

## **Calcium, Osteoporosis Treatment, the Women's Health and the Future Development of Calmodulin**

### **鈣、骨質疏鬆症治療、婦女健康和鈣調蛋白的未來發展**

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### **ABSTRACT**

Osteoporosis is a common disease especially among the elderly female demographic. Its occurrence can be found in cross-culture, region, and social status. There are several treatments existed with proven result to manage the symptom of osteoporosis, and a new research area on calmodulin is emerging. The underlying cause is calcium deficiency, and it ties closely to women in different stages of their life. At each stage, calcium is used for different functions and without sufficient supply, the continuous expenditure on the body's calcium deposit will eventually result in osteoporosis.

**Keywords: osteoporosis, calcium deficiency, women's health, nutrition supplement, calmodulin.**

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## 摘要

骨質疏鬆症是一種常見疾病，尤其是在老年女性人群中。它的發生是跨文化、地區和社會發展的。已有多種治療方法能有效地防止骨質疏鬆症，鈣調蛋白正成為一個新的研究領域。根本原因是鈣不足，它與女性的生活不同階段密切相關。在每個階段，鈣都有不同的功能，並且鈣供應不足，加上人體的持續消耗，最終將導致骨質疏鬆症。

**關鍵詞：**骨質疏鬆症、鈣缺乏症、婦女健康、營養補充、鈣調蛋白

## 1. Introduction

Men and women have different physiologies, thus different types of nutrition may have different levels of impact on their health supports. If you want to name one nutrient that is critical to life support, calcium is likely to be many experts' answer. It is a mineral with the largest amount of deposits in the human body which is in the bones. Calcium plays a role in human life since the fetus stage, its function continues when people reach adolescence, maturity and elderly time of their life. Calcium is particularly important for women's health throughout their life stages. Calcium's complex functions (digestive, nerves, muscles, immune, hormone, enzyme, circulatory, bone) aside (Zhang, 2010), this article will focus on the relationship between women's health and calcium; and the treatment for one of the common diseases caused by calcium deficiency among the elderly female population, Osteoporosis.

## 2. Calcium for Women

Calcium is particularly important for women, it is a critical mineral required through different stages of a life time. On average, a newborn baby has about 25-30 gram of calcium in the body, all the calcium come directly from the mother. 30 grams of calcium is equivalent to about 4% of a mother's calcium count. Therefore, a pregnant woman will have calcium loss if she fails to intake enough calcium to compensate for the loss of calcium to supply the baby's nutrition. The hormone change during pregnancy also increases the speed of calcium loss (WHO, 2013). All the losses of calcium without adequate intake lead to weaken the bone density. "The general definition of osteoporosis is "a skeleton condition characterized by decreased density (mass/volume) of normally mineralized bone. The reduced bone density leads to decreased mechanical strength, thus making the skeleton more likely to fracture" (Glaser & Kaplan, 1997).

Calcium is also very important for breastfeeding. A baby needs a certain amount of calcium to grow healthily, and the supply comes from the mother's breast milk where the milk's calcium content is drawn from the mother's body. Thus, when a woman does not have enough calcium intake during the pregnancy and the breastfeeding period; she will face a significant risk of osteoporosis in the later stage of her life (National Health

Institute, 2018a). There are significant differences in the percentage of men and women who are at risk of osteopenia and osteoporosis. For example, Alswat (2017) pointed out the likelihood to suffer from osteoporosis over the age of 50 is four times higher for women than men.

Table 1 Recommended Dietary Allowances for Calcium by National Institute of Health, U.S. Department of Health & Human Services (National Institute of Health, 2018b; 2020)

<b>Age</b>	<b>Male</b>	<b>Female</b>	<b>Pregnant</b>	<b>Lactating</b>
4–8 years	1,000 mg	1,000 mg	-	-
9–13 years	1,300 mg	1,300 mg	-	-
14–18 years	1,300 mg	1,300 mg	1,300 mg	1,300 mg
19–50 years	1,000 mg	1,000 mg	1,000 mg	1,000 mg
51–70 years	1,000 mg	1,200 mg	-	-
71+ years	1,200 mg	1,200 mg	-	-

Table 2 Recommended Dietary Allowances for Calcium by The National Academies Press (Institute of Medicine, 2011)

<b>Age</b>	<b>Male</b>	<b>Female</b>	<b>Pregnant</b>	<b>Lactating</b>
4–8 years	1,000 mg	1,000 mg	-	-
9–13 years	1,300 mg	1,300 mg	-	-
14–18 years	1,300 mg	1,300 mg	1,300 mg	1,300 mg
19–50 years	1,000 mg	1,000 mg	1,000 mg	1,000 mg
51–70 years	1,000 mg	1,200 mg	-	-
71+ years	1,200 mg	1,200 mg	-	-

Table 3 Recommended daily calcium requirement by Dietitians of Canada (Dietitians of Canada)

<b>Age</b>	<b>Male</b>	<b>Female</b>
19–50 years	1000 mg	1000 mg
51–70 years	1200 mg	1200 mg
71+ years	1200 mg	1200 mg

The tables above show similar recommended daily allowances for calcium from different institutions. Among the research found, the World Health Organization's recommendation has the least amount of calcium for daily intake, which is only 500 mg per day (WHO, 2004a), and Harvard University's Harvard Women Health Watch agrees with WHO's recommendation (Harvard Medical School, 2019).

Women grow from infant to adolescent and from pregnancy to menopause age, calcium plays an important role in every stage's health support. It is recommended to pay more attention to the calcium supplement intake on a regular basis. Although there is not a unified recommendation of calcium intake amount for each age group across the world, the recommended daily dose from different scientific research institutions are in a close range. From the public health perspective and its wide range of benefits, we recommend health care practitioners to emphasize to the public the importance of having enough calcium intake to maintain good health status.

## **2.1 Osteoporosis among women in Taiwan**

Taiwan's society becoming super-aged is now imminent, a media, Focus Taiwan, cited the National Development Council's (NDC) report stating Taiwan's population will be super-aged by 2025 (Focus Taiwan, 2020). Aging is directly associated with osteoporosis particular for women over the menopause age due to the estrogen level drop. The prevalence of osteoporosis for postmenopausal women shall not be overlooked (Ji & Yu, 2015). In the previous section, the importance of calcium is discussed for its critical role in bone's health which determines the possibility of developing osteoporosis. In this section, the state of osteoporosis among women in Taiwan is examined to present the situation's severity.

The total population of Taiwan is approximately 23.2 million and 48% are the female population. It is estimated that 2.78 million of women are experiencing menopausal transition and another 2.75 million of women are already in the menopause stage of their life (The Taiwanese Menopause Society, 2016). With this number in mind, there are almost a quarter of the population of Taiwan is prone to osteoporosis. It is a serious issue to consider from the public health point of view. The Ministry of Health and Welfare concluded from a census that 80% of the patients that are diagnosed with Osteoporosis are women (Chou & Yang, 2018). The percentage of women developing osteoporosis is far greater than men's, there are few causes may contribute to this difference.

Men's bone mass density is typically better than women's, and the speed of women losing bone mass increases drastically after they enter the menopause phase; both contribute to the fact that there are much more women having osteoporosis than men do (National Osteoporosis Foundation, 2021). Another reason is the life expectancy for woman is longer than man's, it means women will have to face the threat of osteoporosis

for a longer period of time in their life. Diet composition may also play a role in Taiwanese' osteoporosis development, the consumption of dairy product is merely half of the western counter-part. It could be directly tied to the prolonged insufficient calcium intake level which leads to the development of osteoporosis (Chou & Yang, 2018).

The first step of diagnosing osteoporosis is to measure a patient's score (American Bone Health, 2016). In "Taiwan Osteoporosis Practice Guidelines" published by Bureau of Health Promotion, it claims that the widely used "T-score" suggested by the World Health Organization (WHO) as a mean to diagnose osteoporosis is only applicable to certain ethnicities such as Caucasian women; yet it remains to be a sound methodology for establishing reference values. Unfortunately in a clinical setting, osteoporosis is usually identified after patients suffers from fragility fracture. It became an acceptable practice to diagnose osteoporosis without using the T-score and this approach is recognized by the North American Menopause Society (Bureau of Health Promotion, 2012).

To look at the number from an international perspective, International Osteoporosis Foundation identified that 1 in every 3 women worldwide over age of 50 will experience osteoporosis fractures in their remaining life time and secondary fracture is always a threat after the primary fracture (Sozen, Ozisik, & Basaran, 2017). National Osteoporosis Foundation also claims that the risk for women suffering from a hip fracture is equal to the risk of suffering from breast, uterine, and ovarian cancer combined (National Osteoporosis Foundation, 2021). Women at age of 50 years have twice of the probability to suffer from osteoporotic fractures than men according to the World Health Organization (2004b), Another study estimated that there are 41 million women are affected by osteoporosis related issues worldwide (Kass-Wolff, 2004).

There are three locations where osteoporosis-related fractures often occur, spine, femoral neck, and wrist. Spine fracture refers to the deformity of the spine since it can no longer support the body weight due to bone density loss. Femoral neck or hip fracture are associated with a higher mortality rate. Wrist fracture is usually caused by one attempts to support themselves when falling down. According to the Bureau of Health Promotion's study across major cities in Taiwan, the result indicated the occurrences of hip or spine fracture were higher than the world averages for the middle-aged and mature population (Bureau of Health Promotion, 2012; Chou & Yang, 2018).

Clinically, osteoporosis' occurrences seems inevitable for a great portion of the men and women population worldwide. In the Taiwan Osteoporosis Practice Guideline, there is a chapter dedicated to discuss possible approaches to prevent and treat osteoporosis without the use of medication. Using medication to treat osteoporosis is often the last measure because its effectiveness and the possible side-effects preventing it from being the best course of action. The notable approaches recommended by the practice guide are

diet, exercise, and lifestyle. The main intakes recommended are calcium, vitamin D and K, phosphorus, protein, and dairy products for diet because they are the main drive to aid the maintenance of the bone mass. (Bureau of Health Promotion, 2012). Different levels of weight-bearing exercises are important for its evidence of improving one's bone mineral density (BMD) in body parts that are vulnerable to osteoporosis such as lumbar spine, proximal femur, and femoral neck (Brahm, Strom, Piehl-Aulin, Mallmin, & Ljunghall, 1997). In terms life style, the guideline promotes having healthier habits' direct link to one's wellbeing. Avoiding smoking and the consumption of alcohol are encouraged; and it identified the body mass index (BMI) between 18.5 to 24 is the ideal range for the Taiwan population. Even though the guideline claims that a higher body weight will result a healthier and higher bone mass, to take other weight related chronic diseases into account, the recommended BMI range is 18.5 to 24 (Bureau of Health Promotion, 2012).

There are evidences worldwide showing the threat of osteoporosis to women as presented in the previous section. Due to the nature of the disease's pathology, osteoporosis prevention measure seems to be the key to diminish the potential consequences from the diseases whether than the treatment itself. The comment treatment measures for osteoporosis may have their merits, yet it is still an irreversible disease. The modern medicine is now investigating a new page of osteoporosis research and attempt to develop an even more effective treatment.

### **3. Osteoporosis' Treatment and the Future Direction**

Osteoporosis occurs when the balance of osteoclast and osteoblast is compromised due to various reasons such as environment, habits, genetic, disease, and malnutrition. Osteoporosis' treatment has been developed over the past few decades to regulate the process of osteoblast and osteoclast. Traditionally, hormone treatments and nutritional support are more common methods of treatments for osteoporosis and osteopenia. From a study in Taiwan, the researchers examined the latest developments in the treatment method of osteoporosis and their merits as well as the side-effects.

The researchers identified estrogen or hormone replacement therapy is one of the common clinical options to relief the postmenopausal symptoms and it also has the effect of increasing bone mass density. However, administering estrogen or hormone replacement therapy over a period of time will increase the risk of cancer development (breast) and other female hormone-related diseases especially for elderly women (Chen, Ko, & Chen, 2019). Another treatment is to use bisphosphonates compound which can effectively inhibit osteoclast and increase the bone density. However, bisphosphonates' effectiveness on osteoporosis patients and osteopenia patient are different; and the prolonged use of bisphosphonates also have negative impacts (gastrointestinal issues,

inflammation, ulcers) on patients' health. A usual practice is to discontinue bisphosphonates intake for a few years and the research has evidence to prove it would not affect the patients' bone health after the discontinuation. Some researchers even concluded the negative side effect of the drug may offset the positive effect of the drug (Boskey, 2013).

Selective estrogen receptor modulator (SERM) is a therapy particularly effective against vertebral fracture. It targets the estrogen receptor in the bone thus reducing the side effect of taking the medication. Yet, its overall efficiency may not be as good as estrogen therapy. Also, the parathyroid hormone has a direct contribution to regulating bone's calcium metabolism. Finally, vitamin D and Calcium supplements are often alternatives to medications (Chen, Ko, & Chen, 2019).

In Taiwan, other than nutritional support, the medication prescribed to osteoporosis patients aim to either achieve anti-osteoclast or activating osteoblast. For anti-osteoclast medication, they include calcitonin, bisphosphonates, SERM, osteoclastic enzyme inhibitors, and RANKL monoclonal antibodies. The osteoblast activators may include parathyroid hormone (PTH) whereas the strontium has effects on both osteoclast and osteoblast activities (Bureau of Health Promotion, 2012).

### **3.1 Future direction: Calmodulin**

Human's bone is constantly undergoing the process of osteoblast and osteoclast. It is the bone remodeling process which controls the growth of the bones. The speed of osteoblast is faster for children and teenagers than osteoclast so their bone grows faster and they grow in height. When one grows older, the speed of osteoclast and osteoblast are close thus humans stop growing. Finally, when one reaches an older age around 50, the speed of osteoclast will take over and osteoblast will not be able to catch up, it is when one starts to lose calcium at a significant speed. It is the reason why aging is one of the major causes of osteoporosis. In recent year, some researches revealed the critical rule that calmodulin plays in the bone remodeling process (Cary et al, 2013); it is a new direction for the study in this field.

Calmodulin is a protein which has a calcium regulation function. This function ensures the balance of calcium level in the human body and the proper performance of calcium-dependent physiological processes. There are researchers who found that calmodulin has a potential therapeutic effect in the clinical treatment of osteoporosis by stimulating osteoblast while inhibiting osteoclast. This is a very important finding for future research if the nature of how calmodulin behaves in the human body can be fully analyzed and proven its benefit to prevent and treat osteoporosis (Chen, Ko, & Chen, 2019).

Calmodulin acts as the primary intracellular calcium receptor which is heavily

involved in the entire osteoclast process for many aspects. Other than the known fact that calmodulin's function of anti-osteoclast can preserve bone mass, another direction of utilizing calmodulin's property is discovered (Seales, Micoli, & McDonald, 2006). A hypothesis of calmodulin can prevent bone loss by enhancing osteoclast apoptosis has new value to osteoporosis therapy. It has a similar effect to the existing bisphosphonates treatment which is able to simultaneously promote the apoptosis of osteoclasts while preventing the osteoblast from apoptosis (Plotkin et al., 1999).

To take a closer look at calmodulin, there is an international patent, international publication number WO 03/061565 A2 from the World Intellectual Property Organization. It specifically explained the use of calmodulin can promote bone regeneration. Its summary claims orally administered calmodulin is effective in promoting bone regeneration for the subject with osteoporosis, osteopenia, or suffering from non-union bone fracture (Mcmichael & Gurney, 2003).

There is also a study explaining the calcium-binding protein, calmodulin's role in the osteoblast and proliferation process. The researcher of this article concluded most of the treatment for osteoporosis targets the osteoclasts process; however, they found there is a real potential on the osteoblast proliferation process through calcium signaling to be an effective treatment of osteoporosis. Calmodulin plays a critical role during the calcium signaling process (Zayzafoon, 2006). There are other studies on Calmodulin as well. Research found in a lab experiment indicates calmodulin inhibits mouse osteoclastogenesis in vitro in a controlled manner (Zhang, Feng, & McDonald, 2003). More studies also thoroughly explained calmodulin inhibiting ability in osteoclast (Seales, Micoli, & McDonald, 2006; William, Micoli, & McDonald, 2010).

#### **4. Conclusion**

The authors first presented an overview of the relationship between the women's health and calcium as well as the state of osteoporosis in Taiwan. Osteoporosis is a chronic disease threatening women near and after menopause due to the nature of physiology; a much smaller men population is affected by osteoporosis. Even with the modern medicine and the developed medical system, there is no cure to the disease, active preventions via various means are recommended by the authorities and research organizations such as the World Health Organization and International Osteoporosis Foundation. In Taiwan Osteoporosis Practice Guidelines, nutritional support including calcium is highly recommended for the at risk group, strengthening bone mass through nutrition, exercise, and healthy living habits are the key before medicines need to be introduced to the treatment.

Despite the fact that there are several approved medications with proven positive effects on osteoporosis treatment, the influences and side effects under the prolonged



exposure to such drugs are still adverse to the human body. The key to prevent osteoporosis and osteopenia is bone mineral density, hence the bone's health; and one of the keys to the bone's health is still calcium intake. Besides nutritional support, some common osteoporosis medicine's function is to inhibit osteoclast process while the others' are to promote the osteoblast process. They aim to manage the imbalance between these two natural bone formation processes in order to achieve preserving more bone mass than losing it.

In recent years, the studies on calmodulin may shed the light to the field of bone biology. So far, calmodulin's role and function are becoming clear to the scientists. Yet, a more comprehensive analysis are still required to enable calmodulin's application becoming clinically valuable. Future researchers are encouraged to investigate the behavior of calmodulin and its clinical value for osteoporosis prevention and treatment.

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