body. Moreover, bone remodeling is tightly regulated to conserve bone integrity. The bone formation is tightly coupled to the resorption. Dietary intake of sodium (Na) cannot be ignored as well. High intake of Na is negatively associated with bone health. The DASH diet with low sodium intake positively affects bone mineral density to some extent.

Keywords: Bone Mineral Density, Calcium, Vitamin D, Sodium, Osteoporosis.

1. Introduction

Bone health has been aroused attention increasingly, not only in the elderly population, but also in the younger population. Osteoporosis poses a double burden for both the older population and the healthcare system. Osteoporotic fractures decrease life quality and increase mortality risk in the elderly. Peak bone mass will be achieved during one’s childhood and adolescence. The development of bone mineral density (BMD) as people grow becomes essential since it could decrease the possibility of getting osteoporosis in later life [1]. It was suggested that bone health could be described to be a three-legged stool, nutrition (predominantly calcium), hormones (predominantly estrogen), and lifestyle choice (predominantly weight-bearing exercise); these three legs cannot substitute for another and all of them are essential to bone health [2]. It might affect the integrity of the three-legged stool (bone health) if one leg is reduced or removed. A variety of factors could potentially affect the development of bone density during growth and increase the risk of osteoporosis in adulthood [3]. Thus, people should take actions during the growth period, which could have significant effects on BMD, and ultimately overall bone health in adulthood.

Many factors including genetic factors and dietary factors could affect BMD. Calcium (Ca) has already been recognized as a primary factor affecting bone health. The association between intake of Ca and bone health has been studied widely. Calcium homeostasis and balance are regulated tightly to maintain plasma Ca concentration at a constant level. Vitamin D (VD) also plays an indispensable role in overall bone health [4]. VD contributes to efficient dietary Ca absorption. Ca and VD are considered together to investigate their efficacy since each of them requires the other for specific functions and expresses its effects fully. Moreover, the consumption of highly processed foods is increasing remarkably because of the development of technology in food science. The intake of sodium (Na) increases significantly via the consumption of processed foods. More emerging evidence suggests that Na might affect bone health negatively and potentially increases the risk of osteoporosis [5]. High Na intake might increase urinary Ca excretion (calciuria), thereby disturbing Ca balance. The objective of this article is to specifically analyze the metabolism of calcium and sodium in the body, and to investigate how calcium and sodium affects bone health.
2. The Impact of Calcium on Bone Health

2.1. Calcium Balance and Homeostasis

Calcium takes an essential role in a series of biological processes of the body, including skeletal mineralization. The concentration of blood Ca ranges between approximately 8.8 and 10.4 mg/dl for healthy people [6]. The total serum Ca concentration exists in the three forms: ionized calcium (~55%), ionic complexes (~10%), and protein-bound complexes (~35%) [7]. Non-protein-bound Ca can be filtered by the glomerulus for renal reabsorption. Calcium homeostasis and balance are critical for bone health. Ca balance is the state of Ca stores in the body, primarily stored in the bones as hydroxyapatite $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$, due to the overall impacts of intestinal absorption, urinary excretion, endogenous secretion, and bone turnover [8].

Calcium homeostasis is the maintenance of extracellular Ca concentration by controlling Ca transport in the intestinal tract, kidney, and bone via the integrated actions of hormones [6]. Parathyroid hormone (PTH), calcitriol, and calcitonin are the three fundamental Ca regulatory hormones. The disruption of calcium homeostasis could lead to hypercalcemia and hypocalcemia. PTH is a hormone generated and secreted by the parathyroid gland [9]. The release of PTH by the parathyroid gland into the blood is signaled by low blood calcium (Hypocalcemia). PTH affects the Ca concentration directly by binding bone cell receptors to increase resorption of breakdown of bone mineral to release Ca from bone, and by increasing Ca reabsorption in the kidney tubular cells. PTH also promotes the production of $1,25(\text{OH})_2\text{D}_3$, the activated form of VD [9]. The enzyme 1α-hydroxylase helps to hydroxylate $25(\text{OH})\text{D}_3$ into active calcitriol. Calcitriol stimulates the synthesis of calbindin, a class of Ca binding proteins, which helps absorption of Ca across the brush border membrane of intestinal cells [10]. Thus, PTH also promotes Ca absorption from the intestine indirectly through calcitriol. PTH accounts mostly for the minute-to-minute control of plasma Ca concentration while calcitriol accounts mostly for the day-to-day control [11]. Figure 1 provides a visualization of how PTH and calcitriol regulate blood calcium regulation when blood calcium concentration is low [10]. In the thyroid gland, one of the peptide hormones generated by the C-cells named calcitonin, is another essential Ca regulating hormone [12]. Its secretion is stimulated when serum Ca concentration is high. Calcitonin exerts opposite effects of PTH, which increases bone mineralization and deposition of Ca for storage, and reduces Ca absorption from the kidneys. Therefore, calcitonin could contribute to the prevention of the development of hypercalcemia. These three calcium regulatory hormones predominantly help to maintain the plasma Ca concentration constant together.

![Figure 1. Parathyroid hormone and calcitriol regulate blood calcium concentration to avoid low blood calcium levels [10]](image-url)
2.2. Bone Remodeling

Bone remodeling is a tightly regulated process of osteoblasts and osteoclasts forming and resorbing bone [11]. The resorption of bone by osteoclasts and the creation of bone by osteoblasts are inextricably linked. This carefully controlled cycle repairs bone defects and maintains Ca levels in the blood optimal. Disruption of the bone remodeling process or a slight imbalance between bone destruction and formation could lead to decreased bone mineral density and metabolic bone disease such as osteoporosis. The remodeling cycle comprises mainly five steps: activation, resorption, reversal, formation, and termination over 120-200 days [13].

2.3. Osteoporosis

Osteoporosis is a serious bone disease, which contributes to lower bone mass and compromised bone strength, which could ultimately result in a variety of health complications [14]. It gets attention that the development of BMD in younger age might attenuate the incidence of osteoporosis as getting old [1]. Two primary causes of low BMD in the elderly: (a) inadequate attainment of maximum peak BMD in younger age; and (b) failure to maintain bone mass and bone strength as aging. Research stated that initial bone mass has a significant impact on the quantity of bone mass in later life [1]. In addition to doing some weight-bearing activities regularly, adequate Ca intake is highly related to elevated BMD, especially in children and adolescents, since substantial BMD and bone mineral content (BMC) gains are present in early life. One research conducted in 373 healthy young girls suggested that a positive correction was found in Ca intake and BMC, BMD [15]. Another cross-sectional study conducted in Korea between 2008 and 2010 in 3448 men and 3812 women who are beyond the age of 50, revealed that Ca is essential for preventing low BMD and decreasing the incidence of osteoporosis during aging [4]. This study also showed that even a small dose of Ca supplementation might be beneficial for slowing bone loss in individuals with low dietary Ca intake. Moreover, it illustrated that VD also contributes to protecting the skeleton by compensating the adverse impacts of low dietary Ca intake on overall bone health [4].

2.4. Association Between Calcium and VD

Both Ca and VD are directly related to bone health. It suggested that VD helps effective Ca absorption. More evidence showed that they are more effective when used in combination [16]. They act in two ways: (a) neutralize the obligatory losses of Ca from the body; (b) decrease excess bone remodeling. As previously mentioned, bone mineralization will occur to keep serum Ca level within the common range if there is no adequate supply of Ca from the diet. It is well established that menopause contributes to bone loss in adult women. Bone remodeling rate doubles across menopause, and triples at the age of 65 years, and remains elevated in osteoporosis [17]. Bone remodeling is considered as an osteoprotective process since it is necessary for replacing old bone with new bone. However, it appears to be not beneficial when the rapid bone remodeling in the midlife is driven by hormonal changes rather than by the requirement of repairing the damaged bone [16]. The rate of bone remodeling could be reduced if both Ca intake and VD increases due to the reduced secretion of PTH. Ca alone acts via passive transport if the Ca intake can be in excess of 3000mg/d, but VD used in combination with Ca could help this process by facilitating active Ca transport [16]. Moreover, the serum VD concentration promotes Ca absorption rather than the oral dose of VD [16]. It is possible for people to have a normal VD level if people do not have any dietary intakes of VD. The majority of VD used by the body comes from cutaneous synthesis during exposure of sunlight. Aging, time, environment, skin, and sunscreen have significant impacts on the cutaneous synthesis of VD [18]. Figure 2A shows serum VD levels for people with and without the use of sunscreen after the exposure of 1 minimal erythemal dose (MED). Figure 2B shows serum VD level after the exposure of 1 MED to the whole-body for healthy young people and the elderly. Furthermore, the body needs VD to absorb Ca. People could have insufficient Ca absorption from the diet if they do not have adequate serum VD level [19]. A study was conducted in 34 postmenopausal women to analyze Ca absorption at two different VD concentrations in Omaha, Nebraska [19]. Ca absorption was 65
percent higher at 86.5 nmol/L serum VD concentrations than at 50 nmol/L serum VD concentrations, according to this study. As a result, serum VD levels have a beneficial effect on Ca absorption.

Figure 2. A: Serum VD levels for people with and without sunscreen after the exposure of 1 minimal erythemal dose of simulated sunlight. B: Serum VD levels after 1 MED exposure to whole body for young and older populations [18]

3. The Impact of Sodium on Bone Health

3.1. Sodium Metabolism

Sodium is one of the important minerals for people since it plays an essential role for maintaining osmotic homeostasis and fluid balance. Fluid balance is required for osmotic homeostasis, and ion transport is required for fluid balance. If someone has a higher daily Na consumption, which has been seen to bear a series of health problems, including stroke, hypertension, and cardiovascular disease. It is recommended that Na intake should be between 1000-1500 mg per day and should not eat more than 2300 mg Na per day in the US [20].

The kidneys are responsible for the maintenance of osmotic homeostasis by regulating both water and electrolytes balance, controlling blood pressure, secreting hormones, and regulating acid-base balance [21]. Each nephron (kidney’s functional unit) is composed of a glomerulus, and a long folded renal tubule. Precise mechanisms for solute transport could vary depending on the different parts of the nephron, so the filtrate composition varies when it flows through different segments [21]. Selective permeability in the countercurrent multiplier system (Loop of Henle) and passive diffusion in the countercurrent diffusion system generate and sustain the osmotic gradient (vasa recta) [22]. Water and solutes from the loop of Henle move into the blood vessel (vasa recta).
Different hormones work together to help maintain osmotic balance and blood pressure in the body. Different fragments of the nephron have specialized cells that have different receptors to respond to hormones. Aldosterone conserves water via Na reabsorption and potassium excretion using Na/K exchange channels by acting on the late distal tubule and the collecting duct of nephrons [23]. Aldosterone secretion increases the amount of Na channels and Na/K pumps, which leads to the influx of Na into cells, and Na will be pumped into the blood by the activated mechanism [23]. Overall, the net effect is retention of both salt and water and excretion of potassium into the urine. Aldosterone is also part of the renin-angiotensin-aldosterone system (RAAS). RAAS regulates aldosterone release from the adrenal glands. RAAS normalizes the blood pressure and volume if the arterial blood pressure is decreased [24]. Decreased blood pressure activates the cleavage of prorenin to renin, which is contained in specialized cells, juxtaglomerular (JG) cells in the afferent arterioles of the kidney. Angiotensinogen in the liver will be converted to angiotensin I by renin, and then catalyzed to angiotensin II by angiotensin converting enzyme (ACE) in the capillary endothelial cell of the lungs and kidneys [24]. The binding of G protein-coupled receptors by angiotensin II results in a secondary messenger cascade. Figure 3 shows the generation of angiotensin II from the prohormone angiotensinogen [25]. The vasoconstriction and aldosterone-secreting actions of angiotensin II are mainly regulated through angiotensin receptor type 1 (AT1) [26]. Angiotensin II stimulates the release of ADH by the posterior pituitary. ADH increases the transcription of aquaporin-2 gene, so the intracellular pool of aquaporin-2 channels then inserts into the apical side of the principal cells in the distal tubule or collecting duct [24]. Water floods into the principal cells via those aquaporin-2 channels, and rapidly exits cells into the blood via aquaporin-3 channels in the basolateral side. Overall, those hormones act together to increase body Na and conserve body water in response to decreased blood pressure or severely dehydrated (hypovolemia).

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Figure 3. Synthesis of biologically-active angiotensin II from angiotensinogen [25]

3.2. Relation Between the Renin-Angiotensin System (RAS) and Bone Metabolism

A study on a high renin and angiotensinogen mouse model and an infusion of angiotensin II in rats without ovaries showed that bone remodeling is also highly regulated by the renin-angiotensin system (RAS) [27]. It was also shown that RAS is involved in activation of osteoclast [28]. The activation of RAS could lead to osteoporosis by elevating osteoclastic bone resorption [27]. Furthermore, angiotensin II induces osteoclast activation, so angiotensin II receptor blockers help decrease the risk of osteoporosis [24]. Absence of angiotensin receptor type 1 could also improve bone strength [29]. Moreover, another study was conducted in 3887 Chinese people beyond 65 years old to investigate
how ACE inhibitors could affect BMD. This study suggested that ACE inhibitors could improve bone metabolism [30].

3.3. Association Between Sodium and Calcium for Bone Health

Hypertension (high blood pressure) is related to irregular calcium metabolism which could result in elevated Ca loss and increased release of Ca from bone, so hypertension increases the risks of suffering from osteoporosis [31]. Blood pressure is negatively associated with BMD, thereby sustained hypercalciuria in patients with hypertension increases bone mineral loss [28].

A randomized, repeat cross-over trial was conducted in postmenopausal women to investigate adaptive mechanisms if dietary sodium and calcium intakes were changed [32]. This study showed that moderately high Na intake raises urinary Ca excretion significantly with a p-value of 0.0008. Also, it stressed that low intake of Ca induces negative bone Ca balance with either high or low Na intake, whereas Na accounts for the change of Ca balance in the bone from positive to negative if the Ca intake is high [32].

Some studies showed that high Na intake could increase urinary Ca excretion (calciuria), thereby the calcium metabolism will be disturbed and bone loss will be increased, especially if the Ca intake is inadequate [5]. The DASH diet focuses on the importance of vegetables, fruits, and whole grains. The diet contains enough Ca and potassium, but low in salt, sugar, and fat contents. The DASH diet has been shown to effectively control blood pressure. A study investigated the effects of DASH and control diets (what Americans typically eat) and three Na levels (50, 100, and 150mmol/d) on bone and calcium metabolism [5]. This study demonstrated that the DASH diet could reduce bone turnover, in turn affects the status of bone positively, and decrease the risk of osteoporosis. Therefore, the DASH diet and reduced dietary Na intake could exert positive impacts on bone health [5]. Many factors including higher intakes of Ca and potassium, and antioxidants or phytochemicals could be the reason why the DASH diet has a beneficial impact on the health of bone.

4. Conclusions

The development of BMD during growth is important since the peak bone mass is achieved at this time. A variety of factors could contribute to the health of bone. Calcium is the primary factor affecting bone health by regulating calcium homeostasis and balance. The primary regulatory hormones are parathyroid hormone, calcitriol, and calcitonin. Furthermore, when VD is combined with Ca, it may aid in the absorption of dietary Ca from food. Positive serum VD status contributes to good Ca absorptive performance. In addition to Ca and VD, dietary Na has an impact on bone health. Bone remodeling is also highly regulated by the renin-angiotensin system. The activation of RAS leads to osteoporosis by inducing osteoclast activation. Moreover, hypertension could potentially increase the incidence of osteoporosis. Blood pressure is negatively associated with BMD. Urinary Ca excretion could be elevated by high salt intake. The DASH diet with lower salt intake influences bone health positively. Thus, it is essential to regulate dietary Na intake tightly in addition to adequate Ca intakes. Physical activity helps to conserve bone mass. It has been recommended to participate in weight-bearing activities and have a balanced and nutritious diet with adequate levels of calcium.

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