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停經後骨質疏鬆婦女運動訓練計畫之效果與成本評估

Effectiveness and Cost Analysis of Exercise Programs for Postmenopausal Women with Osteoporosis

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本論文係李瑋君君（D94428005）在國立臺灣大學物理治療學系暨研究所完成之博士學位論文，於民國 100 年 7 月 29 日承下列考試委員審查通過及口試及格，特此證明

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中文摘要

隨著老年人口的快速增加，骨質疏鬆已成為一個全球性的公共衛生課題，亞洲地區及台灣也不例外。骨質疏鬆病患骨密度會降低且骨組織構造會受到破壞，導致骨頭變得較脆弱，容易引發骨折，而骨折後所引發的相關併發症與後遺症往往帶給醫療及社會相當大的成本與負擔。運動治療無副作用，對於這類病患是極被推薦的非藥物性治療方式，運動對於增加骨密度、減緩骨流失、預防跌倒等成效已被很多研究證實，但對於不同運動介入方式所產生之效益的研究則頗為有限。對於醫療提供者而言，如何能達到有效益又可節省成本是重要的考量。因此，本研究之目的為：研究一，探討不同運動介入方式，包含居家運動組、群體運動組及衛教組之療效差異；研究二，比較三種執行方案之成本效益。

研究一設計為前瞻性隨機分組臨床試驗，共徵召 87 名 50 歲以上停經後骨質疏鬆婦女以隨機分組介入的方式，探討居家運動組、群體運動組及衛教組之療效差異，運動介入時間為三個月，在介入前、介入停止後及追蹤至一年各有一次評估，評估項目包括：骨密度(於 6 個月時做第二次評估)、肌力、平衡能力、功能活動、生活品質、與跌倒次數。資料分析以 SPSS 11.0 版本作為統計分析之工具，所有分析之 α 值定在 0.05。將以敘述性統計呈現三組基本資料的特性；以 Kruskal- Wallis test 檢測三組在各個不同時間點組間之差異。以 Friedman test 檢測各組在不同時間點之組內差異。研究二進行上述三方案之成本效益分析：成本為執行方案所需之經費，效益為骨密度、肌力、平衡能力、功能活動、生活品質及跌倒次數之改變；以及與衛教組比較所增加之成本效益比。

研究一結果顯示，各組在運動介入後大部分變數均有進步之趨勢。在各個不同時間點，三組間在各變項均無顯著差異($p > 0.05$)。故將三組結果加以整合分析，結果顯示上肢抓握力相較於第一及第二次測試，在第三次之測試有顯著進步；功能活動、平衡及整體生活品質表現，第一次與第二次及第三次之測試間有顯著進步。而跌倒的人次，在介入完成後半年內三種執行方式均有明顯減少。

研究二結果顯示，對於提高病患生活品質而言，居家運動為三種模式中最符合成本效益之方式。而對於跌倒的預防，衛教組最具成本效益。當以不同方式支付治療費用及不考慮產值損失時，敏感度分析結果並未改變。然而不考慮產值損失時，居家運動組幾乎為大部分變項中最具成本效益的介入模式。

由介入結果可提出結論，三種不同運動執行方式對功能活動及減少跌倒的效益是相近的，未來對於此類病患教導其執行居家運動並給予完整的疾病相關衛教應是避免骨質疏鬆及預防跌倒的有效方式。若加入成本之考量，衛教及居家運動皆為較符合成本效益的執行方式。

關鍵字: 骨質疏鬆、停經後婦女、衛教、居家運動、群體運動、成本效益分析

Abstract

Elderly population is rapidly increasing in number and proportion, osteoporosis has become a major global public health issue, including Asia and Taiwan. Osteoporosis is a systemic disorder and is characterized by low bone mass, leading to bone fragility and an increased susceptibility to fractures. The complications and sequelae that coming with osteoporotic fractures always cause great burden to the society and medical care system. Many studies have proven that exercise can improve the bone mineral density, decrease bone loss, prevent fall and so on. However, most studies focused on the effects of different types of exercises, few studies compared the therapeutic effects among different delivery modes. To the medical providers, what is the most cost-effective program is important. The purposes of this thesis are as follows: Study 1: To compare the effectiveness of home-based exercise, group exercise and education group. Study 2: To conduct a cost-effectiveness analysis (CEA) for the 3 programs and the incremental cost effectiveness analysis (ICEA) comparing with the education group.

Study I was a prospective randomized controlled trial. Eighty seven postmenopausal women with osteoporosis and age older than 50 years old were recruited. They were randomized into home-based exercise, group exercise or education group. The intervention was for 3 months, evaluation was done before and after the intervention and one year after starting the program. The outcome measures included: bone mineral density (BMD: the second evaluation was done at the 6^{th} month), muscle strength, balance, functional mobility, quality of life, and numbers of fall. Data was analysed using the 11.0 version of SPSS and α was set at 0.05 for all analyses. Descriptive statistics was used to show the baseline characteristics of the three groups. Kruskal–Wallis test was used to compare difference among groups. Friedman test was

used to analyze the differences among all three time points within the groups. Study II, a CEA and ICEA for the 3 programs was executed. The cost was based on the budget for performing the programs, and the effectiveness was measured including the changes in BMD, muscle strength, balance, functional mobility, quality of life, and numbers of fall.

The result of study I showed that three groups had a trend of improvement in most outcomes. There was almost no significant difference among three groups at each time point ($p > 0.05$). The data of all modes was pooled together, the results showed that grip strength had significant improvement at 12- month follow- up comparing to baseline and 3- month assessments; functional mobility, balance (using one leg standing with eyes opened), and total score of Qualeffo- 31 all showed significant improvements between baseline and 3- month and between baseline and 12- month assessment ($p < 0.05$). All fall numbers of 3 modes declined till half year after intervention.

The results of study II showed that home- based exercise was the most cost effective one among 3 delivery modes of exercise for improving QOL. For fall prevention, education program might be the most cost effectiveness program. The sensitivity analysis was conducted, the results did not change. However, if the productivity cost was neglected, home- based exercise was the most cost- effective option in most variables.

We concluded that all 3 modes of exercise could get similar effects on mobility and lowering the fall risk. A comprehensive education program with home exercise

program may be an effective way to prevent osteoporosis and fall. When cost effectiveness is considered, education program or home- based exercise may be the better options.

Key Words: osteoporosis, postmenopausal women, education program, home based exercise, group exercise, cost- effectiveness analysis

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Chapter 1 Introduction

1.1 Background

Elderly population is rapidly increasing in number and proportion, osteoporosis has become a major global public health issue[1, 2], including Asia and Taiwan [3-6]. Osteoporosis is a systemic disorder and is characterized by low bone mass and structural deterioration of bone tissue, leading to bone fragility and an increased susceptibility to fractures, any bone can be affected, especially of the hip, spine and wrist [7-10]. Moreover, the complications and sequelae that coming with osteoporotic fractures always cause enormous burden to the society and medical care system [10]. Patients with osteoporosis will suffer not only pain, lower physical activities, but also their quality of life. For patients with osteoporosis, exercise therapy is a strongly recommended nonpharmcological therapy without any side effect.

Many studies have proven that exercise can improve the bone mineral density, decrease bone loss, prevent fall and so on. However, most studies focused on the effects of different types of exercises, few studies compared the therapeutic effects among different delivery modes. For medical care providers, the most important is to maximize the efficiency of treatment with lowest cost. Cost effectiveness analysis would be the best way to help the decision makers to reach a conclusion.

1.2 Purposes of this study

1.2.1 Purpose of study 1

The purpose of study I : To investigate the therapeutic effects among different delivery modes of exercise in postmenopausal women with osteoporosis.

The effects include bone mineral density, muscle strength, balance, quality of life and number of fall in postmenopausal women with osteoporosis and delivery modes include supervised group- exercise, home- based exercise and education intervention.

Hypothesis of study 1: The supervised group- exercise program has greater effects than home- based exercise and education intervention groups on bone mineral density, muscle strength, balance, quality of life and number of fall in postmenopausal women with osteoporosis; and the effects of home- based program are better than those of education group.

1.2.2 Purpose of study 2

The purpose of study II: Cost effectiveness analysis is conducted among three strategies for improving bone mineral density, muscle strength, balance, functional mobility, quality of life and number of falls in postmenopausal women with osteoporosis.

Hypothesis of study 2: To conduct the CEA of three strategies, the C/ E ratio is different among the 3 groups. The cost of group exercise is the highest than home-based exercise and education group, and the home- based exercise is higher than

education group; the effectiveness of group exercise is better than another two strategies, and the effects of home- based program is better than those of education group.

Chapter 2 Literature review

2.1 Global problem of osteoporosis

Osteoporosis is a progressive systemic skeletal disease characterized by low bone mass and micro- architectural deterioration of bone tissue that results in enhanced bone fragility and increased susceptibility to fractures. Two hundred million people are affected by osteoporosis in the world [6]. It is a costly and debilitating disease that is related with higher morbidity and mortality [11]. The clinical importance of osteoporosis lies in the happening of fractures [12, 13]. A woman with low bone mass at 50 years old would have a 40% risk of experiencing a fragility fracture during her remaining lifetime [11]. Johnell's study in 2005 reported that the lifetime risk for osteoporotic fractures at the age of 50 years in UK was 20.7% and 53.2% in men and women respectively. In US, the risk was 13.1% and 39.7% in men and women [10]. Hip fracture risk in women with osteoporosis is higher than the combined risk of developing breast, uterine and ovarian cancer [14]. Higher mortality rate of osteoporosis- related fracture was reported than the rate from breast and ovarian cancer combined [11]. Thus, osteoporosis and its related fractures is a serious public health problem and also is a significant burden to the health care system and the society. Consequently, effective prevention and management strategies for osteoporosis to decrease the osteoporosis-related fracture risk are urgently needed to be developed[11, 13]. Fractures may occur in any bone from inadequate or low energy trauma, but common osteoporotic fractures include those at the forearm, vertebra and hip [7-10].

Hip fracture is always considered a cause of severe disability and loss of independence in the elderly. It leads to acute pain and functional limitation. Nearly most of the circumstances require to hospitalization, recovery is slow and often

incomplete, and many of the victims are permanently institutionalized in nursing facilities [15]. In the United States, about one third of patients with a hip fracture are admitted to nursing homes in the year after a fracture, and the mortality rate increases up to 20% during this time.

Vertebral fractures are the extremely common type of osteoporosis- related fracture. They may associate with acute pain and impairment of physical function, but also may pass without serious symptoms. Therefore, they do not always come to clinical attention. Vertebral fractures often recur, and increased risk for future fragility fractures [11, 13-17].

Forearm fractures cause acute pain, loss of physical function, but they are frequently treatable in an outpatient setting, the functional recovery is usually good or excellent and long term complications are rare [11, 13-17]. Osteoporosis related fractures may lead to decrease physical function and mobility, social interaction, also cause emotional problems (low mood, depression). All of them can adversely affect people's quality of life [15, 16, 18].

2.2 Classification of osteoporosis

A formal diagnostic criteria was established by the World Health Organization (WHO) in1994 [19, 20]. The definition of "normal" is BMD within 1 SD of the young healthy adult mean (T score≥ –1); "osteopenia" is BMD between 1 SD and 2.5 SD less than the young healthy adult mean (-1> T score >–2.5); "osteoporosis" is BMD 2.5 SD or more below the young healthy adult mean (T score≦ –2.5); and "severe osteoporosis" (established osteoporosis) is osteoporosis with one or more fragility

fractures [19-24].

The classification of osteoporosis was shown as the following table [20, 24] (modified from Lane NE, 2006 and Gass M, 2006 [20, 24]):

Definition	Criterion
Normal	BMD≦1SD below young healthy normal adult mean (T- score≥ -1)
Osteopenia	BMD> 1SD but <2.5 SD below young healthy normal adult mean (-1> T- score> -2.5)
Osteoporosis	BMD≥ 2.5 SD below young healthy normal adult mean (T- score≦ -2.5)
Severe osteoporosis	Osteoporosis with fractures

There are two common forms of osteoporosis: involutional (primary) and secondary osteoporosis.

In involutional osteoporosis, the loss of bone mass happens naturally and progressively with age. There are two types in involutional osteoporosis. Type I occurring in postmenopausal women is associated with estrogen deficiency, cessation of estrogen leads to a decrease in interleukin- 6 (IL- 6) and other cytokines, all of them in turn cause increasing activation of osteoclasts, trabecular bone is mainly

involved. This type of osteoporosis occurs majorly in postmenopausal women, it occurs in women between 51 and 75 years of age, and occurs in men about 10 years later than women due to testosterone deficiency. The ratio of occurrence of type I osteoporosis in female and male is 6:1. Type I osteoporosis increases risk of fractures primarily in wrist fractures and also including vertebral fractures [17, 23, 25]. Type II osteoporosis represents part of the aging process and includes increased osteoclastic activity. It results in steady bone loss and involves trabecular and cortical bone. This type of osteoporosis develops after 70 years of age, and it is twice as frequent in women as in men. Type II osteoporosis is thought to be primarily responsible for hip and vertebral fractures [17, 23, 25].

Two types of involutional osteoporosis and their characteristics are described as the following table [25] (modified from Riggs BL, 1995 [25]):

	Type I	Type II
Age	51-75	>70
Gender (Female:Male)	6:1	2:1
Type of bone loss	Trabecular	Trabecular/Cortical
Rate of bone loss	Accelerated	Steady
Fracture sites	Distal radius Spine	Spine Hip
Major cause	Menopause	Aging

About 5% of osteoporosis cases are considered secondary in nature, it usually occurs after people suffer a prior medical condition, such as endocrine disorders, or malabsorption syndrome, or commonly chronic renal disease. Still, there are others who have experienced this type of secondary osteoporosis due to drug therapy, such as corticosteroids or anticonvulsants. It is impossible to ignore this type of osteoporosis, since it accounts for 20% of osteoporotic fractures [17, 26-28].

2.3 Risk factors of osteoporosis

Osteoporosis is largely underdiagnosed and undertreated because of clinically silence and asymptomatic nature, and is most notable by fractures [29, 30]. Osteoporotic fractures may result in chronic pain, disability and increased morbidity and mortality [30, 31]. There are many risk factors for osteoporosis. If people can acknowledge the risk factors, and intervene accordingly as early as possible to maximize the maintenance and improvement of bone mass, they will effectively reduce the spread of osteoporosis, and future complications involving osteoporotic fractures [32].

Risk factors of osteoporosis include which cannot be modified and can be modified, they will be described as follows:

2.3.1 Risk factors which cannot be modified: genetics, race, gender, age, and family history

2.3.1.1 Genetics

Genetic predisposition to osteoporosis is a proven risk factor, as is the level of peak bone mass acquired, and the rate of bone loss that occurs thereafter. Genetic factors involved in the regulation of bone mass, and the onset and development of osteoporosis. The likelihood of osteoporosis and its associated fractures is directly linked to the level of peak bone mass acquired during the maturation of skeletal development, and the rate in which bone loss occurs [2, 26, 33]. The development of peak bone mass begins in utero, and is fully attained in the 25- 30 years old. After 30 years of age, bone loss begins around 1% a year in average in both male and female [7, 26]. However, the rate of bone loss accelerates at a rate of 4% a year in the postmenopausal women because of the ovarian function cessation. From 20 to 80 years old, the bone density of trabecular bone decreases approximately 50% [2, 34]. This phenomenon of bone mass attainment and loss are genetically programmed. The genetic factors account for 80% of the variance in bone mineral density, and also for the vitamin D, estrogen and type I collagen receptor genes, they are promising genetic determinants of bone mass. Nevertheless, most molecular mechanisms of osteoporosis still remain unclear [7, 26, 33].

2.3.1.2 Race

In the different ethnic groups, it has been shown that the blacks have greater bone mass than the Caucasians and Asians, whereas Asians have lower bone mass than Caucasians, correcting body size attenuates these differences (BMD: black > Caucasians> Asians) [35, 36].

2.3.1.3 Gender

The bone width differs in genders since peripubertal period. In males, periosteal bone formation results in cortical width increase while more endocortical apposition in females than males. That's why long bones of males are longer and wider but not much thicker cortex than females [37]. A study in 2000 reported that there were 39% higher total body bone mineral content (BMC) but 22% greater total bone area in men comparing to women. According to these, the bone mineral density (BMD) in men was only 15% higher than women (1.2 and 1.0 g/ cm^2, respectively and $p< 0.001$). After adjusted BMD for height, the difference between the genders reduced to only 6% [38].

2.3.1.4 Age

Peak bone mass is acquires by age 25- 30 [7, 39]. The negative bone balance sets in at about 30 years of age, and the rate of bone loss is on an average of 1% every year, independent of gender [7, 39]. The bone loss accelerates and the proportion of osteoporosis increases quickly and fractures increases steadily in women with the onset of menopause and estrogen insufficiency (about 50 years of age), men are also

the same consequence but with 10 years time lag (about 65 years of age) [23, 40, 41].

In Taiwan, the data from Department of Health in 2005 showed that about 16% of population older than 60 years old were diagnosed as osteoporosis, and 80% are female (about 12.8%). Another study reported that the annual prevalence of osteoporosis in men and women aged 50 years or older from 1999 to 2001 was 1.63% and 11.35% respectively [42].

2.3.1.5 Family history

A family history of osteoporosis and osteoporotic fractures in a first-degree relative is an important genetic preditor of osteoporosis development [43, 44]. Lane et al. reported that comparing with women without family history, women with a maternal hip fracture history are about double risk of hip fractures [2].

2.3.2 Risk factors which can be modified: physical activity, body weight, smoke, alcohol, nutrition, hormones, medications and diseases

2.3.2.1 Physical activity

Contraction of muscle and tendons can produce stress or mechanical loading on bone and will have a direct effect to induce bone formation and remodeling, its mechanism is to follow the Wolff's law [45]. Under the loaded area, the osteoblasts and osteocytes will be activated and response to the mechanical loads immediately, it will lead to change the balance of bone resorption and formation [46-48]. According to

Wolff's law, the bone adaptation is based on the physical load and stresses exerted on it [43, 46]. Some evidence suggested that there is a minimum requirement of effective strain for both bone modeling and remodeling. If the strain on bone is lower than the threshold that initiates bone remodeling will increase bone loss. While the strain is greater than the threshold will increase bone mass [25, 34, 45, 46]. Physical activity and exercise of every day exerts the force on bone that causes bone mass and bone strength to be developed and to be maintained. Bone mass attainment will be benefit from these functional loading resulted from physical activity [46].

The beneficial effect on bone geometry, mass, and mineral density was proved if starting exercise from childhood. The most critical period which exercise has the best benefit in BMD is found during growth. In young adults, exercise may increase peak bone mass and lower the risk of fractures later in life. In early menopausal women, exercise may decelerate the rate of bone loss following the estrogen deficiency. In older adults, exercise could slow down the age-related bone mass loss and reduce the risk and severity of falls [49].

Chronic insufficient physical activity would cause a rapid bone loss. Research on bed ridden patients showed that the rate of trabecular bone loss was about 1% per week, and the return of about 1% trabecular bone needed one month, so that restoration of bone mass is much slower than bone loss [26]. Immobilized patients may

lose 40% of their original bone mass in 1 year [49].

Excessive sport in athletes particular in female is possibly leading to osteoporosis later in life. Extreme low body fat and reduction of estrogen resulted from constant and lengthy training with diet and weight control, it would make the menstrual periods irregular or ceasing, consequently, the risk of fractures is clearly increased [26, 50].

2.3.2.2 Body weight

Weight is an important predictor of bone mineral, it is positively related to bone mineral [51]. Low body weight is related to low bone mass and higher risk of fractures, whereas the obese people has higher bone mass [41, 51, 52], lower bone turnover and bone loss [53-55]. Even though the obese people have a higher fall risk than thinner ones, but they do not get fracture more easily. The possible explanation of this result is that bone density of the obese people is higher and the surrounding fat of crucial area plays as cushion effect [41]. The BMD in obese subjects is more about 0.5 kg or 1% of body weight comparing with lean subjects, and it is nearly equal to the amount of 20% of total bone mineral content[41]. Previous studies revealed that there was higher rate of osteoporosis in lean subjects than obese ones [41, 53]. Other studies also found great bone density disappears in individuals successfully losing weight [51, 56, 57].

Losing 10% body weight is suggested to reduce risk factor of comorbid and

improve health for overweight or obese individuals [58]. However, it was reported that losing 10% body weight would lead to 1- 2% bone loss [41].

In 2009, a review study showed that the risk of lower BMD would increase when weight loss greater than 1% per year. Men lost 5% of baseline weight had doubled bone loss rate than those who maintained stable weight [59].

The potential mechanisms for the influences of weight on bone mass might be from: (1) weight bearing effect [41, 51, 60], (2) bone active hormones from the adipocyte, such as estrogen, leptin, adiponectin [34, 41, 51, 61-644], (3) bone active hormones from other organs, such as ghrelin, GLP- 2 (glucagons- like peptide- 2), GH (growth factor), IGF- 1 (insulinlike growth factors- 1), and cortisol [25, 41, 65, 66], (4) lower level of 25(OH)D (25- hydroxycholecalciferol) [25, 41, 67-69].

The effects and mechanisms of bone active hormones from the adipocyte and other organs are summarized on the following tables:

Hormones from the adipocyte	Changes when losing weight	Potential mechanism
Estrogen	decrease	1. estrogen ↓→↑osteoclastic activity directly→↑bone resorption 2. estrogen ↓→↑ cytokines (IL 1, IL 6, tumor necrosis factor)→↑osteoclastic activity indirectly→↑bone resorption
Leptin	decrease	Peripheral: leptin ↓→↓ bone formation Central: leptin ↓→↑ bone formation
Adiponectin	increase	adiponectin↑→↓ number of osteoclast adiponectin↑→↑osteoblastogenesis

Hormones from other organs	Changes of when losing weight	Potential mechanism
Ghrelin	increase	ghrelin ↑→ ↑osteoblast proliferation and differentiation
GLP- 2	decrease	GLP- 2↓→ ↓ bone mineralization and ↑ bone resorption
IGF- 1	decrease	IGF- 1 ↓→ ↓osteoblast proliferation and differentiation
Cortisol	decrease	cortisol ↑→ ↑osteoclast activity and/ or ↓ Ca absorption

In summary, when weight loss, the level of estrogen, leptin, GLP- 2, GH, IGF- 1 in serum will decrease and cortisol will increase, these changes will have negative influence on bone mass; however, the level of adiponectin and ghrelin will increase, and these will have beneficial effect on bone mass.

During weight loss will induce changes of hormones and their effects on bone, these changes will be also influenced by other factors such as gender, age, amount and types of weight loss [41].

2.3.2.3 Smoke

Cigarette smoke is a major risk factor of many diseases. Most molecular components of cigarette could have potential noxious effects. Development of osteoporosis results from smoking through several interacting mechanisms [70]. The possible mechanisms affecting bone mass and inducing osteoporosis are: (1) the direct effect of smoke components inhibiting bone formation [27, 70]; (2) premature ovarian failure: the secretion of estrogen is inhibited and the breakdown of estrogen in liver is activated by smoking, the onset of menopause is also accelerated in smoking population [26, 27, 70, 71]; (3) initiation of inflammatory responses in the lung: the cytokines released during inflammation such as interleukin-6 have systemic effects and modification of bone function and then result in the development of osteoporosis [70, 72].

Furthermore, the level of certain nutrients in the body would be reduced by smoking such as vitamin C, it plays an important role for bone building. The calcium absorption and mineralization are also influenced by smoking, bone mass would be affected by these negative effects [26].

BMD of women who smoke one pack a day during adulthood was 5-10% less than nonsmokers at the age of menopause [26]. Recent studies showed that the life- time risk of vertebral fractures in women and men increased 13% and 32% in smoking population. These negative effects on bone would be reversible after quitting smoking [70].

2.3.2.4 Alcohol

It was reported that alcohol abuse could lead to an apparent rate of bone loss, it suggested bone resorption predominates to bone formation [73]. Underage drinking could influence bone health, including the amount of peak bone mass would be reduced and would result in a lower threshold to develop osteopenia later in life. Chronic alcohol abuse having negative effects on bone mass was supported by many evidences, however, moderate alcohol consumption having positive effects on bone mass was proved, especially for postmenopausal women [74].

The mechanisms of effect of alcohol on bone turnover are not fully understood and include direct and indirect actions.

Direct actions include (1) Alcohol could inhibit osteoblast proliferation and differentiation, and increase the osteoclast activity [75, 76]. (2) The remodeling rate and remodeling balance: Alcohol abuse will reduce the rate of bone remodeling and a

negative remodeling balance will be activated, the effect will lead to bone loss. However, few to moderate alcohol consumption will also reduce the bone remodeling rate but the remodel balance between resorption and formation will not be disturbed [73]. (3) Changes of local expression of cytokines: The rate of initiation of bone remodeling and coupling between bone formation and resorption are mediated by the cytokines, alcohol may disturb the local expression of cytokines (such as IGF- 1 and and tumor necrosis factor) lead to alter these processes [73, 77].

Indirect actions include (1) Decrease of mechanical loading: Alcoholics often decreased body weight, that could reduce mechanical loading on bone and lead to bone loss [73]. (2) Changes on mineral homeostasis and calcium regulating hormones: Alcoholics often have hypomagnesmic, hypocalcemic and may have hypocalciuria, the metabolism of vitamin also could be influenced. It will lead to disturb the regulation of these calcium- regulating hormones, and result in the bone loss [73].

2.3.2.5 Nutrition

Nutrition has influences on growth and development of peak bone mass, maintenance of adult's bone mass, and modification of postmenopausal bone loss. It also affects bone loss and bone health in advanced age [78]. The relationship between nutrition and bone can be described in following aspects. First, bone tissue is composed of nutrients such as calcium, phosphorus, and proteins. Second, some

nutrients influence bone metabolism indirectly. For example, calcium inhibits PTH secretion and bone resorption, vitamin K contributes to the stabilization of bone matrix, and proteins play as stimulators of IGF which acts on bone[78].

Nutritional strategies may be effective on preventing and managing osteoporosis. Acceptance and compliance rates to drug therapy are often low due to the potentially adverse side effects associated with these therapies and an overall reluctance of women to take medications to prevent "silent diseases" [11]. Calcium and vitamin D are two major focused nutrients for bone mass and they are also important to be used alone or combinated with conventional therapies to maintain bone mass and prevent fracture in elderly. Other nutrients also have important roles for bone composition such as magnesium, fluoride, phosphorus and zinc ……. Furthermore, the phytoestrogens may have positive effect on bone health [11, 79].

A. Calcium

The importance of calcium and vitamin D had been viewed as therapeutic focus hitstorically for practitioners and patients who care or pursue nutrition suggestion about osteoporosis [79]. The most essential mineral for osteoporosis prevention and treatment is calcium.

There is more than 1 kg calcium in the body for adult, and 99% of them stores in the skeleton [27]. People being short of calcium or vitamin D will lead to decrease calcium absorption and a lower level of ionized calcium in blood. It will result in stimulating parathyroid hormone (PTH) secretion and increasing PTH levels. Secondary effect to deficient in calcium and vitamin D levels, higher PTH levels (secondary hyperparathyroidism), will increase bone remodelling and lead to significant loss of bone and an increased fracture risk. Vitamin D supplementation is often combined with calcium, it appears to decrease the degree of secondary hyperparathyroidism related with poor nutrition [80]. Chronic calcium deficiency, negative calcium balance and mobilization of the skeleton may continue and lead sooner or later to the condition of osteoporosis [81].

A lot of studies reported the relationship between calcium intake and bone density. Peak bone mass is achieved during young adulthood, and intake more calcium to the adequate level can maximize the peak bone mass. People who have higher calcium intake have more bone mass in all ages [82, 83]. However, in most studies, when supplementation is discontinued, the effect of added calcium on bone mass will disappear, these data suggested that adequate calcium intake needs to be maintained throughout childhood, adolescence, and young adulthood to have a lasting effect on peak bone mass [80]. The positive effect of calcium supplementation on retarding bone

loss in postmenopausal women has also been supported [81, 84]. Furthermore, the greater effect of calcium was found at the areas with more cortical bone, in elderly, in late postmenopausal women, and in women with low baseline calcium intakes. In addition, enough doses of calcium can lower the PTH levels and the bone remodeling rate. Calcium supplementation can improve the efficacy of antiresorptive therapy on bone mass, for example, take calcium supplementation along with hormone replacement therapy (HRT) [80].

Adequate calcium intake is required. Very low calcium intake leads to higher risk of fracture. In postmenopausal women with low calcium intake level, calcium supplementation provides the positive effect on reducing the risk of hip and vertebral fracture. There were also study reporting the lower hip fracture incidence was found in elderly with high level calcium intake from food or supplements [78, 847].

Prevention of osteoporosis should begin from childhood. As the skeleton develops and grows, a calcium rich diet provides the need to reach a peak bone mass at about 25 years of age. Even after menopausal, which is the period of significant bone loss, it is still worthwhile to start the bone conscious diet [27]. The recommended calcium intake should change with age and the suggested intakes by Institute of Medicine in Washington DC- Food and Nutrition Board are described as following

table [80].

Food and Nutrition Board Dietary Reference Intakes [80]

Age (y)	Calcium (mg)	Vitamin D (IU)
3- 8	800	200
9- 17	1300	200
18- 50	1000	400
51- 70	1200	400
>70	1200	600

Highest daily intake is required after age 50. If an adequate calcium intake is not possible in the diet, a calcium supplement may be required. In most healthy individuals, calcium intake up to 2500 mg/d are safe. Important dietary sources of calcium are dairy products (milk and milk products, yogurt, cheese), dark green vegetables, fruits, canned fish with bones (but not fish fillets), wheat products, nuts, fortified foods (including juices, waffles, cereals, crackers, and snack foods). Patients have allergic response to milk or milk products, fruit juices are suitable choice for calcium intake, especially if they have been fortified by addition of calcium. The absorption of calcium increases from 30% to 40% when adding vitamin D in fruit juices. Calcium absorption in intestine will further increase when vitamin D is added.

When mineral water is enriched with calcium, it can help to positive calcium balance. However, the amount of calcium in different types of mineral water is different and range may be from 10- 650 mg/ l. Calcium tablets, it should be taken on medical advice. One dose should not be greater than 500 mg, so if neceaasry, the amount needed every day should be taken in divided doses. [27, 80].

B. Vitamin D

Vitamin D is a regulator of bone mineral homeostasis by promoting the transport of calcium and phosphate from the intestine, and increased reabsorption of calcium in the kidney to ensure the ion levels in the blood are sufficient for the normal mineralization of collagen matrix in the skeleton [79, 85, 86]. Thus, vitamin D promotes bone formation by improving intestinal absorption of calcium and phosphate and by stimulating maturation and mineralization of the osseous ground substance- the osteoid [27]. In addition to these vital calcemic actions, the discovery of the nuclear receptor of $1,25(OH)_2D_3$ opened the possibility that vitamin D might exert variable non- calcemic actions [85, 86].

(a) The mechanism of vitamin D action on bone

The action of $1,25(OH)_2D_3$ in bone includes a genomic and a non-genomic mechanism. They are described as follows:

(1) Genomic effect: The genomic activation of vitamin D

receptors (VDR) will bring out several proteins' expression in the osteoblasts. It is the most important of the transcription of receptor activator for nuclear factor kappa B ligand (RANK-L). It is responsible for the stimulation of osteoclastic activity and differentiation through a complex mechanism of osteoblast/osteoclast communication. Osteoblasts are stimulated by vitamin D to release RANK-ligand which interacts with the membrane located RANK in the osteoclasts inducing osteoclast recruitment and activation [85, 86]. In addition to the stimulation of osteoclastic activity, vitamin D may also play a role in bone formation either through the protection of osteoblasts inhibiting apoptosis or stimulating the differentiation of adipocytes into osteoblasts within the bone marrow [69, 85, 86].

(2) Non-genomic effect: In addition to the genomic action of vitamin D in bone, the non-genomic effect includes to open calcium and chloride channels, they are necessary to increase the calcium levels stored in the endoplasmic reticulum and to enhance the mobility and changes in conformation that are needed for the normal osteoblast function [69, 85, 86].

(b) The effect of low vitamin D status

Deficiency of vitamin D would lead to the decrease in the efficiency of intestinal absorption of calcium and phosphorus. This would cause a transient

lowering of the ionized calcium, it will be corrected immediately by the increased secretion of PTH. PTH interacts with its membrane receptor on mature osteoblasts to sustain the ionized calcium level in blood, which will induce the expression of RANKL. RANK is present on the plasma membrane of preosteoclasts to identify this plasma membrane receptor protein. The production and maturation of osteoclasts will increase by interaction between RANKL and RANK. The osteoclasts destroy bone, lead to the stored calcium out of the skeleton and correct the ionized calcium level. Thus secondary hyperparathyroidism would be induced by vitamin D deficiency and leads to the wasting of the skeleton, which can precipitate and exacerbate osteoporosis [68].

Many studies suggest that lack of vitamin D action is an important predisposing factor for fragility fractures. In fact, bone strength relies on the well regulated bone turnover and coordinated function among bone cells. Reduction of bone turnover which results from lower osteoclastic activity will be initiated when there is vitamin D deficiency and followed by the PTH induced compensatory osteoclastic response [68, 85]. In addition, osteoblast apoptosis will decrease osteoblastic activity, it will induce a reduction in bone formation and also in the differentiation of new osteoclasts because osteoblasts are responsible for this action [68, 85].

Severe vitamin D deficiency will markedly suppress intestinal Ca absorption and

the impairment of Ca balance, it will result in an under-mineralization of the growing skeleton for child and in demineralization of the skeleton for adult leading to rickets and osteomalacia, respectively. For elderly, an insufficient vitamin D status will contribute to osteoporosis is a general agreement now. Low 25(OH)D levels are related with decreased Ca absorption rates, hyperparathyroidism and increased bone turnover leading to bone loss [69].

(c) Vitamin D status assessment

The gold standard for determining the vitamin D status is to measure the 25(OH)D. Calcitriol level ($1,25(OH)_2D$) is not a valid way to measure vitamin D status in serum [69]. $1,25(OH)_2D$ levels are 1000 times lower than 25(OH)D levels and secondary hyperparathyroidism will increase the renal production of $1,25(OH)_2D$. So the measurement of $1,25(OH)_2D$ can not provide insight about the vitamin D status of a patient. For vitamin D deficient patients, its level often is normal or occasionally increased [68]. In addition, low calcitriol levels may be observed, it is possible due to an insufficient substrate for the renal 1α-hydroxylase [69].

25(OH)D level between 50 and 80–100 nmol/l can be reflected as hypovitaminosis D, it indicates that body stores are already depleted and PTH levels are still in the normal range but would be slightly elevated. Most studies suggest that the PTH levels reach their plateau and are at their optimal physiologic level when

25(OH)D is above 80 nmol/L (32 ng/mL) [69, 86]. The 25(OH)D level in serum between 100 and 200 nmol/l can be agreed as adequate concentrations, in this status, the disturbance in vitamin D-dependent body functions will not occur [69, 86].

(d) Treatment for vitamin D deficiency

It has been estimated that body uses 3000– 5000 IU of cholecalciferol on average every day [6868]. The possible explanation for this amount is that there is VDR in every tissue and cell which makes the needs of vitamin D. Studies suggest that when in absence of sun exposure, 1000 IU of cholecalciferol is needed to keep a healthy blood level of 25(OH)D (between 80 and 100 nmol/L). During lifelong, vitamin D plays a very important role to maintain calcium metabolism and good skeletal health [68, 69, 80]. For older adults, vitamin D adequacy means the 25(OH)D concentration in serum needed to maximally inhibit PTH levels. Rise in serum PTH starts when serum 25(OH)D falls less than 80 nmol/L. It is therefore recommended that the optimal 25(OH)D level in serum may be at least 80 nmol/L for postmenopausal women from these data [80]. 25(OH)D level in 80 nmol/L (32 ng/mL) or greater can improve muscle strength and bone mineral density for adults [68, 87].

The sources of vitamin D come from sunlight exposure, diet and multivitamin, they are described as follows:

(1) Sunlight exposure: Skin has a huge ability for vitamin D production and provided 80 to 100% of required vitamin D for the body. [68, 86].

In skin, under the influence of ultraviolet B radiation, 7-dehydrocholesterol absorbs UVB and is photoconverted to previtamin D_3, which is unstable and rapidly converted to vitamin D_3 (cholecalciferol). Vitamin D_3 is transported to the liver by binding to a vitamin D binding protein (DBP) in the serum, it is hydroxylated to 25(OH)D_3 in liver. 25(OH)D_3 is rapidly released by the liver into the blood. 25(OH)D_3 is further metabolized to 1,25-dihydroxyvitamin D_3 [1,25$(OH)_2$D] (calcitriol) in kidneys, the most important for most of the biologically active form of vitamin D [68, 88]. Renal synthesis of calcitriol is homeostatically tightly regulated by parathyroid hormone (PTH). Synthesis of PTH is controlled by a negative feedback regulation by serum level of Ca [69, 86].

Exposure to sunlight for no more than 5–15 min/day (between 10 AM and 3 PM) on body surface in all seasons except winter can provide the needed vitamin D about 1000 IU of cholecalciferol . To avoid adverse effect and burning damage from excessive sun exposure, application of a broad spectrum sunscreen with an sun protection factor (SPF) of at least 15 is required after the limited exposure. Even though aging would decrease the production of 7-dehydrocholesterol of skin,

elderly people are still able to obtain enough cholecalciferol by sunlight exposure [68, 87]. Higher level of melanin pigmentation would reduce the synthesis efficiency of U.V. B-mediated vitamin D and therefore increase necessity of the sun exposure time to reach the maximal vitamin D formation, however, the total content of daily vitamin D production does not be influenced [68, 87].

Aging, latitude (e.g. live in the extremes of the hemisphere where the ultraviolet energy is not adequate in winter months), time of day, season of year, increased skin pigmentation, and obesity are associated with vitamin D deficiency. 7-dehydrocholesterol levels in the skin decline with age. Compared with a healthy young adult, a 70 years old person has 25% of the ability to produce cholecalciferol. Sunscreens can efficiently absorb UVB radiation, so they are effective at preventing sunburning and skin damage. Using a sunscreen with a SPFof 8 will reduce 95% ability of the skin to produce cholecalciferol, therefore, it is at higher risk of vitamin D deficiency when people always wear a sunscreen before going outside. Melanin is an extremely effective UVB sunscreen. Thus, comparing with whites, African Americans who are heavily pigmented need at least 5 to 10 times longer exposure to produce sufficient cholecalciferol in skin [11, 68, 86].

(2) Diet:

Through supplementation from the diet, the Vitamin D status could be improved. The natural sources of Vitamin D include fatty fish, fish-liver oils (cod liver oil), orange juice, liver, milk, margarine and cereals. But the diet contains variable amount of vitamin D. Generally, if the elderly who were in absence of sun exposure could not get sufficient Vitamin D only via diet [68, 80, 87, 88]. Thus, they should depend on the Vitamin D supplementation or sun exposure.

(3) Multivitamin:

Currently US recommended for adequate intake of vitamin D in people age 51 to 70 years old and over age 70 years old is 10 μg/day (400 IU/day) and 15μg/day (600 IU/day) respectively [27, 80, 89]. However, in the elderly (age≧65 years old), taking higher doses of vitamin D (800–1000 IU/day) may be necessary for optimal bone health, because these doses of vitamin D have been proved to reduce fracture risk[27, 80].

The treatment goal of patients with vitamin D deficiency is to reach the required amount of vitamin D as soon as possible [68, 87]. Usual diet with additional vitamin D supplementation can help patients to get the recommended 1000 IU of cholecalciferol [6868]. Thus, increasing vitamin D intake by taking vitamin D fortified foods and vitamin D supplements along with sensible sun exposure would maximize

the amount of vitamin D and promote individual health [68, 90].

(e) Treatment effects of vitamin D

Many studies discussed about vitamin D supplementation, typically in combination with calcium (500 to 1200 mg/day) [80]. The effect on bone mass was supported by many studies [80, 91, 92].

Vitamin D has direct effects on muscle strength, it was reported that vitamin D supplementation could improve muscle strength, function and balance in people with vitamin D deficiency. It is very important, the effects would translate to a reduction in falls [93].

Falls often cause hip fractures, they are the leading cause of death, morbidity, and admission to a nursing home. Adults with vitamin D deficiency will result in muscle weakness and will be more likely to fall [8080]. Vitamin D supplementation with or without calcium reducing the risk of falls and fractures was proved [79, 94-97].

To sustain the benefits of increased calcium and vitamin D, higher intake of these nutrients must be maintained [98].

C. Protein and acid load

An adequate amount of dietary protein is necessary for bone health. Protein malnutrition can result in growth retardation and fail to achieve peak bone mass

during childhood and adolescence. The positive effect of proteins is explained partly by its stimulatory effect on the secretion of hormones and growth factors that modulates bone synthesis (e.g. IGF) [11, 78]. The effects of protein are paradoxical, excessive protein intake has a higher risk for osteoporosis and osteoporotic fractures, but this probably present in animal protein (meat) and not proteins producing from fruits and vegetables [78, 99-101]. Excessive animal protein will produce acid load, this lowering of PH will increase urinary calcium excretion and stimulate osteoclast activity, and will lead to bone resorption. Bone would provide the main source of buffer system, the release of calcium and inhibition of osteoblast activity will be induced by this stimulation of bone resorption [27, 99, 101]. However, this acid load effect can be regulated by consumption of alkali- rich foods, such as fruits and vegetables [99, 100].

For any age, it is important to get the balance of the total dietary acid and alkaline load to the calcium excretion, especially for those with marginal amount of calcium intake. This is achieved with a balance in protein foods those generate acid and those provide alkali (fruits and vegetables). When the bone calcium which is mobilized to act as a source to neutralize the blood pH is spared by alkali- producing foods, then leads to less bone mass loss [11, 99].

D. Phytoestrogens

Phytoestrogens are plant-derived compounds and their chemical structure is similar to endogenous estrogen, this makes them acting like estrogen on bone tissue [11, 101]. The possible mechanism of phytoestrogens for bone is a direct interaction with estrogen receptors [101]. In addition, there were some mechanisms have been postulated based on the knowledge of estradiol effects on bone including actions on cytokines, growth factors, their associated regulatory molecules, and enzymes which function as signal transduction, cell proliferation and apoptosis [101, 102]. Certain isoflavones can also suppress the action of aromatase and may lead to inhibit the synthesis of endogenous estrogens, thus additional questions are raised about the action mechanisms of phytoestrogens [101].

There are less consistent conclusion about the effects of phytoestrogens on bone health. Some studies reported positive effects on bone mineral density of lumbar and bone mineral content of hip, but some studies showed that no significant effect on bone mineral density of lumbar or hip [11, 37, 101, 103].

E. Sodium

Excessive sodium intake increases urinary calcium excretion, reduces reabsorption of calcium and leads to a negative calcium balance, it will increase the bone resorption [78, 80, 100, 104].

The adequate amount of intake and sources of the nutrients for bone health

mentioned above are reported as following tables.

F. Other nutritional factors

Many nutrients also have influence on bone, they include: vitamin K, C, A, B12, caffeine, alcohol, phosphorus, potassium, trace elements (magnesium, fluoride, silicon, boron, copper, zinc, strontium, and selenium). Their effects on bone, dosages of recommendation and sources are summarized on the following tables [11, 31, 32, 43, 44, 50, 78-80, 101, 104-118].

Nutritional considerations in osteoporosis			
Nutrition	Bone effects	Recommendation dosages	Sources
Calcium	A deficiency of either calcium or vitamin D → ↓ calcium absorption →↑ PTH levels→↑bone remodeling leading to significant loss of bone	3- 8 y: 800 mg/ day 9- 17 y: 1300 mg/ day 18- 50 y: 1000 mg/ day 51- 70 y: 1200 mg/ day >70 y: 1200 mg/ day	dairy products (milk, yogurt, cheese), dark green vegetables, canned fish with bones, nuts, wheat products, fortified foods (fruit juice, cereals……)
Vitamin D	A deficiency of either calcium or vitamin D → ↓ calcium absorption →↑ PTH levels→ ↑bone remodeling leading to significant loss of bone	3- 8 y: 200 IU (5μg/ day) 9- 17 y: 200 IU (5μg/ day) 18- 50 y: 400 IU (10μg/ day) 51- 70 y: 400 IU (10μg/ day) >70 y: 600 IU (15μg/ day)	Cod liver oil, fatty fish, fortified foods (milk, cereal……)
Protein	*An adequate amount of protein is essential to maintain production of hormones and growth factors that modulate bone synthesis *Excessive animal protein→ acids→↑ urinary calcium excretion and osteoclastic bone resorption, ↓osteoblast function	1.0- 1.25 g/ kg per day	Fruits, vegetables
Phytoestrogen	similar chemical structure to endogenous estrogen with the potential to act like estrogen on bone tissue	?	Soy, flaxseed
Sodium	higher intake→ ↑ PTH → ↑ bone resorption	2400 mg/ day	salt
Vitamin K	significant role in synthesis of osteocalcin, mediates the attachment of calcium to	120μg/ day for men 90 μg/ day for women	Dark green vegetables, fruits, grains

Phosphorus	*adequate intake is essential for bone building during growth *low serum phosphate will limit bone formation and mineralization *excessive intakes combined with low calcium intake→ ↑ PTH→ ↑ bone loss	700 mg/ day	Milk, milk products, poultry, fish, meat, eggs, grains, legumes, sodas
Potassium	*Low potassium → ↑ urinary calcium losses, and high potassium reduce it		Vegetables, fruits, legumes, milk
Trace elements			
Magnesium	activates osteoblasts, increases mineralization density, activates vitamin D, activate many enzyme reactions	420 mg/ day for men 320 mg/ day for women	In most foods- particularly legumes, vegetables, nuts, seeds, fruits, grains, fish, dairy
Fluoride	*It is required for skeletal development *in high fluoride areas, higher hip fracture rates have been seen	4 mg/ day for men 3 mg/ day for women	Drinking water, tea, coffee, rice, soybeans, spinach, onions, lettuce
Silicon	↑ osteoblast activity → ↑ secrete type I collagen → ↑bone cell maturation and bone formation	30 mg/ day	Cereals, fruits, vegetables, beer, drinking water
Boron, copper, zinc, strontium, selenium	They are necessary for absorption of calcium, also for normal growth of bones and bone metabolism		Healthy diet

	bone matrix		
Vitamin C	*maturation of collagen, stimulates the bone forming cells, ↑absorption of calcium *60 mg is enough to prevent scurvy, but not enough to reap all the possible bone benefits	90 mg/ day for men 75 mg/ day for women	Fruits(the best sources are citrus fruits), vegetables
Vitamin A	*Vitamin A is required for bone remodeling and it influences the development of bone cells *excess vitamin A intake from retinol → ↑ risk of fracture	900 μg/ day for men 700μg/ day for women	Retinol: animal sources (beef, calf, chicken), dairy products (milk, butter, cheese) β- carotene: green vegetables, carrots, sweet potatoes, cabbages, fruits (orange, mangoes)
Vitamin B12	It is necessary for formation as well as maintenance of healthy bones	1 mg/ day	Liver, meats
Caffeine	*In large doses→ ↑ urinary excretion of calcium *moderate intake did not appear to have negative effects in pre-menopausal women and healthy post-menopausal women * moderate intake in older women may not be able to maintain calcium balance.	< 300 mg/ day (2 cups/ day)	
Alcohol	*large doses→ negative effects on bone *moderate intake alcohol was associated with significantly lower markers of bone turnover	< 7 drinks per week	

As mentioned above, the nutrition needed for optimizing bone health can be easily met by a healthy diet with adequate calcium and vitamin D intakes through dairy or calcium fortified foods. Micronutrients can also be easily gotten from a healthy diet within fruits and vegetables (5 servings per day) [80].

2.3.2.6 Hormones

A. Sex hormones

Estrogen is a key physiologic modulator of osteoclast formation, its withdrawal enhances osteoclast formation and results in bone loss [34, 119]. Loss of estrogen at menopause initiates an acceleration in bone loss for 5 years [43, 119]. Early menopausal before the age of 45 years is an important risk factor of low bone mass and fracture[43].

The mechanisms of action of estrogen on bone [119] were described as follows:

a. Inhibition of osteoclast activity

b. Stimulation of collagen synthesis by osteoblasts

c. Promotion of gastrointestinal absorption of calcium

d. Stimulation of calcitonin secretion

e. Modulation of PTH secretion

f. Increased blood flow through the bone

Hypogonadism (such as insufficiency testosterone) leading to low bone density is also seen in men [26, 43, 119, 120]. The testosterone deficiency can be the consequence of alcoholism and anorexia nervosa [26].

B. Parathyroid hormone (PTH)

PTH is secreted by the parathyroid gland, it is regulated by a negative feedback regulation from serum concentrations of calcium [69, 86, 121], PTH secretion will be suppressed within seconds when calcium increases in serum. PTH plays an important role for maintaining body calcium homeostasis, it has direct and indirect effects on the intestine, kidneys and bones [121, 122]. PTH increases calcium concentration by three ways: it stimulates the release of calcium and phosphate from bone, synthesis of active vitamin D in kidney and promotes the reabsorption of calcium from gastrointestine [121, 123]. The feedback and regulation in vitamin D metabolism is presented in the following figure [88]:

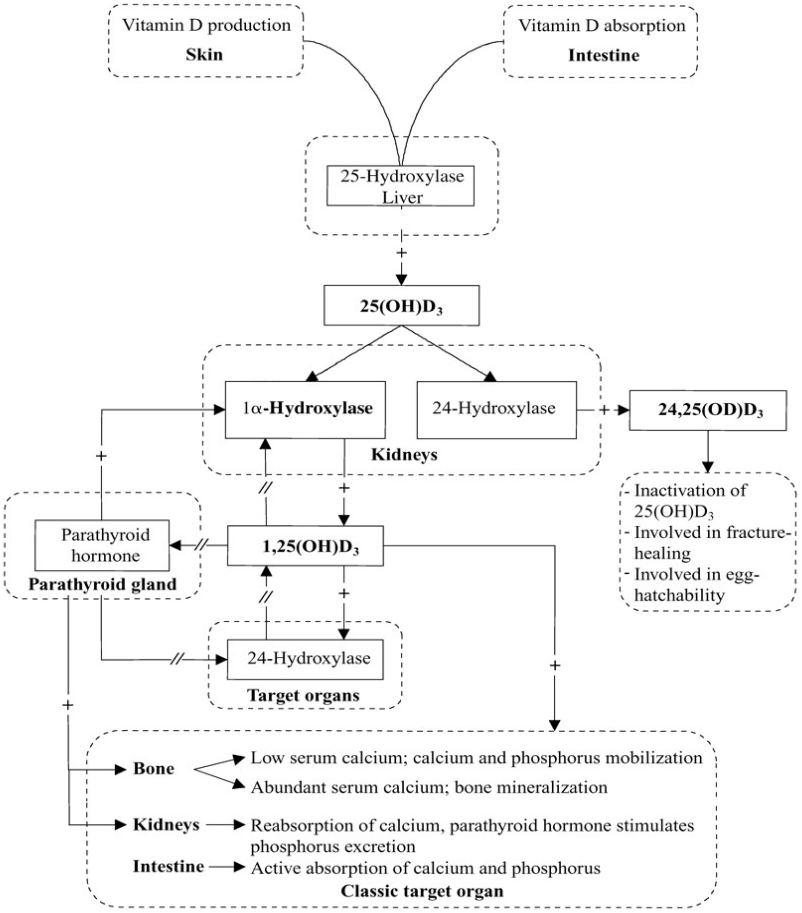


Figure: The feedback and regulation in vitamin D metabolism (From: Janssen H CJP, et al. Am J Clin Nutr 2002; 75: 611-615 [88].)

Increasing secretion of PTH (hyperparathyroidism) will induce calcium release from bones and disturb the calcium homeostasis by increasing the rate of bone turnover and resorption, it is an example that the hormone may determine the generalized osteoporosis [28, 122].

C. Calcitonin

Calcitonin is secreted by thyroid gland, it directly inhibits osteoclasts by binding to specific receptors on the cell surface [121, 124].

D. Thyroid hormone

Thyroid hormone is needed for regulating skeletal development and bone mass maintenance in adults [125]. Thyroid hormone increases the production of the osteoclastogenic cytokines, including interleukin-6 (IL-6), interleukin-8 (IL-8),and, prostaglandin E2 (PGE2), and the important bone growth factor, insulin-like growth factor (IGF-I). The proposed mechanism of thyroid hormone effects on stimulating both bone growth and loss may be regulated by these local factors [126].

Hyperthyroidism speeds up both bone formation and resorption, and lead to osteoporosis because bone formation cannot keep up with resorption [28]. It means that hyperthyroidism contributes to imbalance between bone resorption and formation and leads to accelerate skeletal remodeling and increase bone loss [125, 127]. Hyperthyroidism can lead to 12–15% reduction of bone mineral density (BMD), the dominant affected area is cortical bone. Too much thyroid hormone in adult would cause higher risk of osteoporosis development and fractures [126]. Many studies reported that the consistent increased relative risk of hip fracture is twice to threefold, particularly in postmenopausal women [126].

E. Vitamin D: Same as mentioned before (part B of section 2.3.2.5).

F. IGF-1, GH

The effects of GH include to enhance the type I collagen fiber synthesis, induce the proliferation of osteoblast and stimulate the IGH- I secretion from liver. The effects of IGF-1 are to promote osteoblastic proliferation and differentiation. The lower level of these hormones may have a deleterious effect on bone mass [25, 41].

G. Prostaglandins (PGs)

Prostaglandins modulate skeletal metabolism including bone formation and resorption, it means it has both anabolic and catabolic effects on bone [124, 128]. The possible mechanism for bone formation may be to stimulate the proliferation and differentiation of the precursors osteoblasts[7, 124]. The possible mechanism for bone resorption may be to stimulate the osteoclastic differentiation [128]. It is hard to predict that PGs will stimulate bone formation or resorption and lead to bone loss or gain, it depends on the factors inducing the PGs production and on the local cellular milieu [128].

H. Glucocorticoids

It is reported that glucocorticoids is needed for inducing the differentiation of osteoblasts [7]. Nevertheless, the inhibitory effects on osteoblasts are inconclusive [129].

2.3.2.7 Medications

A. Glucocorticoids

Excess of exogenous glucocorticoids will lead to secondary osteoporosis. Steroid induced osteoporosis mostly comes from long term therapy. Only a period of days or weeks even with very high dose will not lead to significant bone loss. Apparent bone loss starts within months of beginning therapy. Bone loss is up to 20% of the bone mass in the first year of therapy [27, 39]. Bone loss would become slower and persistent after the initial rapid bone loss stage [129].

The major negative effects of glucocordicoid on bone are shown as follows [7, 39, 129]:

a. Inhibition of osteoblast proliferation, differentiation and function

b. Activation of osteoclast activity

c. Decreased intestinal absorption of calcium

d. Increased renal excretion of calcium

e. Decreased secretion of gonadal hormone

f. Increased secretion of PTH

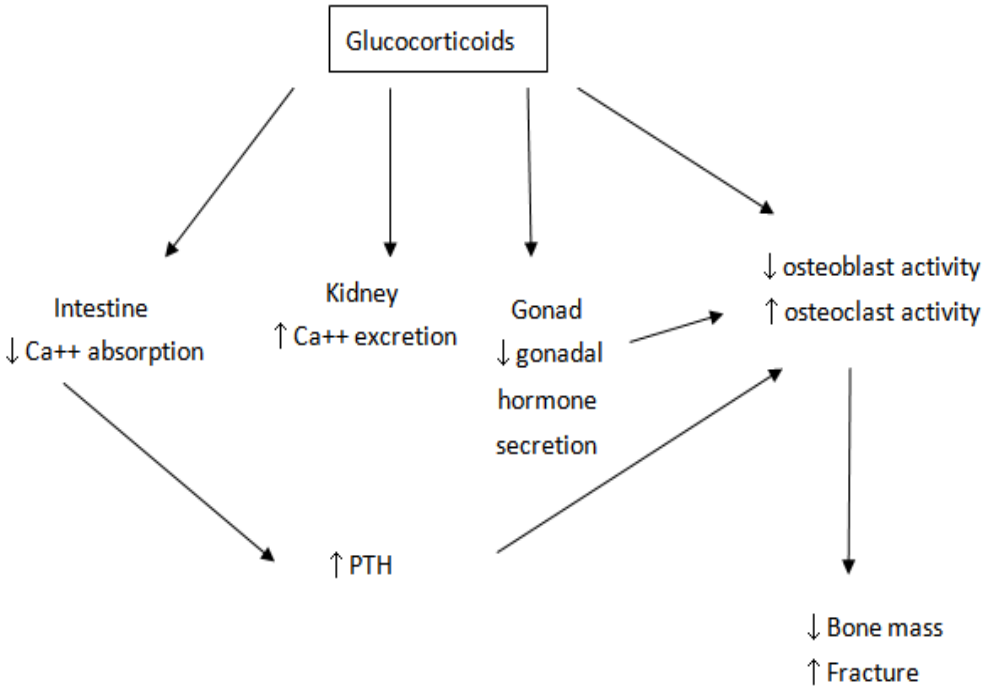


Figure: negative effects of glucocorticoids on bone (figure modified from Bartl R, 2004 [39])

B. Thyroid hormone: same as mentioned before (part D of section 2.3.2.6).

2.3.2.8 Diseases

Several diseases were reported to associate with low bone mass such as cardiac disease, hypogonadism, hyperthyroidism, hyperthyroidism, hypercortisolism, diabetes mellitus, the chronic gastrointestinal disorders, chronic renal insufficiency, chronic neurologic disorders, malignant tumors, chronic pulmonary disease, rheumatoid arthritis.

A. Cardiac disease:

Patients who receive the cardiac valves operation and anticoagulant therapy

for long periods are particularly vulnerable to bone loss. In addition, inactivity of cardiac patients also may lead to bone loss [28].

B. Hypogonadism: same as mentioned before (part A of section 2.3.2.6).

C. Hyperthyroidism: same as mentioned before (part D of section 2.3.2.6).

D. Hyperparathyroidism: same as mentioned before (part B of section 2.3.2.6).

E. Hypercortisolism

The endogenous form of excess glucocorticoid is rare, but glucocorticosteroid induced osteoporosis is common [6, 28].

F. Diabetes mellitus

For diabetes mellitus, the secretion of insulin would be insufficient and collagen production would be inhibited. It will lead to bone loss oftentimes than generally realized [28].

G. The chronic gastrointestinal disorders

The chronic gastrointestinal disorders such as malabsorption syndromes, lactose intolerance, pancreatic insufficiency……commonly cause bone loss due to deficiency of vitamins D, K and C [6, 28].

H. Chronic renal insufficiency

Chronic renal insufficiency leads to bone loss due to deficiency in vitamin D metabolism [28].

I. Chronic neurologic disorders

Chronic neurologic disorders such as stroke, parkinson's disease, Alzheimer's ……. They associate with low bone mass due to immobility (reducing physical activity), poor nutrition and drugs [7, 28].

J. Malignant tumors

The secretion of cytokines such as IL- 1 and IL- 6 will increase and activate the osteoclast activity, these effects will lead to the bone loss [7].

K. Chronic pulmonary disease

Chronic pulmonary disease such as COPD and asthma with long term steroid dependent should be regularly monitored for prevention of bone loss [28].

L. Rheumatoid arthritis

The patients commonly combine with joint pain, immobilization and glucocorticoid therapy, these effects will lead to bone loss [6, 7, 28].

Any risk factor would not exist alone, they interacted with others, therefore must make the overall considerations.

2.4 Risk factors of osteoporotic fractures

Osteoporosis is asymptomatic until fractures occur, it would result in impairing physical and psychological function and quality of life would be affected [44,

[130, 131], Prevention of osteoporotic fracture is very important for postmenopausal women and elderly.

There are many risk factors of osteoporosis- related fractures, they will be discussed as follows:

2.4.1 Risk factors which cannot be modified: advanced age, gender, low BMD, previous fracture history and family osteoporotic fracture history, race

2.4.1.1 Advanced age

The fracture risk is increased with increasing age [44, 132]. After 50 years old, when increasing every 7 or 8 years, fracture risk is double in women [44]. A review study for postmenopausal women reported that the risk ratio of hip fracture was 2.77 to 3.42 with increasing every 10 years interval [132].

2.4.1.2 Gender

Risk of fracture is higher in women than in men [130]. It was reported that women have 2 times higher hip fracture risk than men, and it may be due to menopause, higher risk of fall and longer life expectancy [133].

2.4.1.3 Low BMD

Lower BMD is closely associated with higher fracture risk, mainly for women older than 65 years old [44, 50].

Many studies reported that lowering each SD of BMD, the fracture risk increased from 1.4 to 2.6 times [116]. A decrease of 1 SD in T score increases the risk of fracture relative risk (RR) of 1.54 [35, 134]. Another study in 2006 showed that lowering

every 1 SD of BMD would result in increasing 2.3 and 2.6 times of fracture risk at spine and hip [44].

However, the change of BMD (such as drug therapy leads to BMD change) does not fully express decreasing risk of fracture [31, 44].

2.4.1.4 Previous fracture history and family osteoporotic fracture history

There is a consistent conclusion that a previous fracture would increase the risk of future fracture [50, 135]. People with a history of fragility fracture after 40 years old have a higher risk for another new incident. The risk is ranged from 1.5- 9.5 folds according to age at assessment, number of previous fractures and the site of the fracture. The result of pooling data from many studies and for all fracture sites reported that those with a prior fracture had 2.2 times (95% CI: 1.9- 2.6) of further fracture risk than those without a prior fragility fracture [136]. It has been reported that the risk of another vertebral fracture is as high as 5 times after one vertebral fracture incident, while the risk is increased to 12 times in those with history of two or more fractures [26, 44]. The risk ratio of hip fracture was 9.79 with prior osteoporosis- related hip fracture history [132].

The increased fracture risk will associate with the fracture history of first-degree relative [44, 136]. If one of parents had hip fracture history, about 50 to 127% more risk of hip fracture would occur [44]. A review study showed that risk ratio of hip fracture was 1.53 to 2.00, 1.75 and 1.38 with history of maternal hip fracture, parental hip fracture and any parental fracture, respectively [132].

2.4.1.5 Race

According to be mentioned before about BMD, the Asians are expected to have the highest risk of fracture, followed by Caucasians and blacks have the lowest risk. Nevertheless, the differences in fracture risk and BMD do not necessarily parallel. In most studies, white women have higher hip fracture rates than blacks and Asians, a lower fracture risk for black women has been shown. Hip fracture risk of Asians women is 40- 50% lower than Caucasians; and the risk of black is 50- 60% lower than Caucasians [2, 137]. Black women have higher BMD because of higher peak bone mass and a later onset or slower rate of bone loss [138, 139]. This conflicting result demonstrated that bone density is a major but not the only one factor to influence bone strength [137, 140], race as well as the factor influence the fracture risk [2, 141].

Many studies reported that hip bone strength is not only associated with BMD but also with the hip geometry between ethnic groups [142], the hip axis length (HAL) is a particularly interesting issue in that, it is a factor to predit hip fracture risk, and it is an independent factor and not affected by other factors, such as age, femoral BMD and body size….. [134, 140, 143]. The difference of HAL in different race may lead to ethnic differences of hip fracture risk [138]. The reason may be associated with the biomechanical principle that the longer the length, the smaller force was needed to destroy it. Greater trochanter combining with a longer hip axis will stick out further,

when fall occurs, it may be the point to be hit commonly, this is another possible reason [143]. Many previous studies have demonstrated that black and Asian women have significantly shorter HAL than Caucasians [35, 137, 138, 142, 144]. Cummings's study in 1994 showed that Asians and blacks women would have a 47% (95% CI: 32- 63%) and 32% (95% CI: 15- 45%) lower hip fracture risk respectively than white women due to their shorter HAL, so a shorter HAL may be important to explain the lower risk of hip fracture in Asian women and the lower risk in black women [137].

2.4.2 Risk factors which can be modified: life style, medical disease, low body weight, medications, risk factors for falling

2.4.2.1 Life style

The risk factors of osteoporotic fractures contain many life style factors, they are very similar to osteoporosis risk factors mentioned before. The factors include:

A. Nutrition: such as vitamin D and calcium level insufficiency [44]

B. Physical activity: such as the effect of prolonged immobilization [44]

C. Smoking: smokers lead to rapid bone loss and earlier menopause (average 2 years earlier) than nonsmokers. Postmenopausal women with smoking habit recently comparing with nonsmoker would result in higher risk of fracture [44].

D. Alcohol consumption: intake heavy amount of alcohol would lead to higher fall and hip fracture risk (more than 7 oz or 200 ml/ week, or more than 2 drinks/ day, or more than 2 units/ day) [31, 44, 130].

E. Caffeine intake: for elderly women, too much caffeine intake would associate with higher hip fracture [2]

2.4.2.2 Medical disease

Disease resulting in secondary osteoporosis would be the risk factor of fracture, such as hyperthyroidism, gastric surgery, hypogonadism, premature menopause (< 40 years old), chronic malabsorption, RA, hyperparathyroidism, type I diabetes mellitus, chronic renal disease, and chronic liver disease [1, 50, 130, 132, 141, 145].

2.4.2.3 Low body weight

Low body weight is a risk factor of low BMD and fracture. In US, low weight means the lower quartile of weight (about 127 lb or 57.7 kg) or lower BMI (small than 21 kg/m^2) for women older than 65 years old [44]. WHO reported that low body weight was BMI <19 kg/m^2 [, 50].

2.4.2.4 Medications

Prior or recent using of glucocorticoid therapy is a reason leading to fracture (such as prednisone 7.5 mg/ day or more for more than 3 months) [24, 116, 130, 141] . The risk ratio of hip fracture was 2.07 with ever using of corticosteroids [132].

2.4.2.5 Risk factors for falling

Fall is an important risk factor to increase fracture risk, factors lead to fall including visual impairment, muscle weakness, poor balance, arthritis, poor psychological condition (such as depression), cognitive impairment, hemiparesis, Parkinson's disease, dementia, vertigo, poor health condition, low physical activity, alcoholism and history of recent falls [1, 116, 141, 146]. Medications which may induce dizziness or balance problem would also increase fall risk [32].

2.5 Self screening tool for risk of osteoporosis and osteoporotic fracture: OSTA (the osteoporosis self assessment tool for Asians)

Treatments of osteoporosis can decrease the risk of fracture half [147], but the bone microarchitecture has been destroyed and the bone strength can not be restored. So, the treatment should begin when BMD is lower than the range of normal and before it drops into the range of osteoporosis [147, 148]. Because of the cost and inconvenience to monitor the BMD, a simple questionnaire for Asian postmenopausal women (OSTA: the osteoporosis self assessment tool for Asians) has been developed to estimate the subject's risk of osteoporosis. Potential risk factors associated with BMD and/ or fracture were used in this questionnaire, statistical analysis was used to find a simple index from these risk factors, simplifying the index by reducing the number of factors to as few as possible while yielding similar good performance. The result indicated that only age and weight perform well for identifying women with osteoporosis [147, 148]. The indexis calculated as: (weight in kg- age in years) × 0.2 and truncate to integer [20, 149]. When the index being smaller than -4 (age- body weight > 20), it is at the highest risk. This group is recommended to treatment without checking BMD. The lowest risk group is that index > -1, in this group, the prevalence of osteoporosis is low unless they combine other risk factors, so it is reasonable to postpone BMD measurements and considerable cost will be saved. The moderate risk is index= -1 to -4. For this

group, if the budget is sufficient, all women could be measured, if the budget is limited, the measurement could be focused to those combine other risk factors [147, 149]. The tool is simple and easy to use. It is altered the range of risk category in Europe, US and Latin American, they also performed well to identify risk of osteoporosis for women [150]. This tool also used to predict fracture risk [148]. Using OSTA to predict the nonvertebral fracture risk in Chinese postmenopausal women, -1 as cutoff value, the sensitivity and specificity were 75% and 48% respectively, for discriminating subjects with nonvertebral fracture, and area under the ROC curve (AUC) was 0.64. It is a simple, effective and cost- effective clinical tool to predict the risk of nonvertebral fracture in postmenopausal women [148]

The classification of OSTA risk by the index and the treatment suggestions are summarized as follows:

Index	Risk	Treatment suggestion
＜-4	High	Treat without checking BMD
-4< index <-1	Moderate	Sufficient budget: checking BMD for all

		Limited budget: checking BMD for those with other risk factors
>-1	Low	Postpone checking BMD

2.6 Treatment of osteoporosis

Treatment of osteoporosis includes pharmacological therapy and non-pharmacological therapy, they will be described as follows:

2.6.1 Pharmacological therapy

There are three categories of pharmacological therapy for osteoporosis: (1). antiresorptive drugs; (2). anabolic drugs; (3). combination of 1and 2 [151, 152].

2.6.1.1 Antiresorptive drugs

The common therapies of osteoporosis were antiresorptive drugs for the last 50 years. They are used to inhibit overactivity of osteoclasts through many mechanisms and result in reduction of bone loss, the average change in bone mineral density is about 1- 8% [151, 153]. These drugs include calcitonin, estrogens, selective estrogen receptor modulators (SERM), and bisphosphonates [151]. They are discussed as follows:

A. Calcitonin

It is an endogenous peptide of 32 amino acids [50] and produces by the parafollicular C cells of the thyroid [124], it can inhibit the activity of osteoclast [50, 124]. However, comparing with HRT or the bisphosphonates, the effect of calcitonin is weaker [154]. It is also thought to inhibit the differentiation of pre- osteoclasts and lead to reduce the lifespan and number of mature osteoclasts [50]. It exerts rapid, transient and reversible inhibition of bone resorption [32]. Calcitonin has an analgesic effect on pain relief, its effect is equal to or stronger than NSAIDs [7, 145, 155], it is used for patients with vertebral fracture, particularly in acute stage [50, 124, 145, 155, 156]. The possible mechanism is that the calcitonin may stimulate the secretion of β- endorphins and lead to relieve pain [7]. It may also have positive effect on reducing spinal fracture. A study in 2000, 287 postmenopausal women with osteoporosis received intranasal calcitonin 200 IU/ day for 5 years, the results showed that the risk of new vertebral fractures significantly decreased about 33% compared with control (relative risk = 0.67, 95CI= 0.47- 0.97, P= 0.03) [157]. However, its effect on reducing hip and nonvertebral fractures remains questionable [145, 155].

Calcitonin is given either by intramuscular injection or nasal spray [50, 124], serious side effects of calcitonin have not been found [154]. The side effects of calcitonin include nausea, flushing of the face and hands, heat feeling and injection site reactions when it received intramuscular injection and mucosal irritation when it received nasal

spray [31, 124, 145]. It is too expensive to be used as the first line treatment [145, 155].

B. Estrogen (HRT: Hormone replacement therapy):

Estrogens are traditionally the first line strategy for preventing rapid bone loss and increasing bone mass after the menopause [154].

The mechanisms of estrogen on bone are discussed as follows [119]:

a. Inhibition of osteoclast activity.

b. Stimulation of collagen synthesis by osteoblasts. These two mechanisms may be the classical estrogen receptors mechanism, presumably via the osteoblast. The estrogen effects include to induce cell proliferation and differentiation, the substance- genisten may activate bone formation activities, as well as inhibit the interleukin-6(IL-6) secretion and synthesis and this effect results in suppressing osteoclasts differentiation and activity through osteoblast- mediated effect [119].

c. Promotion of gastrointestinal absorption of calcium.

d. Stimulation of calcitonin secretion.

e. Modulation of PTH.

f. Improvement of central nervous functions and therefore decrease the tendency of fall.

The use of estrogen will lead to decrease the risk of fractures [31, 119, 145]. The major effect of HRT is on trabecular bone. The greatest effect is on the vertebral column [119]. It is reported that the bone density of lumbar spine will increase up to 10% and up to 4% in femoral neck after 2- year HRT. Other positive effects of HRT use are decreasing risk of colon cancer, being beneficial to lipids and lipoproteins, increasing high density lipoprotein (HDL) amount and lowering LDL amount [119, 154]. As soon as HRT is discontinued, bone loss immediately resumes with the rate of menopause [25, 32, 119], and after 3- 4 years the bone density will return to its initial value [25, 119, 158]. After the therapy cease, the BMD will decrease up to 4.5% and 3.3% at lumbar spine and hip in the first year [32].

The major side effects of estrogen include:

a. Withdrawal bleeding: Estrogen is related to uterine hyperplasia, patients take estrogen may have the inconvenience of periodic bleeding, a lot of women quit the treatment in a short time due to this reason. To prevent the monthly withdrawal bleeding, the combination of estrogen and progestogen for 12- 14 days per month is useful, this combination can also prevent endometrial hyperplasia and carcinoma [6, 119, 154].
b. Endometrial cancer: For women aged 50 years who have about 3% lifetime risk of endometrial cancer. The use of estrogen increases this risk by 4 and 10 times after 5 years and 10 years of use, respectively. The endometrial cancer risk will decrease and almost

return to the background rate if using the progestogens along with estrogen for 12 days or more every month [119, 154].

c. Breast cancer: One of major reasons that many patients do not take HRT and many doctors do not recommend it for postmenopausal women, is that the fear of increasing the breast cancer risk. Some evidence reported that the using of HRTs will result in the higher risk of developing breast cancer, [6, 119, 154, 155], nevertheless, some studies reported the lower mortality rate of breast cancer in women who use the HRTs [119, 154].

d. Venous thromboembolism: The using of HRT will increase two to fourfold risk of venous thromboembolism. The hemostatic assessment before the treatment is necessary for those women who have previous venous thromboembolic events or a strong family history of thromboembolic disorders [119, 154].

The minor side effects of estrogen include abdominal bloatedness, muscle cramps, headache, and breast tenderness [154]. In addition, the evidence reported that the risk of cardiovascular events, stroke and myocardial infarction increased during the course of the estrogen combined with progestin, the risk of stroke increased and failed to decrease the incidence of coronary heart disease by estrogen alone [6, 31, 32, 50].

Estrogen has positive effect on prevention and management of osteoporosis, however, the overall harm outweighed the significant benefit on bone[119, 145, 151], HRT is no longer recommended as a first choice therapy of osteoporosis for postmenopausal women[50, 155]. Many patients consider using other drugs unless other drugs are unable to be considered[32].

C. SERM (selective estrogen receptor modulator)

SERMs are estrogen like compounds, they decrease osteoclast activity by acting on estrogen receptors[145, 155] . SERMs have been developed to provide many of the beneficial effects of estrogen as possible but without its unwanted side effects. It has estrogen agonist effects on bone and lipids, and estrogen antagonist effects especially on breast and uterine stimulation [32, 154, 159]. Raloxifene (Evista) was the first SERM developped specifically for the prevention and treatment of osteoporosis[160], and it is the only licensed drug for osteoporosis [31, 50, 145, 161].

It is assumed the actions of the SERM occur through binding with high affinity to classical estrogen receptors. Two different types of receptors were identified, ER- α and ER- β. There are different tissue expression of these receptors, because of the interaction of receptors and ligands, there is the specific tissue response to individual ligands. Raloxifene can bind with both receptors but serve for different function. It functions as antagonists when bound to ER- β and as agonists when bound

to ER- α. In addition, there are a variety of coactivators and corepressors which can modify the ligand- receptor complex activity. Thus, the receptor expression, conformation of ligand- receptor complex, and cofactors' expression and activity will affect the activity and expression of any tissue[155, 159, 160]. The effect of SERMs inhibit bone resorption may have the same mechanism as estrogen, it can decrease the production of cytokines to limit its function of osteoclast differentiation promotion. It can also inhibit the activation of osteoclast by stimulating TGF-β3. TGF-β3 also reduces to induce bone resorption by decreasing the activation of IL-6. It may also have effect on osteocytes which play a role on the control of bone remodeling, cause completely normal bone structure and without mineralization defects[159].

Raloxifene is particularly helpful for postmenopausal osteoporosis. It has been approved for preventing bone loss and may have advantages for the long term maintenance therapy. Although its action is weaker than estrogen, Raloxifene does not lead to breast tenderness and may decrease the risk of breast cancer [6, 154, 162]. The MORE study reported that the frequency of breast cancer was decreased about 70% using Raloxifene than placebo (RR= 0.3, 95%CI: 0.2- 0.6) [163]. It would not stimulate the endometrium and cause uterine bleeding either. In addition, it can prevent cardiovascular disease [6, 154, 162].

The decreasing risk of one or more new vertebral fractures is 43% (RR= 0.57,

95CI= 0.48 to 0.69) and 36% (RR= 0.64, 95CI= 0.53 to 0.76) respectively with high dose (120 mg/ day) and low dose (60 mg/ day) raloxifene therapy over 4 years. However, no effect was found on the risk of nonvertebral fractures[164]. Another study in 2003, the result reported that a 5- year raloxifene therapy significantly increasing BMD at lumbar spine and hip as 2.8% and 2.6% when comparing with placebo ($p < 0.001$)[165].

The major side effects of Raloxifene are increasing the risk of deep vein thrombosis and pulmonary embolus to about the same degree as estrogen and HRT[31, 160], and it may increase the incidence of vasomotor symptoms (e.g. hot flushes)[6, 31, 145]. Withdraw of long term raloxifene therapy for one year, the rate of bone loss would be similar to placebo[166]. For women, if the side effects of bisphosphonates can't stand or the risk of breast cancer increased, Raloxifene would be the preferable choice [145].

D. Bisphosphonates:

Bisphosphonates are the synthetic analogues of pyrophosphate characterized by a P- C- P bond, the structure of bisphosphonates has a strong affinity of binding to hydroxyapatite at the selective sites of active bone remodelling, this effect will lead to higher concentration of the drugs in areas of active bone resorption [32, 50, 155, 167, 168]. The main effect of bisphosphonates is to decrease osteoclasts activity to inhibit bone resorption. In addition, it may inhibit important intracellular proteins and can lead to

osteoclast apoptosis [31, 32, 155, 167, 168]. Bisphosphonates have a short half life in plasma, but they have a several years half life in bone, their excretion from the bone is slow[50]. Bisphosphonates are successfully approved for the prevention and management for osteoporosis including Alendronate (Fosamax), Risedronate (Actonel), Ibandronate (Boniva) and Zoledronic acid (Reclast). Bisphosphonates is now recommended as first line medications for postmenopausal women with osteoporosis [31, 32, 145, 152, 155].

The action mechanism of bisphosphonates [168]:

a. Bisphosphonates has a strong affinity into hydroxyapatite crystals and into the bone matrix, by this process, the solubility of bone substance and mineralization disturbances will be reduced.
b. Reduction in recruitment and in fusion of osteoclast precursors (direct influence on the monocyte- macrophage system)
c. Inhibition of enzymes metabolism.
d. Induction apoptosis of the osteoclast may shorten the osteoclastic survival period, and probably associated with lengthening osteoblastic survival period. It means that the phase periods in the remodeling cycle may be changed.
e. The production of prostaglandin E2, proteolytic enzymes, IL- 1 and 6, and many other cytokinesare inhibited.

f. The factors which are produced by osteoblasts coupling in the osteoblast- osteoclast cycle are disturbed, and this effect will inhibit osteoclastic resorption indirectly.

g. Inhibition the adherence of osteoclasts to the bone surface.

1- 3 years is the optimal recommended duration for bisphosphonate therapy. During the first year, since the resorption lacunae are repaired and refilled, the most prominent effect of the therapy on increasing bone density can be noted. However, the positive effect will be less since the structure and width of the trabecular have been reapired during the rebuilding and maintence phases [168]. When stopping therapy, the bone turnover rate is only partial increased and the bone loss rate is slowered [167], the beneficial effect on mineral density can last for one year for cortical and trabecular bone [168]. All drugs have positive effect on decreasing risk of fracture, the use of Alendronate, Risedronate and Zoledronic acid would prevent vertebral, hip and nonvertebral (arm or wrist) fractures, however, Ibandronate prevents vertebral fractures but just little effect on hip and nonvertebral fractures [145, 151].

Maximal absorption of these drugs is poor from the gastrointestinal tract even under the best condition. The absorption is less than 10% of a dose and most of it is only 1%. Therefore, for the drugs absorption, using the drugs after an overnight fast with large water only is suggested, and after intake of drugs, the fasting state is

maintaining and does't lie down for an additional 30 to 60 minutes. The side effect of three bisphosphonates has been noted is upper gastrointestinal tolerability (including acid reflux, trouble swallowing, heartburn, and nausea) in clinical practice [6, 145, 151]. The less common side effect is musculoskeletal (bone, muscle, joint) pain, osteonecrosis of the jaw is one possible side effect, it is severe but rare [145, 155].

2.6.1.2 Anabolic drugs

The effects of antiresorptive drugs are to protect and maintain bone architecture, however, the anabolic drugs have the unique effect to restore the deteriorated architecture of osteoporotic bone [151]. PTH can exert an anabolic effect by intermittent dose, it directly stimulates osteoblast and increases in bone formation, which results in increased trabecular bone density and connectivity. However, continuous exposure to PTH would cause opposite effects to increase bone resorption and reduce bone mass [31, 32, 50].

Teriparatide (recombinant human PTH (1- 34)) is the first approved and the only formulation of PTH available anabolic drug for the management of osteoporosis [31, 50, 151, 169].

This type of drug is opposed to antiresorptive drugs, it has a longer residence in bone and inhibition of bone turnover [151]. It reported that the positive benefits of

18 to 24- month administration of teriparatide may last for many months (up to 30 months) after the drug is discontinued [155]. In the same time intervals, the drug showed better effect on increasing bone mass and reducing risk of fractures comparing with the antiresorptive drugs. The information of clinical trial data for teriparatide is limited to 18to 24 months. Therefore, the effect of the drug is approved for only a 24- month administration and the longitudinal information is lack [13, 31, 50, 151]. In Neer's study, the results showed that postmenopausal women treatment with teriparatide reduced 65% and 53% risk of vertebral fractures and nonvertebral fractures respectively compared with placebo. In the same study, the BMD of lumbar spine significantly increased about 13.7% and total hip increased about 3.6% compared with placebo ($p < 0.001$) [169].

The common side effects of teriparatide include muscle cramps, pain in the limbs, nausea, headache, slight and transient hypercalcemia, and dizziness [13, 31, 155]. Its short term side effects are relatively few, however, its long term safety has not been developed [145]. Parathyroid hormone is high cost and reserved only for women with a very high risk for fracture [13, 145].

2.6.1.3 Combination of antiresorptive and anabolic drugs: Strontium Ranelate (SR)

Strontium renalate is a new agent and it has the anabolic and antiresorptive effects [50, 151, 170], the effects of SR treatment for postmenopausal women with osteoporosis have been approved by European Union [50]. SR does have both effect on increasing bone formation and decreasing bone resorption simultaneously [13, 155, 170]. This drug acts as blocking antibody to inhibit the activity of osteoclastic RANK by disturbing the binding of the stimulatory protein which is released by osteoblasts [151, 170].

A study in 2004 reported that postmenopausal women with strontium renalate therapy would reduce the risk of new vertebral fractures about 49% by first year, and about 41% over the 3- year study period (RR= 0.59, 95% CI= 0.48 to 0.73). In the same study, strontium renalate therapy would increase BMD at lumbar spine about 14.4%, and about 8.3% at femoral neck at month 36 [171]. It is proved that this therapy could reduce the risk of hip, vertebral and nonvertebral fractures, and the magnitude of effect is similar to oral bisphosphonates [13, 155].

The common side effects of strontium renalate are nausea, diarrhea, increased risk of venous thromboembolism [13], particular attention should be given in patients at high risk of venous thromboembolism including with a past history [155].

Who and when should administer what kind of drug is very important question, however, there is no clear guideline but opinion alone nowadays. The higher cost of the anabolic therapy is a main consideration of patients and clinicians. Generally speaking, the effect of all kinds of antiresorptive drugs for postmenopausal osteoporosis is proved. The effects of bisphosphonates, alendronate and risedronate, have been approved for glucocorticoid induced osteoporosis. It is not good to use multiple antiresorptive drugs simultaneously, one drug is enough. If one drug is lack of efficacy, selecting another one is suggested [151]. It is very important for practitioners to make sure that patients use the prescribed drugs and with correct manners. It is approved that good compliance of osteoporosis therapy would lead to reduce risk of fractures, decrease the bone turnover rate, and larger gains of BMD [31, 151, 155]. However, it has been demonstrated that the compliance of osteoporosis medications is poor and one year later, only few patients keep using prescribed drugs [31, 151, 172, 173].

2.6.2 Nonpharmacologic therapy

Appropriate treatment is very important for osteoporosis, it will lead to reduce fracture risk, morbidity, mortality, and hospital and long term care cost. Non

pharmacologic therapy should be combined with pharmacologic therapy for osteoporosis, including calcium and vitamin D intake, exercise, and fall prevention [31].

It is necessary for all women paying attention to the risks of osteoporosis development and learning how to decrease the bone loss and fracture risks [32]. There should be general life style assessment for all subjects with risk of osteoporosis [50]. Education on the value of bone health to reduce fracture risk may motivate and encourage subjects to make behavior changes and keep healthy lifestyle [32]. Nonpharmacologic interventions (lifestyle changes) to maintain bone health and prevent osteoporotic fractures will be discussed in detail as follows. It includes (1). nutrition, ((2). physical activity, and (3). other lifestyle factors [6, 13, 32, 155].

2.6.2.1 Nutrition

A well balanced diet is necessary for general health and good bone health. The adequate intake of vitamins, minerals, and protein is important for maintaining optimal bone mass [31]. The suggested dosage of nutrition is discussed in detail as aforementioned. For maximizing peak bone mass, the intake of adequate vitamin D and calcium every day is the most important consideration[66]. The optimal nutrients are from dietary sources, however, if it is not possible to get suggested amount of daily intake by diet alone, supplements should be used [32]. The recommendation of the National Academy of Sciences is 1200 mg calcium and 400 to 600 IU of vitamin D as

adequate daily intakes for 50 years or older age women [174]. Increase in the required level of calcium during advancing age is necessary, particularly for postmenopausal women, due to declined intestinal calcium absorption and increased renal calcium excretion. The amount of calcium absorbed is primarily influenced by the amount of calcium ingested [44]. It is reported that most adolescents and the elderly are vitamin D insufficient or deficient [50]. Most elderly had low dietary intakes of vitamin D. The low serum level of vitamin D is reported in about 10% and 37% of community dwelling and institutionalized elderly [50].

Protein is also commonly insufficient in elderly. Sufficient protein intake is important for maintaining the integrity and function of several organs or systems, including musculoskeletal system and reduce the risk and complications of fractures in the patients with osteoporosis. 1 g/kg body weight of protein is usually recommended for subjects with osteoporosis [13, 155].

2.6.2.2 Physical activity

Physical activity is recommended to prevent and treat osteoporosis, we will discuss the details in section 2.8.

2.6.2.3 Other lifestyle factors

Cigarette smoking and excess alcohol consumption should be avoided since they are well known adverse factors on multiple organ systems as well as on

decreasing BMD and increasing risk of fractures [6, 44]. Moderate alcohol consumption is recommended for postmenopausal women (< 7 drinks/ week). An increased adverse effects on bone health was noted when alcohol consumption is more than seven drinks a week [31, 32, 175]. One drink is viewed as one 12-oz (360 mL) beer, 4 oz (120 mL) of wine, or 1 oz (30 mL) of liquor by North American Menopause Society [44]. Another study in 2009 reported that one drink is equal to 13.7 g pure alcohol or 12 ounces of beer, 8 ounces of malt liquor, 5 ounces of wine, 1.5 ounces, or a shot of 80-proof distilled spirits or liquor (gin, rum, vodka, whiskey) [141]. Some studies reported that alcohol intake more than 2 units per day (1 unit about 10 ml or 8 gram of pure alcohol) associates with the increase risk of fractures [116, 155].

Smoking is related with lowering BMD and increasing fracture risk [6]. Quit smoking should be strongly recommended to all smokers [6, 31, 44, 50].

2.7 Management for reducing fracture risk

2.7.1 Exercise

Muscle strength, agility and balance can be improved through regular weight-bearing and muscle strengthening exercise, this effect greatly contributes to lower fall risk and then reduce fracture risk [31, 32]. The effects of exercise on fractures is in section 2.8.

2.7.2 Change lifestyle

Same as osteoporosis prevention and treatment

2.7.3 Fall prevention

Nearly 90% of fractures of elderly have been documented to be caused by falls [31, 44, 176]. About a third of older people fall at least once a year and nearly one half have recurrent falls. The risk of falls increases with advancing age, it rises to about 50% per year in the elderly aged larger than 80 [44]. When the force of fall impact to the bone larger than the bone strength, fracture would occur [6]. The major reasons for falling are summarized as follows (the following information table is from Bartl R, 2004 [146]):

Major reasons for falling in the elderly
General deterioration
Poor postural control Weakness Abnormal gait Poor vision Slow reaction time Anxiety and agitation Fear of falling
Specific diseases and drugs

Cerebrovascular disease Parkinson's disease Arthritis Blackouts Sedatives Medications that may contribute to hypotension Alcohol
Environmental causes
Low level lighting Slippery surfaces Uneven pavements Lack of assistive devices in bathrooms Loose rugs Bad weather, wind and rain Tripping over mats or child's toys

Prevention of falling is very important for elderly and postmenopausal women, the programs include [6, 31, 32, 177]:

2.7.3.1 Exercise

Exercise is to improve balance, muscle strength, agility, and muscle coordination. The combination of weight- bearing exercise and muscle strengthening should be recommended. The effect of exercise on falls is in section 2.8. It should be considered that vigorous exercise may cause increase of risk of fractures. Forward flexion exercises should be avoided for patients with osteoporosis of spine to prevent development of kyphosis.

2.7.3.2 Medications

Reviewing medications is necessary, using some medications may affect balance or stability especially psychotropic drugs (including sedatives, narcotic analgesics, antidepressants, anticholinergics, and antihypertensive agents)

2.7.3.3 Checking and correcting vision and hearing

2.7.3.4 Assessing neurological problems

2.7.3.5 Vitamin D supplementation

Vitamin D supplementation results in decreasing the risk of fall, it may be via increased muscle strength and improved balance [6, 32].

2.7.3.6 Reducing home hazards

Safety hazards in the home are summarized as follows [44] (the recommendation for safety home environment for fall prevention is from North American Menopause Society, 2006):

Lighting
- Provide ample lighting
- Have easy-to-locate light switches for rooms and stairs
- Use night lights to illuminate walkways

Obstructions
- Remove clutter, low-lying objects
- Remove raised door sills to ensure smooth transition

Floors and carpets
- Provide nonskid rugs on slippery floors
- Repair/replace worn, buckled, or curled carpet
- Use nonskid floor wax

Furniture
- Arrange furniture to ensure clear pathways
- Remove or avoid low chairs and armless chairs
- Adjust bed height if too high or low

Storage
- Install shelves and cupboards at accessible height
- Keep frequently used items at waist height

Bathroom
- Install grab bars in tub, shower, near toilet
- Use chair in shower and tub
- Install nonskid strips/decals in tub/shower

2.7.3.7 Devices

For patients of high falling risk or who have previous hip fracture history, hip protector should be considered to reduce the risk of hip fractures [6, 31, 32, 44, 50, 155]. If necessary, an external protective and asssitive device is used to improve the safety and reduce the impact force transmitted to the proximal femur and may reduce the risk of hip fracture in the elderly people [158, 178].

2.8 Physical activity for osteoporosis and osteoporotic fractures

The interventions for prevention and treatment of osteoporosis include

pharmacologic and nonpharmacologic interventions. For postmenopausal women, the pharmacologic interventions have the positive effects for increasing bone mass and reducing the risk of fractures, however, they need high cost and suffer from negative side effects [14, 179, 180]. For example, every day intake 10 mg of alendronate will cost about $ 50 every month, and patients may suffer side effects such as nausea and abdominal pain. The therapy of estrogen- progestin combinations will be cheaper than alendronate, the average cost of every month is about $ 10- 15, however, it may have severe side effects such as vaginal bleeding, breast tenderness, and may increase breast cancer risk. Some patients using intranasal calcitonin will induce nasal dryness and irritation, and it costs about $ 50 every month [14]. In contrast, nonpharmacologic intervention such as aerobic exercise is cheaper, accessible and without obvious adverse effects [14, 181]. Aerobic exercise has been recommended to prevent and treatment for osteoporosis [14, 179].

A very important factor leading to bone loss is inactivity. Bed rest one week would cause loss bone as much as the loss in a year [155]. For this reason, it is recommended to avoid inactivity and establish a lifelong physical activity as a part of lifestyle [13, 155].

Aerobic exercises are not as effective as most pharmacologic therapies on bone mineral density at hip. It is reported that took 10 mg alendronate every day, the

femoral neck bone density increased about 6% over 3 years and aerobic exercise got the effects about 2 % [14]. However, many studies had proved the positive effect of exercise on bone mineral density (BMD), prevention of falls or osteoporosis-related fractures [31, 48, 182-185] and also decreasing the severity of falls [49]. Additionally, an exercise program can reduce pain, improve fitness, and provide psychological benefits related to preserved cognitive function and self-efficacy, thereby improving overall quality of life [14, 47, 186, 187].

2.8.1 Effects of exercise on BMD

2.8.1.1 Child (prepubertal and very early pubertal stage)

Physical activity from childhood (before pubertal growth spurt) would make bone be subjected to mechanical loading [188]. It could stimulate greater accumulation of peak bone mass and geometrical changes in bone size and shape, thus physical activity plays an important role for optimizing peak bone mass and strengthening bone. The effects will extend to adult life [188-192]. During this stage, weight bearing and high impact exercise has particular stimulation on bone [188]. A review showed that a positive correlation between physical activity level and BMD in athletic and nonathletic children. For growing children, exercise combining resistance training and impact exercise may have larger positive effects on BMD [192]. Another review article

reported that strength training could lead to higher skeletal density and weight-bearing exercise also has similar effects, endurance exercise has less effect on bone mass [188, 190].

Calcium is needed during this stage to maximize peak bone mass, concurrent application of proper calcium intake and physical activity has more benefits for more bone mineral acquisition. But their long term effects remain to develop [188, 191].

2.8.1.2 Adolescence

It is recommended to maintain physical activity throughout adolescence to keep BMD gains achieved from prepuberty [192].

In 2007, a study in 254 healthy young Japanese women (19- 25 years old) showed that BMD could be predicted by many significant factors including BMI, past physical activity habit and current total energy expenditure [191].

A review study reported that exercise training (including impact loading, muscle stress, and gravitational force) is sites specific with impact loading. Weight loading exercise may be emphalized to maximize peak bone mass at this stage [188], 12-15% more BMD was reported on most athletes in weight bearing exercise than nonathletes [193].

For young female athlete, there should be special medical concern [188]. The prevalence of decreased BMD was 10.7 to 21.8% among them [193]. It is a fallacy in

athletes that continuing weight loss would improve the performance. A continuing abnormal eating patterns can be related with menstrual dysfunction and lead to low bone mass or osteoporosis [188, 194]. Female athlete triad is a serious syndrome combining 3 conditions including: low energy availability, functional hypothalamic amenorrhea, and osteoporosis, it was published by the new ACSM female athlete triad position stand [188, 193]. Exercise should be for health and enjoyment, and dietary is also important [188].

2.8.1.3 Premenopausal women

Peak bone mineral density and rate of bone loss with advancing age are two major factors for adult bone health. So, it is important to maximize premenopausal BMD for prevention of osteoporosis and future osteoporotic fracture [195]. A review study showed that small bone loss (0.25- 1%/ year) occurs and most in femoral neck in healthy premenopausal women. Premenopausal low impact traumatic fractures appear to be positively associated with future postmenopausal fracture risk by 1.5 to 3-folds. [196]. There are similar risk factors of low bone mass in premenopasual and postmenopausal women [196]. Healthy lifestyle is important for premenopausal women, it includes adequate calcium (1000mg/day) and vitamin D (400- 800 IU/ day) intake, regular exercise (weight bearing and resistance exercise), decreasing intake of caffeine (≦ 2 servings/ day) and alcohol (≦ 1 servings/ day), and avoidance of

smoking [196].

Women start high impact weight bearing exercise and strengthening exercise from young age had significantly higher BMD in premenopausal period [188-191, 195]. A study in 2006 reported that the women in a sport club (most of them participated high impact weight bearing exercise) in adolescence had significantly higher BMD in adult than those not in the club, the mean difference was 5.1 to 17.5%. For maintaining the BMD gained from exercise, it is recommended that mechanical loading should be continued after puberty and throughout adult. In this same study, women were in the sport club at 16 years old and kept high impact weight bearing exercise to 36 years old also had significantly higher BMD than who were not active from adolestence, the mean difference was 5.3 to 18.8% [189]. Another review study reported that female athletes with high impact exercise had higher BMD than low or non- impact exercise, e.g. swimming [195].

Weight bearing exercise is important for preserving bone mass in premenopausal women [197]. The recommendation of exercise in Vondracek's review study was moderate intensity of weight bearing exercise (walking, jogging, aerobic……) for 30- 60 minutes for most days of a week [196]. Besides, 20- 30 minutes of resistance exercise (resistance bands, free weight……) at least 2 times/ week was also recommended in this study [196]. A meta- analysis in 2006 showed that high

intensity progressive resistance exercise had positive effect on lumbar spine BMD, the weighted mean difference (WMD) of BMD between exercise group and non- exercise control group was 0.014g/ cm^2 (95% CI: 0.009- 0.019, p< 0.00001). However, no significant finding on femoral neck, the WMD was 0.001g/ cm^2 (95% CI: -0.006- 0.008, p= 0.78). In this study, the protocol of included studies consisted of 2-5 sets of 6-20 repetitions of exercise, the intensity of exercise was about 60- 80% 1RM, the frequency was 2-3 days per week, and the duration was 5 months to 3 years. The results also pointed out that the different loading pattern of resistance training may have different site specific response [197, 198].

2.8.1.4 Postmenopausal women

Many studies discussed the influence of different kinds of exercise on bone mass for postmenopausal women. Kelley's study in 1998, it was a meta-analysis of 6 aerobic exercise studies to examine whether they can improve bone density at hip in postmenopausal women. It reported that the bone density changed at hip about 2.13% in exercise group and -0.29% in nonexercise group [14]. In 1998, Kelley had another meta- analysis from 10 studies to assess the aerobic exercise effects on BMD at lumbar spine in postmenopausal women. The results showed that aerobic exercise had positive effects on BMD of lumbar spine, the change in exercise group was 0.32% and in nonexercise group was -2.51% [199]. Kelley conducted another related study in

2001, a meta- analysis to examine the effects of resistance training on BMD in women from 29 included studies (including premenopausal and postmenopausal women). The results showed that the nonsignificant difference of change on BMD of proximal femur was 0.33% and -0.05% in exercise and control group, significant difference of change on lumbar spine was -0.19% and -1.45% in exercise and control group, significant difference of change on radius was1.22% and -0.95% in exercise and control group. The subgroup analysis showed that resistance training had a positive effect on bone mineral density at the lumbar spine of all women, and at the femur and radius sites for postmenopausal women [200].

In 2008, a meta- analysis evaluated the walking effects on spine and hip BMD in postmenopausal women. It included 8 RCTs and non- RCTs, the exercise duration was 6 to 24 months, the frequency of most studies was 3 days/ week, and walking intervention was 20 to 60 minutes. The results showed that there was a positive effect of walking exercise on hip BMD, the WMD was 0.014 g/ cm^2 (95% CI was 0.000 to 0.028, p= 0.05), no significant effect on spine BMD, the WMD was 0.007 g/ cm^2 (95% CI was -0.001 to 0.016, p= 0.09). However, if only RCTs was evaluated, no significant was reported on spine (7 studies) and hip (5 studies) BMD. The WMD was 0.006 g/ cm^2 (95% CI was -0.004 to 0.016, p= 0.21) and 0.012 g/ cm^2 (95% CI was -0.001 to 0.026, p= 0.06) respectively [201].

A review study in 2004 for early postmenopausal women showed that walking would influence BMD at the intensity over 70% $\dot{V}O2_{max.}$ Some studies in this review also reported positive effects on BMD, they used self selected brisk pace walking exercise for 20 to 30 minutes, corresponding to 54 to 69% $\dot{V}O2_{max}$. The frequency of exercise was 3 to 5 days/ week and duration was 6 months to 1 year, BMD improved 0 to 2% in exercise groups [202].

Some studies reported that aerobics, weight bearing and resistance training exercises all had positive effects on maintaining BMD in postmenopausal women, and walking was also a safe, convenient, and effective exercise on BMD [182, 192]. A meta-analysis from Cochrane in 2002 included randomized controlled trials of exercise intervention for healthy postmenopausal women, length of exercise in included studies was 12 months or longer, and the frequency of exercise in these studies was 2-3 times per week. In this study, aerobics (WMD was 0.83, 95% CI: 0.08 to 1.58), weight bearing (WMD was 1.79, 95% CI: 0.58 to 3.01), resistance exercise (WMD was 2.50, 95% CI: 0.44 to 4.57) and walking (WMD was 1.31, 95% CI: -0.03 to 2.65) all have positive effects on spine BMD, weight bearing exercise and walking were also effective on hip BMD (WMD was 0.92, 95% CI: 0.21 to 1.64), and aerobics was effective on wrist BMD (WMD was1.22, 95% CI: 0.71 to 1.74) [182].

Tai Chi is a popular exercise and its many characteristics make it an effective

exercise for maintaining bone density and improving postural stability [203]. Wayne's review study in 2007 showed that Tai Chi has positive effects on BMD of postmenopausal women in most studies, but some did not [203]. Another review study in 2008 evaluated the effects of Tai Chi on BMD in postmenopausal women. The duration of included studies was 4 to 12 months, the frequency was 2 to 7 sessions/ week, and 40 to 60 minutes/ session. Some studies included in this article showed positive effects on BMD, but others did not. A meta- analysis was conducted, the results showed that no significant effect on spine BMD compared with subjects without Tai Chi practice, the WMD was 0.02 g/ cm^2 (95% CI:-0.02 to 0.06, p= 0.31) [204]. The effect of Tai Chi on BMD is inconclusive from these results.

Evidences showed that exercise in adulthood can keep the bone gains which is achieved from childhood and adolescence as well as prevent the bone mass loss, it is only modest effects on improving bone mass. These effects would be lost quickly if exercise is discontinued [192].

2.8.2 Effects of exercise on fall

More than 30% of community- dwelling elderly fell at least once per year and half of them fell twice or more [183, 205]. For elderly, fall is a very important risk factor for morbidity, hospitalization and mortality [206]. Multiple falling can definitely be viewed as a manifestation of physical fragility [183]. Ten to 15% of falls lead to serious

injuries including major fractures, brain injury, related complications and even death. A survey from 1996 to 2000, in Taiwan, hip fracture incidence in men and women older or equal to 50 years old was 225/ 100000 and 505/ 100000 respectively [206]. Fall prevention is very important in elderly [24]. A review study showed that postmenopausal women with low bone mass (osteoporosis or osteopenia) combining fall history of previous year would increase the risk of fracture. Postmenopausal women with normal BMD and without a fall as the reference, the fracture risk in women with normal BMD combining fall history (past 12 months) was 1.1 (95% CI: 0.1 to 9.6), the risk of women with osteopenia and osteoporosis and without a fall was 2.8 (95% CI: 0.9 to 8.9) and 2.8 (95% CI: 0.6 to 12.8) respectively, the risk of women with osteopenia and osteoporosis combining fall history was 21.0 (95% CI: 7.1 to 62.3) and 24.8 (95% CI: 6.9 to 88.6) respectively [207]. Many studies reported that exercise can increase postural stability, improve balance and decrease the risk of falls and related injuries [48, 206]. Poor balance and muscle strength of lower extremity were important risk factors of fall [206].

The effect of balance training on decreasing fall risk was consistent for elderly [192]. A study assessed the effect of balance training in frail older women, the exercise group received visual feedback specific balance training for 4 weeks, the frequency of exercise was 3 times/ week and 20 to 30 minutes/ time. The result showed that the

monthly risk ratio of fall in exercise group compared with control group was 0.398 (95% CI: 0.174 to 0.911, p= 0.029), the balance training exercise showed significant effect on fall prevention [208]. Another study evaluated the effect of unipedal balance training exercise on fall prevention for high risk elderly, the exercise group received the program standed on each leg for 1 minute per time with eyes opened, 3 times in a day. The result showed that the cumulative number of falls in exercise group and control group for 6 months was 118 (number of subjects in exercise group was 314) and 121 (number of subjects in control group was 212) respectively, there was significant different between these two groups (p= 0.0062). However, there was no significant difference between groups for hip fracture risk [209].

A review study of Pfeifer reported that data of 6 studies was pooled to assess the effect of untargeted group interventions showed no significant effect on the number of falls, but another pooled data from 3 studies with community- dwelling elderly women evaluating the individually tailored program including progressive muscle strengthening, balance retraining, and a walking plan over 1 year period indicated that this program reduced the number of falls (pooled relative risk (RR): 0.8, 95%CI: 0.66- 0.98). It also reduced the number of injurious falls (pooled relative risk (RR): 0.67, 95%CI: 0.51- 0.89) [184]. A meta- analysis reported a 10% reduction (RR: 0.9, 95%CI: 0.81- 0.99) in falls risk associated with general exercise and a 17%

reduction (RR: 0.83, 95%CI: 0.70- 0.98) associated with balance training but no significant effect with endurance, resistance or flexibility training [185].

In 2008, a review study reported that the effects of exercise on fall prevention for elderly were significant. The most effective prescription should include at least two out of three different types of exercise: strengthening, balance training (including Tai Chi, one leg standing, tandem walking, weight shifting, positional changes during ADL, dancing, toe and heel walking, bending to pick up objects, walking over obstacles, turning, and stair climbing) and aerobic/ endurance training (including walking, stationary bicycle, and treadmill walking), the minimum frequency of exercise was 3 times/ week for 30 minutes, and duration of training was at least 12 weeks [205].

A study reviewed the effects of Tai Chi on balance and fall prevention. The results showed that Tai Chi has positive effects on organization of proprioception, visual and vestibular systems, in addition, it could improve flexibility, muscle endurance, concentric and eccentric muscle strength of lower extremity, and neuromuscular coordination. All of these would improve balance and prevent falls. Four weeks intensive Tai Chi program may be sufficient to improve balance function [206]. Another review study also supported the effects of Tai Chi on musculoskeletal health, balance function, and decreasing the fall risk for elderly [192]. Tai Chi is

recommended to elderly for balance training, but the prescription of training dosage was inconclusive.

Weight bearing exercise can improve lower extremity muscle strength, balance, reaction time, and walking speed in elderly individuals. The weight bearing training effect on the risk of fall and fracture is controversy [192]. It is suggested to add balance training to decrease fall risk for elderly [192].

2.8.3 Effects of exercise on preventing osteoporotic fractures

The osteoporotic fracture risk factors include: age, prematural menopause, prior fragility fracture, low estrogen level, amenorrhea, glucocorticoid, maternal hip fracture history, low BMI and all risk factors of fall [1, 183].

Lowered bone mass is the most important risk of osteoporotic fractures [180180]. Exercise can decrease the loss of bone mass, improve mobility, muscle strength, and balance. These effects would reduce the fall risk and also decrease the fracture risk [24].

Many evidences proved that exercise can reduce the risk of fractures. Performing moderate to vigorous exercise at least 2 hours per week would reduce the risk of hip fracture in women aged older than 65 years. In contrast, women would increase the risk of hip fracture if they spent more hours to sit per day. Sitting for longer than or equal to 9 hours per day would increase a 43% higer risk than sitting less than 6 hours per day in women [184]. In sedentary individuals, it was demonstrated

that physical activity was related to a 20- 40% decrease of hip fracture risk by prospective and case- control studies [183, 185].

In 2006, a review and meta- analysis study assessed the effect of different interventions on preventing osteoporotic fractures in high risk osteoporosis population (including postmenopausal women and healthy elderly). For spine, the result showed that muscle strengthening exercise (including all large muscles training or back muscle strengthening exercise, the duration of intervention was 2 or 4 years) could have the trend to decrease the risk of spinal fracture, but brisk walking did not have effect on spinal fracture. Pooling data of these studies reported that exercise groups reduced the risk of spinal fracture compared with control groups but the effect was not significantly different (RR= 0.52, 95% CI: 0.17 to 1.60). Subjects receiving multifactorial interventions (including environmental modifications, exercise programs and review of medical condition, and medication and aids; the duration of intervention was 11 weeks and 4 years) found that the intervention group decreased the risk of hip fracture with borderline statistical significance (RR= 0.37, 95% CI: 0.13 to 1.03). Subjects exposed to 15 minutes outdoor sunlight every day over 12 months showed non-significantly decreasing hip fracture risk, the RR was 0.17 (95% CI: 0.02 to 1.35) [180].

In 2000, a review study reported that older women engaging in moderate exercise would decrease 20 to 60% of hip fracture compared with controls, and the similar finding was found in older men. Many studies found that the risk of hip fracture would decrease in more active elderly including walking, other leisure-time physical activity, household labor, physical activity earlier in life, and/or long-term occupational activity……, the range of hip fracture risk reduction was 30 to 49%. It was a dose- response relationship between hip fracture risk reduction and physical activity intensity increasing [183]. For wrist fracture, this study reported that walking and moderate or vigorous physical activity nonsignificantly increased the risk of wrist fracture, performing high level exercise would increase fracture risk of nonweight-bearing sites about 50% (including wrist, proximal humerus, hand and finger). For spinal fracture, the results showed that women who walked more or equal to 30 minutes per day or engaged in moderate to vigorous intensity exercise (such as tennis or aerobics, > 2 hours/ day) decreased the spinal fracture risk about 20 to 33% [183]. It was concluded from the results that exercise was related with decreasing risk of hip fracture.

In 2008, one meta- analysis study (including 13 RCTs) assessed the relationship between physical activity and hip fracture, the results reported that moderate to vigorous physical activity would decrease the hip fracture risk, the RR

was 0.62 (95% CI: 0.56 to 0.69, p= 0.43) and 0.55 (95% CI: 0.44 to 0.69, p= 0.37) among older women and men [210].

It is proved that physical activity has beneficial effects in the prevention and treatment of osteoporosis and related fractures [14, 211]. The importance of physical activity is not only because it can reduce the bone loss, but also because it has significant benefits on preventing falls and decreasing the fractures risk by improving general health, balance, muscle strength, coordination, posture and postural stability [47, 212, 213].

The results of intervention of exercise program are not always consistent, because the design of programs are different in mode, intensity, duration and frequency from study to study and accurate quantification of each exercise exact dose is very impossible [14, 211]. Therefore, it is not yet clear what modes of physical activity will lead to the greatest bone health.

2.8.4 Exercise prescription

a. Intensity

It is reported that high intensity exercise is more effective to bone health than low to moderate intensity exercise [211]. However, many studies also reported that moderate intensity exercise is sufficient for these population to reduce fall and fracture risk, improve fitness, balance, strength, coordination and quality of life [14, 47,

[188, 212]. Moderate intensity means working hard at 64 to 76% HR_{max} (percentage of maximal heart rate), 40 to 60% VO_2max (maximal oxygen consumption) or 12 to 13 of RPE scale (rating of perceived exertion). It also defined by ACSM as 3 to 6 METs (metabolic equivalent nuits) [214].

For the elder individuals, exercise program should be effective, safe and easy to perform and continue. Although high intensity exercise offers greater potential benefits on bone health [211, 215], it is less acceptable and with lower compliance of the elderly subjects [14, 48, 216], and high intensity or long duration exercises may make elderly at higher risk of fall [183].

b. Type

Moderate aerobic exercise may be very acceptable for elderly with osteoporosis, since it is safe and effective to remain general health condition [14, 211]. Weight bearing exercises (such as weight lifting, jumping and running) have positive effect on bone strength and balance, they are viewed as best suited exercises for improving bone mass [141, 212, 213, 217, 218]. High impact exercise is suggested for improving bone health, but patients with osteoporosis perform this type exercise should be with extreme caution, if the impact is excessive such as jogging or skipping, it may lead to fractures or injuries [6, 47, 141, 213, 218]. The high impact exercise is not suitable, safe and recommended for osteoporotic subjects. Exercise which includes vigorous trunk flexing, lifting or torsion movements of spine also should be avoided

for severe osteoporosis [213, 219].

Fast walking is recommended as the first choice of activity mode currently. Fast walking means to walk with faster pace than usual walking, and can not induce any uncomfortable or short of breath [216]. In Martin's study, treadmill was used to train postmenopausal and sedentary women, the training speed was 2.5 to 4 mph (miles per hour) and grade was 3 to 7% grade [220]. Some review studies reported that fast or brisk walking corresponded to about 70% VO_{2max} [221, 222], and it was equal to the pace 5.6 to 6.4 km/ h [222]. The moderate intensity of walking speed reporting by ACSM was 3 to 4 mph [214]. Using walking as exercise has been reported many benefits including slowing the rate of bone loss and reducing the risk of hip fractures and falling, it does not need the specific setting and supervision, effective, inexpensive, socially acceptable and well tolerated for most elderly people with osteoporosis, so it may have the greatest compliance [47, 182, 202, 212, 216, 223].

Tai Chi is one kind of meditative and mind- body exercise which is safe, low cost, low risk of serious side effects and a growing popularity exercise. Tai Chi has been proved that it has health benefits including balance, postural stability, muscle strength and flexibility. In 2004, it was recommended by Surgeon General's that Tai Chi is a safe and effective exercise which has positive effect on fall prevention and bone density maintenance in osteoporosis population [203, 204].

The optimal training program for bone has not to be defined yet. In 1993, a general guideline of exercise is recommended by the American College of Sports Medicine (ACSM). It was suggested to exercise with moderate intensity 5 timesx 30 minutes/ week, but the beneficial effects of exercise will reverse if stop doing exercise [213]. In 1996, Surgeon General's report recommended physical activity for health is 30 minutes of moderate exercise accumulated on most, if not all, days of a week. It is the goal for anyone including osteoporosis [6, 224]. Brisk walking for 30 or more minutes per session in at least 5 days per week is equivalent to Surgeon General's suggested one [14]. The minimum moderate activity duration of 30 minutes can be reached either in a continuous bout, or accumulated 30 minutes by bouts lasting at least 10 minutes [225-227].

2.9 Quality of life of osteoporosis

2.9.1 Quality of life of osteoporotic population

Osteoporosis is the most prevalent metabolic bone disease in elderly. It is related to much morbidity and mortality and leading to much expenditure on health and social services. The subsequent fractures will affect quality of life and activities of daily living by pain, lower physical function and disturbed mobility. It also results

in lower mood, depression and social isolation [18, 228].

Osteoporosis occurs in up to half of older women and negatively affects their life both socially and physically [29, 229]. Decreased health related quality of life (HRQL) and functional status have been described primarily in terms of fracture-related pain and disability in women with severe osteoporosis. One previous study showed that osteoporotic women with fractures were significantly worse in all domains of quality of life than healthy controls [228]. Another study reported that, even without fractures, the quality of life of osteoporotic women was also poorer than that of subjects without osteoporosis (total QUALEFFO questionnaire scores were 39.5 and 25.6 respectively) [230].

2.9.2 Exercise effects on quality of life

Exercise training can provide mechanical stimuli that is important for bone health [186]. Many meta-analyses and review studies had reported on the positive effect of exercise on bone mineral density, prevention of falls or osteoporosis-related fractures [47, 48, 182-185, 231]. Additionally, an exercise program can reduce pain, improve fitness, and provide psychological benefits related to preserved cognitive function and self-efficacy [47, 186, 232].

Fewer studies mentioned about the effects of exercise on quality of life for patients with low bone mass. A pilot study used the Osteoporosis Assessment

Questionnaire (OPAQ) to measure the quality of life, it reported that the effects of exercise on quality of life is questionable. The scores on the capacity to perform daily activities and flexibility were no apparent increase after eight weeks exercise training. And only small improvement for the pain and tension/ anxiety [233]. Another study analyzed the Canadian Database of Osteoporosis and Osteopenia (CANDOO), the mini- osteoporosis quality of life questionnaire (mini- OQLQ) was used to measure the quality of life, it reported that there was a positive association between exercise and health related quality of life, particularly on the symptom, emotion and physical domains [234].

Although increasing studies investigating the effect of exercise intervention on quality of life in postmenopausal women with osteoporosis or osteopenia recently, it remains controversial whether exercise affect health related quality of life of these patients. We conducted a meta- analysis study for the effect of exercise on quality of life in low bone mass postmenopausal women in 2009. The results revealed that the exercise groups got significant improvement in domains of physical function, pain, role physical and vitality. The WMD (weighted mean difference) was 2.77, 4.95, 12.41, and 11.11, respectively ($p< 0.05$). Furthermore, intervention with combined exercise programs had better effects on physical function, pain and vitality domains than control. The WMD was 2.79, 4.96 and 12.00, respectively ($p< 0.05$). Group exercise programs

also had better results in these 3 domains. The WMD was 2.77, 4.93 and 12.00, respectively ($p< 0.05$). A short duration exercise program could improve better in physical function, role physical and vitality (WMD was 6.54, 12.41 and 11.11, respectively), whereas long duration exercise program could improve better in physical function and pain domains (WMD was 2.74 and 4.95 respectively) [187].

2.9.3 Measurement of quality of life

Quality of life for osteoporosis could be assessed with Health status measures and preference-based measures [235]. Health status instruments include generic and disease- specific forms. Examples of generic questionnaires include the Sickness Impact Profile (SIP), and the Short Form 36 of the Medical Outcomes Study (SF-36). SIP consists 12 subscales: body care and movement, mobility, ambulation (these 3 subscales can be aggregated into a physical dimension), social interaction, emotional behavior, alertness behavior, communication (these 4 subscales can be aggregated into a psychosocial dimension), household management, sleep and rest, recreation and pastimes, eating, and work. SF-36 measures 8 health domains: physical function, pain, general health, social, mental health, role physical, vitality and role emotion [15, 18].

Many disease- specific questionnaires are used to assess the quality of life of osteoporotic subjects, which include QUALEFFO (Quality-of-Life Questionnaire of the European Foundation for Osteoporosis)、OQLQ (Osteoporosis Quality-of-Life

Questionnaire)、OPAQ (Osteoporosis Assessment Questionnaire)、OPTQoL (Osteoporosis-Targeted Quality-of-Life Questionnaire)、OFDQ (Osteoporosis Functional Disability Questionnaire)、QUALIOST (Quality-of-Life Questionnaire in Osteoporosis), all 6 instruments will be described and compared in the following table [15, 18, 235]

Instructment	Target population	Number of questions	Health domains assessd	Internal reliability (cranbach α)	Test-retest reliability	Mode of adminstration
QUALEFFO	Women; osteoporosis; vertebral fracture	41	Pain, physical function, social function, general health perception, mental, function	0.72~0.92	0.90	Self- administration
OQLQ	Women; osteoporosis; vertebral fracture	OQLQ: 30 MINI-OQLQ:10	Symptoms, physical function, activity of daily living, emotional function, leisure/social activity	NR	>0.80	interviewer
OPAQ	Women; osteoporosis; vertebral fracture	OPAQ1.0:84 OPAQ2.0: 60; OPAQ-SV: 34	Physical function, emotional status, symptoms (just pain in SV), social interaction (not in SV), overall health-related quality of life (not in SV)	0.72~0.92	0.69~0.94	interviewer
OPTQoL	Women	32	Physical dufficulty, adaptations, fears	>0.89	>0.82	interviewer
OFDQ	Men/Women; osteoporosis; vertebral fracture	59	Pain, depression, functional ability, social activity, confident in treatment	>0.70	>0.75	Self-administration
QUALIOST	Women; osteoporosis; vertebral fracture	23	Physical repercussions, emotional repercussions, global	>0.70	>0.7	Self-administration

Among them, QUALEFFO could be self- administered and had better reliabilities and internal consistency than OFDQ and QUALIOST.

QUALEFFO was developed by the European foundation for Osteoporosis in 1996 for vertebral deformities, it is used to assess the QOL burden of osteoporosis and changes during treatment [236, 237]. It included 48 items originally, and then condensed to 41 items after validation and included 5 domains: pain, physical function, social function, general health and mental function. The score of each domain can be transformed to scores of 0 to 100, the higher score indicates a worse quality of life. It has been reported as a valid instrument with several translated versions [228]. QUALEFFO- 41 has good test- retest reliability (Kappa: 0.54- 0.90), internal consistency (Cronbach's α: 0.72- 0.92), good correlation with other QOL instruments (e.g. EQ- 5D) and the discriminative validity of women with and without vertebral fractures is also approved [235]. In pain, physical function, social function, general health domains and total scores had significant difference between two groups but there was no significant difference in domain of mental health. It also could discriminate the QOL by the number and the location of vertebral fractures. Subjects without vertebral fracture, more than 3 thoracic fractures, and more than 3 lumbar fractures had a mean total score 25.6± 14.3, 35.8±19.7, 53.2±15.8 respectively

[15, 235].

The number of items is the disadvantage of the QUALEFFO- 41, a shorter and more practical instrument was developed by the European foundation for Osteoporosis recently [238] (van Schoor NM, 2006), the Qualeffo–31. It was a shorter version of the Qualeffo–41. It includes three domains: pain domain, physical function domain, and mental function domain. Major advantage of short version for patients is to decrease the time (and burden) on answering the questionnaire since there are fewer items [238]. However, the Qualeffo–31 has not been translated to other language. In van Schoor's study, subjects with osteoporosis were recrucited including 483 non-vertebral fracture and 579 vertebral fractures and Qualeffo- 31 was used to assess QOL of subjects. The results reported that the scores was 23.4± 23.8, 9.8± 10.8, 21.8± 14.2 in pain, physical function and mental function domain for subjects without vertebral fracture. For subjects with vertebral fractures, the scores in pain, physical function and mental function domain was 37.1± 25.2, 17.3± 15.8 and 27.1± 16.3, respectively. Subjects without vertebral fracture had better QOL than with vertebral fractures and reached significant difference. In addition, QOL in subjects with more than 2 vertebral fractures was worse than 1 vertebral fracture and reached significant difference [238].

Preference based instrument is different from the health status instrument. It

intends to value the quality of life of subjects and the utility is to assess the specific health condition and the preferences of subjects rather than only functional performance or ability [15, 235]. The utility is a value from 0 (death) to 1 (perfect health) to assess for particular health situation, this value is used commonly to describe loss or gain of quality- adjusted life years (QALYs) [15, 235].

The EuroQol (EQ- 5D) questionnaire is an instrument commonly used to investigate the utility. It includes 5 domains: mobility, self care, performance of usual activities, pain/ discomfort, and anxiety/ depression. There are 3 levels of difficulty in each domain: no problem, some problem, and extreme problem. 5- digit numbers are used to code the results, and each digit is between 1- 3, total 243 codes are used to express possible health states. The utility values are obtained by an expert panel and method of time- trade- off [15, 239]. In Dhillon's study, 325 subjects were recruited including 159 osteoporosis and 166 without osteoporosis, EQ- 5D was used to evaluate the utility of health. It reported that subjects with osteoporosis had lower utility (0.65± 0.28) than without osteoporosis (0.76± 0.27) and reached significant difference. The utility in subjects aged 65 years and older with osteoporosis was 0.65 and without osteoporosis was 0.71, the utility was lower with advancing age [239].

2.10 Economic evaluation

2.10.1 Cost effectiveness analysis

Economic evaluation is an analysis for different health care options, based on what cost and health outcomes are considered. Basic economic evaluations include cost- minimization analysis, cost- benefit analysis, cost- effectiveness analysis and cost- utility analysis. Different outcomes are evaluated in different types of economic evaluation [240] The outcome of all alternatives is assumed to be equal in cost-minimization analysis; the outcome of all alternatives is converted to money in cost-benefit analysis; the outcome in cost- effectiveness analysis is a natural unit; and the outcome of cost- utility analysis is the value of health status [241, 242].

Cost effectiveness analysis provides the evidence to decision maker under limited resources to select health care intervention with less cost and better effect[240, 243, 244] . For cost- effectiveness analysis, the outcomes of interest are measured in natural units and alternatives are compared in cost of per unit effect (C/E ratio) [240, 242, 243, 245]. Alternatives are all of the relevant health care options. For economic evaluation, one option compares with other options including "do nothing" is most common [240],

Procedure of cost effectiveness analysis is described as follows:

Before analysis, to decide the perspective for evaluation is very important, the

cost and effectiveness included will be influenced from different viewpoint, such as from the view point of society, patient or Ministry of Health [240, 242, 246] . The problem we want to explore should be precisely identified first, then all alternatives should be determined. Once the alternatives are decided, it is necessary to know what are the effects and how to evaluate them[244]. Each intervention should be described in detail and accurately (including the setting, participants, type, frequency and duration of intervention, and so on) for cost and effects estimation[243].

Effectiveness estimation: effects of all the alternatives should be identified and listed as the effectiveness. The effectiveness is measured using a natural unit such as increased muscle strength, decreased blood pressure, or improved QOL[241, 245, 246].

Cost estimation: first step, the ingredients of intervention should be identified, second step, the cost of each ingredient needs be decided, then total costs of all ingredients will be calculated[244]. The cost includes direct, indirect and intangible cost. Direct cost is used for improving health including medical and nonmedical cost. Indirect cost is the time cost associated with health intervention, it means loss of productivity. Intangible cost is very difficult to estimate[243, 245].

Cost effectiveness analysis: the appropriate unit of effectiveness for expressing costs should be decides. Cost effectiveness ratio (CE ratio) is commonly used to make comparisons among different alternatives to find the most cost effective

intervention[244]. If we want to know how much more money will be needed to get per unit gained of health effect compared to the reference intervention, incremental cost effectiveness ratio (ICER) is used to analysis[244, 245].

Discounting: the cost and health effects may become valueless over time, the values in the future should be transformed to present values. The discount rate suggested by many guidelines is 3% [243, 247].

Sensitivity analysis: parameters in the cost effectiveness analysis might be modified and cause a different result for the CEA. Reanalysis to consider the different situations of each parameter is sensitivity analysis. If the result has no significant change under the change of these parameters, we will have more confidence that the original result is robust. Sensitivity analysis is very important to examine the generalizability of the results[243, 246, 248].

2.10.2 Economic evaluation of osteoporosis

Osteoporosis is a systemic bone disease manifested by reduced bone strength and increased fragility fractures that would increase morbidity and mortality, affect patient's function, quality of life and it has a significant influence on the society and results in a large economic burden to society [130, 132, 249, 250]. Common osteoporosis-related fractures are particularly at hip, spine and forearm [9, 250]. About one third hip fracture patients in the United States are institutionalized to nursing homes in the first

year after the fracture, during the period, their mortality rate increased up to 20%. Vertebral fractures are the most commonly type of osteoporotic fracture, they would result in hard to perform activities of daily living, back pain, limited activities and increased recurrence of future vertebral fracture. Distal forearm fractures (including distal radius fracture, Colles fracture, or wrist fracture) lead to severe pain and immediate loss of function. Most patients with this kind of fracture look for clinical help and the healing of fracture and recovery of function are usually good [15, 16]. In Switzerland, the health care expenditures in women on osteoporosis- related fractures are more than chronic pulmonary obstructive disease (COPD), stroke, breast carcinoma and myocardial infarction (MI). Just behind COPD, MI and stroke, osteoporosis is ranked fourth in men [8]

In recent years, the osteoporosis- related fractures are viewed as an important burden of society because of associated morbidity, mortality, and healthcare expenditure. In 2002, the study of Levy in France reported that mean cost per hospital stay varied widely according to the type of fracture, it was from €1300 (wrist fracture) to €5900 (hip fracture), equaled to NTD 52000 to NTD 236000 [251]. In addition, the study of Lippuner in Switzerland, the mean cost of hospitalization per case was about NTD 80000 [8]. In Taiwan, the mean cost per case of the hospitalizations was between NTD 46,000 and 50,000 from 1996 to 2003, there was no significant increase among

these years. To compare the cost according to fracture sites, the wrist, spine and hip was NTD 25000 to 29000, 23000 to 35000, and 65000 to 70000 respectively [252]. The total cost of hospitalized medical expense of osteoporosis- related fractures was approximately NTD 740,000,000 to 1,110,000,000 from 1996 to 2003, the cost of hospitalization during 8 years increased about 50%. In Taiwan, the yearly cost of hip fractures was 1.3 billions, accounted for about 1/5 of the total cost of hospitalized medical expense of all fractures [253], the most cost was osteoporosis related hip fractures.

In Taiwan, the number of osteoporosis-related fracture is still rising because of an aging population. The osteoporosis related fracture is a major cause of morbidity and mortality. Except of the medical cost, it will be an enormous burden of the society and healthcare.

Economic evaluation of therapeutic agents is receiving increased attention. There were many studies about the economic analysis of treatment or drug therapy for osteoporosis related fractures [132, 254-256]. However, the economic evaluation of exercise in these subjects has not been found.

Chapter 3 Materials and Methods

3.1 Study 1: Comparison of the effects of different delivery modes of exercises for postmenopausal women with osteoporosis

3.1.1 Study design

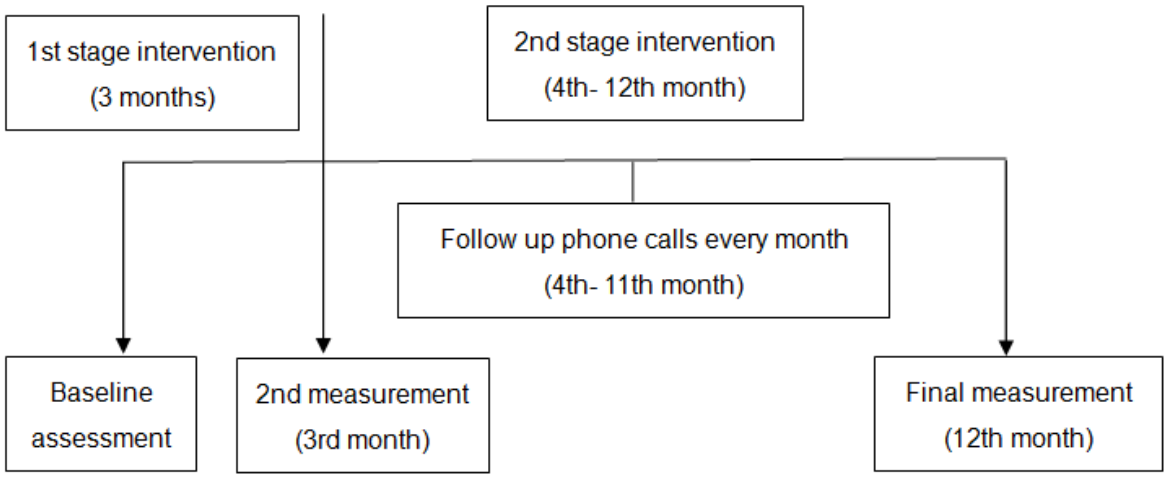
This was a randomized controlled prospective trial with 3 experimental groups (supervised group- exercise, home- based exercise and education). The study was approved by the ethical committee of NTUH (No. 200701056R).

All eligible participants were informed about the study and informed consent was obtained from each subject.

3.1.2 Procedure

After signing the consents, baseline assessment was proceeded, we gave an education class to all the subjects. The subjects were randomly assigned to 1 of 3 groups after completing baseline assessment and the education class. First- stage intervention program was given for 3 months and the second measurement was taken after first- stage intervention. Second- stage intervention lasted to 12th month and final measurement took place at 12 months after the baseline measurement. The supportive follow up phone calls were made monthly following baseline assessment.

The procedure to conduct this study was as follows:



3.1.3 Participants

The postmenopausal women were initially recruited from outpatient orthopaedic clinics of hospitals. All were living independently and they were able to participate in the ambulatory exercise training programs by themselves. The inclusion criteria were: (1) older than 50 years old [16, 257] and menopausal for at least 1 year; (2) osteoporosis was diagnosed, the classification of osteoporosis is according to the World Health Organization published criteria based on BMD measurement at the spine, hip, or forearm with dual- energy X ray absorptiometry (DXA), T score lower

than -2.5 standard deviation; (3) able to walk without any assistive device; (4) willingness to participate and givegave the consent.

The following women were excluded: (1) with any severe neuromuscular disease known to influence gait, balance or muscle strength; (2) acute back pain or fracture within past 3 months; (3) taking medications that would negatively influence bone health or balance; (4) with medical contraindications for exercise; (5) could not understand the verbal instructions of study procedures.

Sample size estimation:

Power calculations focusing on muscle strength as the outcome variable indicated that a sample size of at least 8 was needed per group to achieve 80% power to detect a difference in muscle strength of 29.1 or more (N) (pooled SD: 18.6), at α level of 0.05 for a two sided test. If focusing on Berg balance test, the sample size of at least 7 was needed per group to detect a difference in Berg balance test score of 3.9 (pooled SD: 2.4). These estimates were based on Swanenburg's study in 2007, the women aged 65 years and older with osteopenia or osteoporosis were randomized to intervention and control group. A 12- week intervention program aimed at improvement of balance abilities and preventing falls; the control group received a leaflet about home exercise but did not received house training program [258].

On the basis of information mentioned above, a sample of 7- 8 per group was sufficient to detect difference between groups. However, many outcomes were evaluated in this study, for the sake of having powerful statistics in each parameter, a total of 87 subjects who were recruited and were randomized into 3 groups in masked fashion by drawing of sealing envelopes which were containing the name of the group. To ensure the three groups were allocated in a balanced way, the assignment was by block, with the block size being 15, there was 5 subjects in each group for every 15 subjects recruited. All subjects were instructed not to change their medication until completion of the study.

3.1.4 Outcome measures

3.1.4.1 Questionnaire: all subjects completed the questionnaire about basic data

Basic data:

a. Age

b. Gender

c. Height

d. Body weight

e. Age of menopause

3.1.4.2 Bone mineral density (BMD)

The BMD was measured at the anterior- posterior projection of the hip or spine using DXA, all results were expressed in g/ cm^2. The measurements were carried out with a same machine.

3.1.4.3 Muscle strength

Knee extensor strength: the isometric muscle strength was measured with a hand held dynamometer. Subjects were in a standardised sitting position with hip and knee in 90° flexion, the hand held dynamometer (MicroFET 2, Hoggan Health Industries, USA.) was placed distally at 80% of the tibia length (just proximal to line of malleoli). To maintain body balance, subjects supported their body with their hands at the chair's edge. The dominant leg was measured. Dominant leg was determined through the ball kick or step up test, the leg used to kick a ball or used to step on a bench was identified as the dominant leg [259, 260]. Each subject made three maximal voluntary contractions, each test lasted over 5 seconds until the displayed value reaching a plateau, and at least 1 minute of rest was allowed between repeated tests. For comfort, a towel was used between the dynamometer and tibia. The mean valuewas considered to be the individual strength, all results were expressed in kg [261-265].

Grip strength: grip strength was measured using a hand- held grip dynamometer (T.K.K.5401- Grip D, Takei Scientific Instruments Co., LTD, Japan.), the subject was

in standing position with feet at shoulder width, arms were placed in a comfortable position hanging at the sides with elbow extension. The dominant hand was measured, each subject made three maximal voluntary contractions, each test lasted over 5 seconds until the displayed value reaching a plateau, and at least 1 minute of rest was allowed between the repeated test. The mean value was considered to be the individual strength, all results were expressed in kg [266].

3.1.4.4 Balance test

One leg stance:

The subjects were instructed to take in a standing position with barefoot, comfortable double leg stance, body straight, arms at the side, and eyes directed forward.

The subjects were allowed to practice before testing and the dominant leg which was chosen to lift since only one leg (non- dominant leg) was tested [259, 260]. The initial position stood relaxed with eyes open and weight evenly distributed between both feet. Then subjects were asked to stand freely on one leg for as long as possible. A verbal cue gave to the subject to start one leg stance and the test was interrupted after 30 s, or if the subject moved the foot they stood on, touched floor with the lifted leg, used the suspended foot to support the weight bearing limb and opened the eyes during the eyes- closed trials [267-269]. A digital stopwatch was used to measure balance

performance to the nearest tenth of a second. The subject was instructed to keep arms along the side of the body during initial standing and task performance. However, compensatory arm movements were accepted. One therapist stood close to the subject to protect and prevent falls or injuries during the test [269-271]. Three trials with the eyes open and eyes closed conditions were performed for a total of 6 trials per testing session, there was 20 seconds of rest between trials and 5 minutes rest between 2 conditions. The order of condition was randomized.

3.1.4.5 Functional mobility

Timed up and go test:

The timed up and go test was used to measure the functional mobility. To measure the time (in seconds) that it took the subject to rise from an armchair (about 45 cm height), walked to the mark on the floor at 3 meters away, and returned around to the chair and sit down. All subjects were instructed to walk with their normal speed [272, 273]. The time was measured from a seated position (back against the backrest) with a stopwatch started on the command "ready—go" and stopped when the seat position was reached again. The participant had a practice trial, the final two trials were timed, the time cost of the better performance was recorded as the result.

3.1.4.6 Quality of life

Health related quality of life was measured using two self administered

questionnaires:

(1). Qualeffo- 31: The disease-specific questionnaire- Qualeffo–31 (Quality of Life Questionnaire of the European Foundation for Osteoporosis) was used to measure the quality of life of subjects. It consists of three domains including (a) pain (4 items), (b) physical function (18 items), and (c) mental function (9 items). It is four or five-point ordinal scale of the items. The score of each domain can be transformed to scores 0 to 100, a higher score indicates a worse quality of life [238].

(2). EQ- 5D: EQ-5D (EuroQol) is a generic questionnaire is used to measure the quality of life of subjects. It divides health status into five dimensions: (a) mobility, (b) self care, (c) usual activities, (d) pain/discomfort, and (e) anxiety/depression. Each dimension is divided into three degrees of severity: no problem, some problems, major problems, given a value of 1, 2 and 3, respectively, the subjects mark the degree of severity which best describe their actual health status. The five health dimensions divide health status into 243 (3^5) possible health states. The values for these health states, estimated by time trade off (TTO) utility values, have been developed [274, 275]. The utility of subject deriving from EQ5D was calculated as QALY (quality adjusted life years), it was used to conduct a cost utility analysis.

3.1.4.7 Fall

The definition of fall: a fall was an event which resulted in unintentionally

coming to rest on the ground, floor or other lower level. Neither coming to rest against furniture, a wall or other structure, nor high trauma falls and falling as a consequence of sustaining a violent below were included as falls in this study [258]. The number of falls in the past year was recorded, and during the year of study, all subjects were asked to write down the date that they fall.

3.1.5 Training programs

This study included two- stage intervention:

3.1.5.1 Intervention stage 1**: 3 months**

Education program was given, which included a lecture and a discussion, and subjects received a short, easily read informational handout on bone health.

The educational program was individualized and delivering tailored information to participants. It was held in a quiet space and proceeded about 60 minutes. By this way, the subjects were aware of their risk from osteoporosis and the ways in which they could reduce their risk of bone loss and fracture, more knowledge about osteoporosis was provided, and they had positive attitude and more confidence to face the disease. The program included:

1. To explain the result of previous DXA scan for bone density examination: They were introduced the common vague and non-specific symptoms of osteoporosis to increase the concept and knowledge about osteoporosis, then to

clearly recognized the seriousness of osteoporosis (the change of anatomy, physiopathology of bone loss and risk factors of osteoporosis) and its consequences (relationship between low bone mass and fracture).

2. Nutrition education: Based on the diet quality and quantity, the overall nutritional status of individuals was assessed. A suggestion was given to participants for improving the nutritional status and achieving the recommended levels of each nutrient by better food choices.

3. Exercise education: Based on the frequency, duration, intensity and type of exercise behavior, the condition of physical activity was examined. A suggestion of amount of exercise was provided to participants for improving bone health and fall prevention.

4. Lifestyle modification: The participants should be educated that they needed pay much more attention to change lifestyles, it was very hard but more effective. It included more exposure to sunshine, avoiding smoking and caffeine, suggesting moderate alcohol consumption but not excessive amount, calcium and vitamin D rich foods consumption, and regular exercise.

5. Fall prevention: The environmental barriers were important factors of fall, the participants should be educated to focus on removing these barriers.

After completing the education class, subjects were randomized into 3 groups.

(1) Education group

Subjects in this group did not receive any more instruction except the education class.

(2) Supervised group- exercise

Subjects in this group participated in a 12- week training programs, the exercise program focused on reducing the bone loss, improving bone mass and increasing the strength and balance to reduce the risk of fall. The program included weight bearing exercise, trunk stability exercise, balance training and muscle strengthening exercise. There were 3 sessions per week in group of 5 participants in a clinical setting under the supervision and instruction of a physiotherapist for about 90 minutes each time (including the warm up, cooling down exercise and rest between programs). All subjects were instructed not to change their medication until completion of the study.

The exercise program:

Each class began with a 10- minute warm up exercise, it consisted of general stretching exercise for upper, lower extremities and trunk, the class ended with a 5- minute cool down exercise, it included stretching exercise, stepping or relaxation exercise.

The strengthening training programs for knee flexor, extensor; hip flexor, extensor, abductor; trunk flexor, extensor; and shoulder, elbow, wrist muscle strengthening were about 30 minutes, the aim of this exercise program was to promote trunk stabilization and improve the muscle strength. The program included

a. Sitting down and standing up from a chair slowly, gradually from a higher chair to a lower chair
b. Squatting and standing up if possible
c. Stepping up and down a stool from front and sideways
d. repeated toe standing and heel standing (with hand supported if needed)
e. Drawing in exercise to strengthen deep abdominal muscle (transverse abdominus)
f. Abdominal muscle isotonic contraction to strengthen abdominal muscle from supine position
g. Leg raise to extend the spine, alternate legs initially, then both in prone position
h. Combination arm- leg raise with initially of one arm and opposite leg, then all four limbs simultaneously

i. Alternate arm raises, alternate leg raises or opposing arm and leg raises in all four position

j. Using thera- band to perform the D1 and D2 pattern of PNF for upper extremity multidimensional training, progressing with higher resistance band

Each program was performed initially 3 sets of 10 repetitions and repetition increased along with the improvement, each movement was held for 3 seconds initially except (1)- (3), it was lengthened to a maximum of 10 seconds as strength and endurance increasing, the recovery periods of about 2 minutes between set. The different combinations including upper extremity, trunk and lower extremity of the above mentioned programs were selected during the intervention.

The balance training programs were including dynamic and static training for about 30 minutes, the programs included

a. One leg to reach the marks on ground in different directions

b. Walking on heels

c. Walking on toes

d. Walking sideways

e. Retrowalking

f. Walking in the tandem position (one leg in front of the other)

g. Standing in the tandem position, gradually increasing the period of performance

h. Standing with eyes closed, gradually increasing the period of performance

i. Walking with eyes closed

j. One leg standing, gradually increasing the period of performance

k. Figure of 8 walking with wide circle, gradually progressing from wide circle to narrow circle

l. Kicking a ball

m. Jumping and jogging, gradually progressing to change direction

The training programs were supervised by an experienced physical therapist, the above programs were chosen by therapist during the intervention depending on subject's capacity, and therapist adjusted the amount of exercise according to the subject's level of physical function, to provide the optimal amount of exercise to each one.

When there was no exercise class, subjects were encouraged to accumulate toward 30 minutes minimum of brisk walking from bouts lasting 10 or more

minutes [225] as their moderate intensity exercise program in the other days of a week.

(3) Home based exercise

After giving the education programs, subjects randomised into this group were recommended brisk walking as their exercise program. The distance of 30-minute brisk walking (moderate intensity exercise) was converted to steps as the target steps. It was suggested that accumulation of time (30 minutes) for brisk walking or target number of steps per day was comparable to achieve moderate intensity exercise, a pedometer was used to accumulate steps of daily brisk walking. The subjects were instructed to execute the exercise on most, preferably all days of each week in 12- week period [6, 224, 276, 277]. The follow up telephone calls were conducted monthly, to increase psychological encouragement and help to solve the exercise related problems. All subjects were instructed to keep their physical activity, ADLs, social habits, medication and diet.

Compliance rate:

A log book was provided for subjects to check the compliance and remind them exercise. The compliance was expressed as the number of exercise sessions reported divided by the number of maximum expected exercise sessions [258].

3.1.5.2 Intervention stage 2: follow up program: **the intervention lasted to the 12th month**

(1) Education group:

The pedometer and the same recommendation as home based exercise group was given to subjects in this group from the 3rd- month to 12th- month.

(2) Group exercise:

The subjects of this group were encouraged to continue the exercise behaviour after the initial three months intervention. Moreover, the distance of 30- minute brisk walking (moderate intensity exercise) was converted to steps as the target steps. It was suggested that accumulation of time (30 minutes) for brisk walking or target steps per day was comparable to achieve moderate intensity exercise, a pedometer was used to accumulate steps of daily brisk walking. The subjects were instructed to execute the exercise on most, if not all, days of a week, preferably all days of each week. To remind and follow up with the phone call monthly from completing the intervention to 12 months.

(3) Home based exercise:

Continuing the same program until the study finishes.

Compliance rate:

The compliance rate also needed to be calculated in this stage, all data depended on the record of subjects.

3.1.6 Statistical analysis

Data was stored and analysed using the 11.0 version of the Statistical Package for Social Science (SPSS for Windows Release 11.0; SPSS Inc. Chicago, IL, USA). α was set at 0.05 for all analyses. Intention to treat principle was used for final analysis.

1. Descriptive statistics was used to show the baseline characteristics of three groups.

2. The normality of the variables' distribution was checked with the Kolmogorov- Smirnov one sample test.

3. The differences among three groups were analyzed using Kruskal- Wallis test, and Mann whitney U test was used to compare difference in each two groups.

4. Friedman test was used to analyze the differences among all three time points within the groups, and Wilcoxon signed rank test was used to analyze the differences for each 2 of 3 time periods.

3.2 Study 2: Cost effectiveness analysis of different delivery modes of exercises for postmenopausal women with osteoporosis

3.2.1 Study design

This study was approved by the ethical committee of NTUH. This was a randomized controlled prospective trial to compare the outcome among three groups. All eligible participants were randomly assigned to one of three groups: supervised group exercise, home- based exercise, and education group.

3.2.2 Participants

The postmenopausal women were initially recruited from outpatient orthopaedic clinics of hospitals. All eligible participants who met predetermined inclusion criteria.

3.2.3 Procedure

The interventions included supervised group- exercise, home- based exercise and education group as a control group. All participants got same education program for osteoporosis (Table 1). They were not encouraged to change medication about osteoporosis during the one- year study period.

The supervised group- exercise included 3 months (first 3 months) group exercise and 9 months (4^{th}- 12^{th} month) home- based exercise. The duration of

each exercise session was about 90 minutes, it consisted 10- minute warm up exercise, 75- minute strengthening and balance exercise, and 5- minute cool down exercise. In the first 3 months, subjects l performed group exercise 3 times per week under a physical therapist's supervision, and the other days of a week were recommended to perform 30- minute brisk walking as a moderate intensity exercise program. After 3- month supervised group exercise, the subjects were encouraged to continue the exercise at home, the 30- minute brisk walking or the target steps convert from the distance of 30- minute brisk walking were suggested every day.

The subjects in home- based exercise group were suggested to perform 30- minute brisk walking or the target steps convert from the distance of 30- minute brisk walking per day, it was comparable to achieve moderate intensity exercise. The duration of exercise was 12 months.

Subjects in education group only had the education program in first 3 months and were encouraged to perform the walking program same as home based exercise during 4^{th} – 12^{th} month.

All subjects were reminded and followed up with phone call monthly.

3.2.4 Measurement

After all subjects completing the intervention, we conducted a

cost-effectiveness analysis (CEA) among the three programs. In this study, estimation of the cost and effectiveness were mainly from the society perspective and under health insurance, the main comparison was made among the effects of three programs: 1. Health education group; 2.group exercise intervention for enhancing bone mineral density (BMD) and balance; 3.home- based exercise group.

Decision tree model used to estimate outcome probabilities

The decision tree showed all possible outcomes in three alternatives, both preventive (BMD and falls) and positive (muscle strength, balance, QOL) effects (Figure 1). In this study, the occurrence of fall was based on yearly probabilities. The proportion of subjects was known in each terminal branch, then the cost effectiveness analysis was conducted.

3.2.4.1 Outcome measures

1. Cost of the intervention: The "cost" I was measured bases on the monetary cost of implementation of each program, we got the data of cost from "study 1".

(1) Direct cost

(a) Direct medical cost: it was the cost for intervention, including diagnosis (physician fee, registry fee), drugs, therapy fee, medical care cost if injury happening from the intervention.

(b) Direct non- medical cost: including transportation, equipment for program, staffing, capital cost (including rent of place and equipment of the place).

(2) Indirect cost: including loss of productivity or leisure time of participant, and intangible cost. The intangible cost was not included in this study.

In order to estimate the total cost of the various intervention strategies, the cost model was used as follows [278] (table 2):

Tci= MC $ i+ N MC $ i+ AF $ i+ PHONE $ i+ piII $ + PROD $ i

Tci= total cost through the whole study period

MC $ i= all cost associated with medical care, the care performed in hospital under the national health insurance program in Taiwan, it consisted registry fee, physician fee for check- up and therapy fee for the intervention. The physician and therapy fee was calculated from the Fee schedule for medical services of National Health Insurance (NHI) for a medical center visit (Table 2).The therapy fee included the cost of therapist and covered personnel and capital cost (medical apparatus and the place rental cost of medical provider).

N MC $ i= all cost associated with 3 alternatives but not direct with medical care, it included transportation; equipments for programs; staffing; capital cost; and preparation of handout. For transportation, we assumed that all subjects attended the intervention by public bus and an average two- segment travel distance was necessary, the travel cost of one- segment ticket was NT $ 15. The cost of equipments for program was estimated from a specialized company in physical therapy equipments and devices. The cost of staffing and capital cost was covered by therapy fee. The cost of handout was NT $ 50 for every subject.

AF $ i was the cost of the assistant who performed physical examination before intervention and made supportive phone calls . Assistant cost for physical examination was valued using therapy fee from the Fee schedule of NHI, the cost was NT $ 320. The cost for phone calls was valued using marketing price of a physical therapist. The average cost of physical therapist was NT $ 250 per hour.

PHONE $ i was the cost of supportive phone calls. Eleven supportive phone calls were made by physical therapist for education and home- based exercise and 8 calls for supervised group exercise participants. It was assumed to take about 65 minutes on these calls for education and home- based exercise during this study, and about 40 minutes for supervised group exercise. The telephone average cost of local phone was NT $ 1.6 per 3 minutes.

piII $ was the cost associated with injury happening due to intervention, the therapist detected the physical problems and referred for physician assessment and gave medical cares. “pi” was the probability of an adverse event happening. One subject got knee pain due to overload training in group exercise (pi = 3.6%) and physician evaluation and physical therapy were needed during this study. We assumed that every group had same probability of injury due to training.

PROD $ i was the productivity change or loss of leisure time in evaluations undertaken from the patient’s perspective. Under the assumption that all subjects had the same productivity, the cost of every hour of productivity was calculated using per capita national income from Bureau of Statistics Taiwan in 2010[35]. The average cost of productivity was NT $ 268.5 per hour.

2. Effectiveness: effectiveness was the preventive or positive effects of intervention, the “effectiveness” (E) was measured including:

   (1). Change of BMD

   (2). Change of strength

   (3). Change of balance

   (4). Change of functional mobility

   (5). Number of falls: the percentage of change of falls ([final evaluation-initial evaluation]/ initial evaluation) was used to compare among three

groups and conducted a cost effectiveness analysis.

(6). Change of the QOL: the utility of subject deriving from EuroQol was calculated as QALY (quality adjusted life years), it was used to conduct a cost utility analysis.

We got the data of effectiveness from outcomes of "study 1".

3.2.4.2 Data analysis

The C/ E ratio was measured, it compared the cost per unit of health effect (cost per health effect) among three alternatives. And the incremental cost effectiveness ratio (ICER) also was measured, which was a measure of the cost per unit gained of health effect compared to the reference population, the education group was defined as reference population. ICER in this study was defined as:

$$ICER = \Delta C / \Delta E = (Cost_{exercise} - Cost_{reference}) / (E_{exercise} - E_{reference})$$

Where the numerator was the difference in costs between exercise intervention (including group exercise and home- based exercise) and education intervention, and the denominator was the difference in health effects. The health effects in this study included as mention above: 1. BMD; 2. Muscle strength; 3. Balance; 4. Functional mobility; 5. Number of falls; 6. QOL.

3.2.4.3 Discounting

It was recommended that cost and outcomes should be discounted by discount rate per year. However, this study proceeded for one year, the discounting for both cost and outcomes was therefore not considered.

3.2.4.4 Sensitivity analysis

One sensitivity analysis was used to examine the effectiveness and cost and to check the influence of various parameters. The different therapy fee of group exercise models was considered. Another two reasonable ways to conduct group exercise were self- paid model and government paid model to promote the osteoporosis and fall prevention program. Subjects with different attitude to face this disease would have different productivity estimation, this was another consideration in our analysis.

Chapter 4 Results and discussions

4.1 Study 1

4.1.1 Results of study 1

Totally 87 subjects were included in this study and randomly assigned to 3 groups. There was no significant difference among three groups in basic characteristics (Table 3). Nine subjects dropped out from the intervention (5 in education group, 3 in home based group and 1 in group exercise), the drop rate was 10% (Figure 2).

All outcomes of 3 groups over 3 time points were reported at table 4. There was almost no significant difference among three groups at each time point.

Within the groups, final assessment compared with baseline assessment, subjects in group exercise showed significant improvement on grip strength, functional mobility, balance and total score of quality of life ($P< 0.05$). Subjects in home based exercise showed significant improvement on functional mobility ($P< 0.05$). Subjects in education group showed significant improvement on grip strength and functional mobility ($P< 0.05$).

Because there was no significant difference among the effects of different delivery modes, we pooled the intervention results of all modes together (Table 5). Grip strength showed significant improvement at 12- month follow- up comparing to

baseline and 3- month assessments ($p< 0.05$). Functional mobility (TUAG), balance (using one leg standing with eyes opened), and total score of Qualeffo- 31 all showed significant improvements between baseline and 3- month and between baseline and 12- month assessment ($p< 0.05$).

Fall number of 3 modes was reported at Table 6. The result showed that fall risk declined to the 9^{th} month, and then it increased during 10^{th} -12^{th} months.

The compliance of exercise in three modes was high and no significant difference. It was 0.72, 0.78, and 0.88 at 3- month measurement, and it was 0.54, 0.61 and 0.77 at 12- month measurement in education, home based and group exercise, respectively ($p> 0.05$).

4.1.2 Discussions of study 1

In this study, we expected that supervised group exercise should have greater improvement than home based and education group, and home based exercise should have more effects than education group. However, there were no significant difference of the exercise effects among 3 different delivery modes and showed improvement within each group in most outcome measures.

Before intervention, every subject received same education lecture. This education lecture included a whole concept and essential information about preventing and treating osteoporosis. Through the class may raise awareness of

subjects about the disease and they would pay more attention about the lifestyle modification and performing regular exercise. This might be the possible reason for the similar effects among 3 modes. The education effect was also proved by other study for osteoporosis [279]. In addition, compliance of exercise is very important for the success of exercise program, and it was reported that it was low in elderly [280, 281]. In this study, the high compliance rate might be another reason for the no difference among 3 modes.

The effect on BMD of our study was similar with other studies. It showed bone loss was prevented [282, 283]. It indicates that exercise can stabilize the bone mass and prevent the bone loss with age, which is indeed a valuable accomplishment.

In this study, we can find that grip strength got improvement after 3 months training and reached significantly better at the 12th month. It costs long time to get the improvement. Our training program did not emphasize on grip strength might be the reason. In addition, our study showed that subjects in education and group exercise had significant improvement in grip strength after intervention but those in home based exercise did not. It might because subjects of home based exercise group only focus on performing walking exercise.

The knee extensor strength did not significantly improve after the intervention in this study. The strength of lower extremities was trained through functional activities

in every day and in most regular exercise such as brisk walking and Tai Chi, the threshold was higher for improving muscle strength.

Comparing to the norm and other studies [258, 284-286], the grip strength of our subjects were lesser and strength of knee extensor were greater than those in other studies. This might also be the reason that our subjects improved significantly in grip strength and not in knee extensor.

From the pooling data of all subjects in this study reported that one leg standing with eyes opened had positive effect after 3 months training and the effect could last to 12- month; one leg standing with eyes closed had a trend of improvement but did not reach statistical significance during the intervention. Although there was no significant difference on balance among the 3 groups at each assessment, subjects in group exercise showed significant improvement on the consecutive assessments. It might be because that balance training programs are difficult and not safe for subjects to perform by themselves at home, training program supervised by physical therapist will get more improvement. In 2002, Lewis reported the norm value of balance, one leg standing with eyes opened was 14.2 seconds and with eyes closed was 4.3 seconds for people more than 70 years old [286]. Based on this criteria, we reanalyzed the data of this study, all subjects were divided into 2 age groups: >65 and $\leqq$ 65 (Table 7). The result showed that lesser proportion of our subjects was within the normal range

in older than 65 years old group, it indicates that balance training is much more important for people older than 65 years old.

Functional mobility was assessed by TUAG test. The time needs to complete the task in normal healthy elderly is equal to or less than 10 seconds [272, 287-289]. In this study, it had significant improvement after 3 months intervention and reached the criteria of normal healthy elderly (≦ 10 seconds) and the effect lasted to 12- month. TUAG is strongly correlated with functional mobility including balance and gait maneuvers [289]. Subjects in our study had good performance of TUAG in the baseline assessment, however, their functional mobility still improved after intervention, improvement on balance may lead to the result of improvement TUAG. A study in 2007 reported greater improvement in exercise group, baseline was 14.3± 4.0 seconds and the difference after intervention was reducing 3.7± 3.6 seconds [280]. This might be because the subjects in the study was older than ours (74.6± 4.8 vs. 67.6± 8.8), older people had worse baseline performance and greater improvement after aggressive training. Another study recruited younger postmenopausal women with osteoporosis (56.3± 6.4 years old). Their baseline TUAG was therefore better than our subjects (7.1± 0.6 seconds). After intervention, they got similar effect (6.2± 0.8 seconds) as ours [290].

All 3 groups had the same trend on reducing the fall risk. Fall risk lowered

significantly after intervention and sustained to 6 months later. The significant positive effect at 0-9th months after intervention may be due to the education program before intervention and the reminder calls. These will raise self awareness of the subjects. A similar effect was reported in a previous study offering exercise program for elderly women with low bone mass [258]. The authors suggested that home based and group exercise program can give subjects more confidence to face this disease and may lead to increase physical activity level after intervention. They may become more active and overestimate self ability to perform the task, it might be the reason for these two groups increasing fall risk at 10-12th month assessment than education group in our study. The study in 2006 for elderly men also reported that higher level of physical activity had higher fall risk than lower level of physical activity, the relative risk was 1.18 (95% CI= 1.07- 1.29) [291].

There are some limitations in this study. First, subjects included in this study were healthy women with osteoporosis, they can live independently in community, the generalization to all osteoporosis patients should be cautions. Another limitation of this study was that exercise compliance and fall events was self reported by subjects, it would lead to recall bias and we could not assess the bias from our data.

4.1.3 Conclusions of study 1

This study provided some insights in helping physical therapists have a better

exercise plan for patients with osteoporosis. From the results of this study, all 3 modes of exercise could get similar effects on mobility and lowering the fall risk. A comprehensive education program in community with home exercise program may be an effective way to prevent osteoporosis and fall. However, supervised group exercise got more prominent improvement on balance for this population. For those with worse balance, group exercise will be safer and suggested.

This study provides the information about the effects of different delivery modes of exercise for physical therapists to treat osteoporosis. However, how to set priority and allocate the limited healthcare resources to the optimal alternative is very difficult for decision makers, cost-effectiveness analysis should be performed in the future to determine the best way to reach an optimal therapeutic effect with lower cost.

4.2 Study 2

4.2.1 Results of study 2

Totally 87 subjects were included in this study, and each group had same number of subjects. There was no significant difference among three groups in baseline measurement and characteristics (Table 3). Nine subjects did not finish the program (5 in education group, 3 in home based group and 1 in group exercise, the drop rate was 10%). The missing data was based on intention to treat estimation.

The change of outcomes within one year from different delivery modes were reported in table 8. Moreover, the incremental effectiveness using the education group as reference was also reported.

Cost of each item in different cost models of per participant were summarized in table 9, 9-1. Group exercise cost most, followed by home based exercise and the lowest was education group. The average cost per person in group exercise, home based and education group was NT $ 129864, 101226.3 and 76724.6, respectively. The major costs were on loss of productivity and therapy fee in all groups. The incremental costs of home based and group exercise with education group as the reference were also listed.

The cost effectiveness ratio (C/E ratio) of each group was reported in table 10. The reanalysis by different therapy fee and different productivity was reported in table

10 and 10-1. From the results, we can find that education group had the highest C/E ratio on balance (assessed using eyes opened), and the lowest ratio on grip strength, balance (assessed using eyes closed), functional mobility and fall; in home based exercise group, the highest ratio on grip strength and balance (assessed using eyes closed), and the lowest ratio on knee extensor strength and QALY; in group exercise, the highest ratio on BMD, knee extensor strength, functional mobility and QALY, and the lowest ratio on balance (assessed using eyes opened). Negative C/E ratio on fall in group exercise was reported, it means more cost and more fall risk in this group.

The incremental cost effectiveness ratio (ICERs) of home based and supervised group exercise were also reported in table 10-2, 10-3. A negative ICER means that education group had less cost and greater effectiveness. Home based exercise had better effects on knee extensor strength, functional mobility and QALY; supervised group exercise had better effects on BMD and balance.

The sensitivity analysis was conducted, the different therapy fee of group exercise was considered to examine the influence on results. For self- paid, the therapy cost was estimated from a survey of health promotion club which performed supervised group exercise, the cost of per visit was NT $ 350. For government paid, the cost was calculated according to the aerobic exercise classes for elderly in community by senior citizen’s welfare foundation, the cost of per visit was NT $ 120.

The data was recalculated under these assumptions, the cost and incremental cost had a small reduction in group exercise, but did not influence the primary results (Table 9). There were similar results of C/E ratio on all variables except the knee extensor strength, the highest ratio was in education group, it was different from paid by health insurance. The results of ICERs of different therapy fee showed same results with paid by health insurance (Table 10-2).

The cost of productivity was also reconsidered. We assumed that the subjects were aware of their risk from osteoporosis, results and complications from osteoporotic fracture and exercise could reduce their risk of bone loss and fracture, they would be induced positive attitude to perform and continue the exercise program. Exercise became a part of daily life and as a habitual activity, so the loss of productivity could be neglected. The results of reanalysis showed that the incremental costs had large decrease in home based and group exercise (Table 9-1). If no loss of productivity was considered, different results were showed on C/E ratio. No matter therapy fee paid by health insurance, self or government, the highest ratio of all variables was in group exercise; education group had the lowest ratio on grip strength, balance (assessed using eyes closed) and fall; home based exercise group had the lowest ratio on knee extensor strength, balance (assessed using eyes opened), functional mobility and QALY. For analysis of ICERs showed that no matter what

kind of therapy fee of group exercise, home based exercise may be a dominated option than others on knee extensor strength, balance (assessed using eyes opened), functional mobility and QALY; supervised group exercise had better effects on BMD and balance (assessed using eyes closed). Under health insurance, compared with education reference, knee extensor strength increased per additional 1 kg, NT $ 0.6 more and 94864 more should be paid in home based and group exercise, respectively. For balance with eyes opened, to improve per additional 1 second of standing, NT $ 0.7 and 4216.2 more should be paid in home based and group exercise, respectively. For functional mobility, to decrease per additional 1 second of TUAG, NT $ 5.5 more should be paid in home based and negative effect was shown in group exercise. When gained per additional QALY, home based exercise should pay NT $ 55 more and group exercise should pay NT $ 1897280 more. This sensitivity analysis may lead to change the conclusion.

4.2.2 Discussions of study 2

From the C/E ratio of this study, we concluded that education group and home based exercise group were more cost- effective because of similar effects and less cost. With education group as reference, most ICER also showed home based exercise was better except on balance. These conclusions will not be changed with different payers.

However, if productivity loss was neglected, home based exercise will show its effectiveness for this population.

Exercise is imperative to improve QOL[187] and prevent fall for this population. The effectiveness of the three delivery modes will be discussed below.

From the result we can find that all three modes had positive effect on QALY, however, home based exercise was more effective than other two groups. Based on the standard value reported from other countries [241, 254, 292-294], the cost of home based exercise group was accepted on improving QOL. If the productivity cost was neglected, the C/E ratio had large reduction in three groups. They were in the range of NT $ 53745 to 704050 per QALY gained. There was no threshold level of cost per QALY gained in Taiwan. The suggested threshold value of cost per additional QALY gained based on societal view was about NT $ 866100- 3102500 in other countries[241, 254, 292-294]. Three modes were all within the accepted range on improving QALY. With education group as reference, home based exercise was a more cost- effective option than group exercise. The cost per additional QALY gained was NT $ 1225085 and 5313940 under health insurance in home- based and group exercise, respectively. No matter what kind of therapy fee was considered, the threshold range based on the value mentioned above, the home- based exercise was a cost effective intervention. The cost of per QALY gained in supervised group exercise exceeded the accepted

threshold value, this option was not recommended. The loss of productivity was also retested using zero dollars, cost and incremental cost largely decreased. The result showed that home- based and group exercise was within the range of accepted threshold level, it means that both two modes of interventions were cost effective in productivity at zero and home- based exercise was the most cost effective one among 3 delivery modes of exercise for improving QOL.

Preventing fall is the ultimate goal of delivery exercise for this population. The C/E ratio showed NT $ 426247.8 and 3374210 were needed for prevention of 1 fall in education and home based exercise. Group exercise was more cost and negative effect on fall prevention. It showed education program might be the most cost effectiveness program for fall prevention, and sensitivity analysis did not change the result. For preventing falls lower extremity muscle strength, balance and functional mobility are important training components.

Home based exercise had better C/E ratio on lower extremity muscle strength than other two modes. Balance training was a major part in group exercise, the result showed that subjects in this group got more benefit in balance than the other two groups, however, from the results of C/E ratio, we can find that education and group exercise was most cost effective than the other two modes on the ability of standing with eyes closed and eyes opened, respectively. Education mode was better option

than the other two modes on functional mobility. Sensitivity analysis was conducted, different therapy fee did not influence the results. If productivity was reanalysis, home based exercise had better C/E ratio on lower extremity muscle strength, balance (assessed using eyes opened), and functional mobility; education group was better on balance (assessed using eyes closed), no matter therapy fee paid by health insurance, self or government, same results were reported.

There was no consistent conclusion between physical activity and fall risk. The training effect of exercise might encourage the patients with higher level of physical activity, and improve mobility, muscle strength and balance consequently. All of them are major components for fall prevention. The subjects may overestimate self ability and perform the tasks beyond their abilities and participate more activities in their daily life which increased the fall risk [291, 295]. Our results showed that education and home- based exercise group had positive effect on reducing fall risk, and group exercise reported negative effect on this variable.

There was no reference C/E value for these parameters. The authors suggest to provide education and give detailed instructions of home based exercise for the community dwelling population especially for those with weak lower extremity muscle strength. However, for those with poor balance, supervised training is recommended. When the concept of health promotion is popular and exercise is a part

of daily life, education and give detailed instructions of home based exercise is most cost effective option for fall prevention.

The cost effectiveness on BMD and grip strength was also reported in this study. The effects were small and similar among three groups. A cost effectiveness analysis might not be appropriate and reasonable for the little change on these two variables.

There are some limitations in our study. First, there were some assumptions to estimate the cost, and they may be changeable and may influence the results of study. Second, subjects included in this study were relatively healthier including physical conditions and symptoms, the intervention effects may not be significant and might be underestimated in this study. Therefore, the C/E ratio may be overestimated. Finally, subjects included in this study were only female, relatively healthier and younger. Male, elder group, and those with worse health conditions might reach other conclusions.

4.2.3 Conclusions of study 2

The number of osteoporosis is still rising because of an aging population, exercise will play an important role for prevention and treatment of osteoporosis. The results of cost effectiveness analysis can provide health care decision and policy suggestions for choosing the best alternative. This is the first study to execute the economic evaluation of different delivery modes of exercise in this population.

From the results of this study, we concluded that supervised group exercise was not a cost effective option except those with poor balance, if government can pay more attention to education program or instruction for home- based exercise may be the better options. Trade off between physical activity level and fall risk should be reminded.

Figures

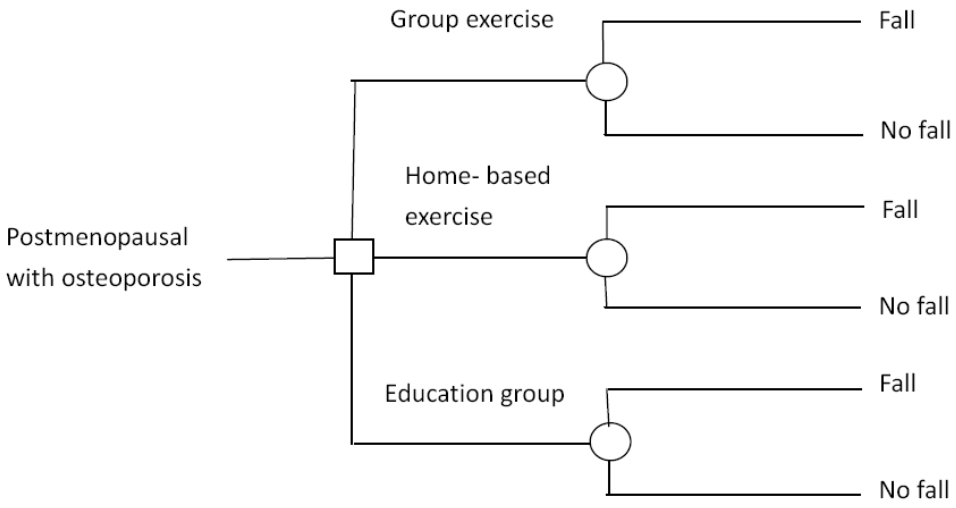


Figure 1 Decision tree model

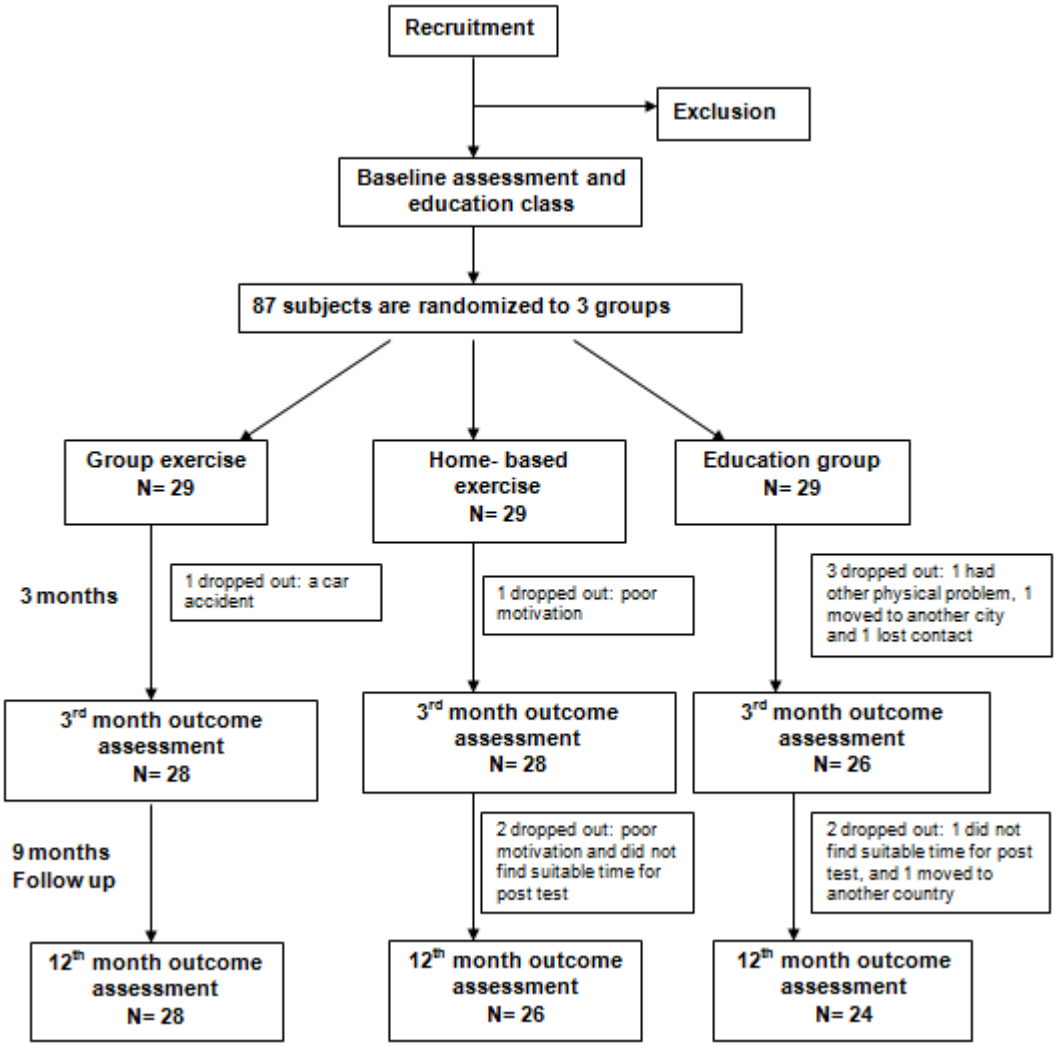


Figure 2 Flow diagram of this study

Tables

Table 1 Features of programs of three different exercise delivery modes

	Education	**Home based**	**Group exercise**
Participants source	Outpatient orthopaedic clinics of hospitals and communities	Same	Same
Modes of education program delivery	Individual	Individual	Individual
Stage 1 (first 3 months)			
Location of exercise program performed	Home	Home	Community or hospital
Major program components	Education program	Education program Brisk walking	Education program Strengthening Balance training
Session duration	---	At least 30 minutes	90 minutes (include the time of rest, warm up and cool down)

Frequency of program	---	7 times/ week	7 times/ week (3 times group exercise+ 4 times home based exercise)/ week
Stage 2 (4th- 12th month)			
Location of exercise program performed	Home	Home	Home
Major program components	Brisk walking	Brisk walking	Brisk walking
Program duration	At least 30 minutes	At least 30 minutes	At least 30 minutes
Frequency of program	7 times/ week	7 times/ week	7 times/ week

Table 2 Unit cost of direct and indirect cost

Cost item	Unit cost (NT $)
Direct cost	
Medical cost (MC $ i)	
Physician (visit)	228
Registry (visit)	460
Therapy (visit)	Health insurance: 320 Self paid: 350 Government paid: 120
Assessment (visit)	320
Non- medical cost (NMC $ i)	
Transportation (segment)	15
Rent of the place and staffing cost (hour)	Health insurance: 0 Self paid: 0 Government paid: 550
Equipments	Education group: 250 Home based: 250 Group exercise: 422.4
Handout (piece)	50
Assistant (hour) (AF $ i)	250
Phone call (minute) (PHONE $ i)	0.5
Indirect cost	
Productivity (hour) (PROD $ i)	268.5

Table 3 Basic characteristics of the three groups

Basic data	Education (n= 29)	Home based (n= 29)	Group exercise (n= 29)	p value
Age	66.9± 9.9	70.4± 7.3	65.4± 8.5	0.081
Weight (kg)	49.6± 7.2	50.0± 5.7	49.9± 5.3	0.927
Height (cm)	152.0± 5.6	152.2± 3.5	153.3± 5.8	0.321
Age of menopause	48.0± 4.9	49.7± 3.8	46.8± 7.8	0.700
BMD (g/cm^2)	0.622± 0.106	0.587± 0.094	0.590± 0.111	0.308
T- score	-3.12± 0.53	-2.90± 0.33	-3.17± 0.53	0.126
Grip strength (kg)	18.9±4.5	20.1±4.1	20.6±3.9	0.234
Knee extensor strength (kg)	26.2±8.7	31.6±9.3	29.3±7.4	0.064
TUAG (second)	10.7±2.4	10.7±2.9	9.7±2.1	0.256
Balance				
eye opened (second)	19.0±11.7	15.7±10.5	19.4±11.3	0.374
eye closed (second)	5.5±4.7	3.3±2.0	4.3±3.3	0.191
Qualeffo- 31				
pain	27.2± 22.7	23.9± 24.3	24.1± 25.5	0.766
physical	11.8± 9.5	11.6± 13.1	10.0± 8.7	0.758
psychological	31.1± 16.1	33.9± 13.4	30.7± 19.0	0.654
total score	19.4± 9.9	19.7± 11.8	17.9± 11.1	0.798
QALYs	0.92± 0.07	0.87± 0.15	0.90± 0.13	0.742

BMD: bone mineral density

TUAG: timed up and go test

Qualeffo- 31: Quality of Life Questionnaire of the European Foundation for Osteoporosis

QALYs: quality adjusted life years

Table 4 The results of each group at each time point

	Education (n=29)			**Home based** (n=29)			**Group** (n= 29)		
	baseline	3- month	12- month	baseline	3- month	12- month	baseline	3- month	12- month
BMD* (g/ cm^2)	0.622±0.106	0.623±0.117	0.626±0.125	0.587±0.094	0.593±0.102	0.587±0.098	0.590±0.111	0.593±0.106	0.595±0.111
Grip strength (kg)	18.9±4.5[c]	20.1±4.3	20.7±4.2	20.1±4.1	19.6±4.0[d]	20.9±4.7	20.6±3.9[c]	21.3±3.6	22.3±4.5
Knee extensor strength (kg)	26.2±8.7	25.7±7.7	26.5±8.3[a]	31.6±9.3	29.5±7.1	33.9±8.8	29.3±7.4	31.0±9.8	29.8±9.3
TUAG (second)	10.7±2.4[ce]	9.9±2.3	9.6±2.3	10.7±2.9[ce]	9.2±2.2	9.4±2.9	9.7±2.1[ce]	8.6±1.8	8.7±2.1
Balance									
Eyes opened (second)	19.0±11.7	19.6±11.8	20.0±11.5	15.7±10.5	17.9±10.4	18.3±10.8	19.4±11.3[ce]	22.6±9.9	24.9±9.3
Eyes closed (second)	5.5±4.7	5.7±4.0	7.1±6.9	3.3±2.0	3.8±2.2	4.6±3.2	4.3±3.3[ce]	7.3±6.1	6.1±4.1
Qualeffo- 31									
Pain	27.2±22.7[e]	14.9±20.3	22.6±22.7	23.9±24.3[de]	19.8±20.0	22.6±26.1	24.1±25.5	21.3±22.4	16.2±21.2
Physical	11.8±9.5	10.5±9.5	12.8±14.2	11.6±13.1	8.6±10.6	11.6±12.5	10.0±8.7	7.7±7.3	7.2±7.4

Psychological	31.1±16.1	31.8±11.6	35.2±15.0	33.9±13.4	32.3±11.4	29.5±11.3	30.7±19.0	27.0±18.8	25.5±15.8
Total score	19.4±9.9[b]	17.3±8.2	20.0±10.6	19.7±11.8	16.9±9.0	17.1±10.7	17.9±11.1[ce]	15.1±10.0	13.7±8.8

BMD: bone mineral density

TUAG: timed up and go test

Qualeffo- 31: Quality of Life Questionnaire of the European Foundation for Osteoporosis

*: second assessment of BMD was at 6 months after baseline assessment

a: significant difference between education group and home based exercise ($p < 0.05$)

b: significant difference between education group and group exercise ($p < 0.05$)

c: significant difference between baseline and final assessment ($p < 0.05$)

d: significant difference between second assessment and final assessment ($p < 0.05$)

e: significant difference between baseline and second assessment ($p < 0.05$)

Table 5 The differences of all subjects among different assessments

N= 87	Baseline	3- month	12- month
BMD (g/cm^2)	0.599± 0.104	0.603± 0.108	0.603± 0.114
Grip strength (kg)	19.8± 4.2[cd]	20.3± 4.0	21.6± 4.4
Knee extensor strength (kg)	29.0± 8.7	28.7± 8.5	30.9± 9.1
TUAG (second)	10.3± 2.5[ce]	9.2± 2.1	9.1± 2.4
Balance (second)			
Eyes opened	18.0± 11.1[ce]	20.0± 10.8	22.0± 10.6
Eyes closed	4.4± 3.6	5.6± 4.6	6.2± 5.3
Qualeffo- 31			
Pain	25.1± 24.0	18.7± 20.9	20.5± 23.4
Physical	11.2± 10.5	8.9± 9.2	10.5± 11.9
Psychological	31.9± 16.2	30.4± 14.4	30.0± 14.6
Total score	19.0± 10.9[ce]	16.4± 9.0	16.9± 10.3

BMD: bone mineral density

TUAG: timed up and go test

Qualeffo- 31: Quality of Life Questionnaire of the European Foundation for Osteoporosis

c: significant difference between baseline and final assessment ($p< 0.05$)

d: significant difference between second assessment and final assessment ($p< 0.05$)

e: significant difference between baseline and second assessment ($p< 0.05$)

Table 6 The person- time (number) of falls in different delivery modes

	Education (N=26)	**Home based (N=28)**	**Group exercise (N=28)**
Previous one year	27 (13)	12 (8)	8 (6)
Intervention			
0-3rd month	5 (5)	5 (4)	4 (3)
4^{th}–6^{th} month	1 (1)	0	2 (2)
7^{th}-9^{th} month	0	0	0
10^{th}-12^{th} month	1 (1)	4 (3)	3 (2)
Total	7 (7)	9 (7)	9 (7)

Table 7 The number (percentage) above cut off point of norm of balance[286] in different age groups and time points

	＞65 (n=52)		≦ 65 (n=35)	
	Eyes opened n (%)	Eyes closed n (%)	Eyes opened n (%)	Eyes closed n (%)
Baseline	22 (42%)	15 (29%)	29 (83%)	24 (69%)
3- month	27 (52%)	15 (29%)	32 (91%)	25 (71%)
12- month	28 (54%)	21 (40%)	31 (89%)	28 (80%)

Table 8 Effectiveness and incremental effectiveness of three groups

	Education	Home- based	Group exercise
Effectiveness (E)			
BMD (g/cm^2)	0.004	0	0.005
Grip strength (kg)	1.8	0.8	1.7
Knee extensor strength (kg)	0.3	2.3	0.5
Balance (sec)			
Eyes opened	1	2.6	5.5
Eyes closed	1.6	1.3	1.8
Functional mobility (sec)	1.1	1.3	1.0
Fall risk	0.18	0.03	-0.04
QALYs	0.02	0.04	0.03
Incremental Effectiveness (ΔE)			
BMD (g/cm^2)	Reference	-0.004	0.001
Grip strength (kg)	Reference	-1.0	-0.1
Knee extensor strength (kg)	Reference	2.0	0.2
Balance (sec)	Reference		
Eyes opened	Reference	1.6	4.5
Eyes closed	Reference	-0.3	0.2
Functional mobility (sec)	Reference	0.2	-0.1
Fall risk	Reference	-0.15	-0.22
QALYs	Reference	0.02	0.01

BMD: bone mineral density

QALYs: quality adjusted life years

Table 9 Total cost and incremental cost of three groups (unit: NDT)

	Health insurance			Self paid			Government paid		
Cost	Education	Home-based	Group exercise	Education	Home- based	Group exercise	Education	Home- based	Group exercise
MC $ i	1058	1058	17818	1058	1058	13658	1058	1058	5378
N MC $ i	420	420	2752.4	420	420	2752.4	420	420	10672.4
AF $ i	590.8	590.8	486.7	590.8	590.8	486.7	590.8	590.8	486.7
PHONE $ i	43.3	43.3	26.7	43.3	43.3	26.7	43.3	43.3	26.7
piII $	36.6	37.7	37.7	36.6	37.7	37.7	36.6	37.7	37.7
PROD $ i	74575.9	99076.5	108742.5	74575.9	99076.5	108742.5	74575.9	99076.5	108742.5
TCi	76724.6	101226.3	129864	76724.6	101226.3	125704	76724.6	101226.3	125344
∆ C	Reference	24501.7	53139.4	Reference	24501.7	48979.4	Reference	24501.7	48619.4

MC $ i: all cost associated with medical care

N MC $ i: all cost associated with alternatives but not direct with medical care

AF $ i: the cost of assistant

PHONE $ i: the cost of phone calls

pill $ i: the cost associated with injury happening due to intervention

PROD $ i: the loss of productivity

TCi: total cost

∆ C: incremental cost

Table 9-1 Total cost and incremental cost of productivity reanalysis of three groups (unit: NDT)

Productivity reanalysis	Health insurance			Self paid			Government paid		
	Education	Home-based	Group exercise	Education	Home-based	Group exercise	Education	Home-based	Group exercise
TCi	2148.7	2149.8	21121.5	2148.7	2149.8	16961.5	2148.7	2149.8	16601.5
∆ C	Reference	1.1	18972.8	Reference	1.1	14812.8	Reference	1.1	14452.8

TCi: total cost

∆ C: incremental cost

Table 10 C/E of three groups and sensitivity analysis of different therapy fee of group exercise

	Health insurance			Self paid			Government paid		
C/E	Education	Home- based	Group exercise	Education	Home- based	Group exercise	Education	Home- based	Group exercise
BMD (g/cm^2)	19181150	101226.3/-	25972800	19181150	101226.3/-	25140800	19181150	101226.3/-	25068800
Grip strength (kg)	42624. 8	126532.9	76390.6	42624. 8	126532.9	73943.5	42624. 8	126532.9	73731.8
Knee extensor strength (kg)	255748. 7	44011.4	259728	255748. 7	44011.4	251408	255748.7	44011.4	250688
Balance (sec)									
Eyes opened	76724.6	38933.2	23611.6	76724.6	38933.2	22855.3	76724.6	38933.2	22789.8
Eyes closed	47952.9	77866.4	72146. 7	47952.9	77866.4	69835.6	47952.9	77866.4	69635. 6
Functional mobility (sec)	69749.6	77866.4	129864	69749.6	77866.4	125704	69749.6	77866.4	125344
Fall risk	426247.8	3374210	-3246600	426247. 8	3374210	-3142600	426247.8	3374210	-3133600
QALYs	3836230	2530657.5	4328800	3836230	2530657.5	4190133.3	3836230	2530657.5	4178133.3

C/E: cost effectiveness ratio

BMD: bone mineral density

QALYs: quality adjusted life years

Table 10-1 C/E of productivity reanalysis of three groups

	Health insurance			Self paid			Government paid		
Productivity reanalysis	Education	Home- based	Group exercise	Education	Home- based	Group exercise	Education	Home- based	Group exercise
C/E									
BMD (g/cm^2)	537175	2149.8/0	4224300	537175	2149.8/0	3392300	537175	2149.8/0	3320300
Grip strength (kg)	1193.7	2687.3	12424.4	1193.7	2687.3	9977.4	1193.7	2687.3	9765.6
Knee extensor strength (kg)	7162.3	934.7	42243	7162.3	934.7	33923	7162.3	934.7	33203
Balance (sec)									
Eyes opened	2148.7	826.8	3840.3	2148.7	826.8	3083.9	2148.7	826.8	3018.5
Eyes closed	1342.9	1653.7	11734.2	1342.9	1653.7	9423.1	1342.9	1653.7	9223.1
Functional mobility (sec)	1953.4	1653.7	21121.5	1953.4	1653.7	16961.5	1953.4	1653.7	16601.5
Fall risk	11937.2	71660	-528037.5	11937.2	71660	-424037.5	11937.2	71660	-415037.5
QALYs	107435	53745	704050	107435	53745	565383.3	107435	53745	553383.3

C/E: cost effectiveness ratio

BMD: bone mineral density

QALYs: quality adjusted life years

Table 10-2 ICER of three groups and reanalysis of different therapy fee of group exercise

	Health insurance			Self paid			Government paid		
ICER (ΔC/ΔE)	Education	Home- based	Group exercise	Education	Home- based	Group exercise	Education	Home- based	Group exercise
BMD (g/cm^2)	Reference	-6125425	53139400	Reference	-6125425	48979400	Reference	-6125425	48619400
Grip strength (kg)	Reference	-24501.7	-531394	Reference	-24501.7	-489794	Reference	-24501.7	-486194
Knee extensor strength (kg)	Reference	12250.9	265697	Reference	12250.9	244897	Reference	12250.9	243097
Balance (sec)									
Eyes opened	Reference	15313.6	11808.8	Reference	15313.6	10884.3	Reference	15313.6	10804.3
Eyes closed	Reference	-81672.3	265697	Reference	-81672.3	244897	Reference	-81672.3	243097
Functional mobility (sec)	Reference	122508.5	-531394	Reference	122508.5	-489794	Reference	122508.5	-486194
Fall risk	Reference	-163344.7	-241542.7	Reference	-163344.7	-222633.6	Reference	-163344.7	-220997.3
QALYs	Reference	1225085	5313940	Reference	1225085	4897940	Reference	1225085	4861940

ICER: incremental cost effectiveness ratio

BMD: bone mineral density

QALYs: quality adjusted life years

Table 10-3 ICER of productivity reanalysis of three groups

	Health insurance			Self paid			Government paid		
Productivity reanalysis	Education	Home- based	Group exercise	Education	Home- based	Group exercise	Education	Home- based	Group exercise
ICER (ΔC/ΔE)									
BMD (g/cm^2)	Reference	-275	18972800	Reference	-275	14812800	Reference	-275	14452800
Grip strength (kg)	Reference	-1.1	-189728	Reference	-1.1	-148128	Reference	-1.1	-144528
Knee extensor strength (kg)	Reference	0.6	94864	Reference	0.6	74064	Reference	0.6	72264
Balance (sec)									
Eyes opened	Reference	0.7	4216.2	Reference	0.7	3291.7	Reference	0.7	3211.7
Eyes closed	Reference	-3.7	94864	Reference	-3.7	74064	Reference	-3.7	72264
Functional mobility (sec)	Reference	5.5	-189728	Reference	5.5	-148128	Reference	5.5	-144528
Fall risk	Reference	-7.3	-86240	Reference	-7.3	-67330.9	Reference	-7.3	-65694.5
QALYs	Reference	55	1897280	Reference	55	1481280	Reference	55	1445280

ICER: incremental cost effectiveness ratio

BMD: bone mineral density

QALYs: quality adjusted life year

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