Hormone & Osteoporosis

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Abstract

It is well defined that osteoporosis is an age related disorder and associated with decreased bone mass. It is one of the most important disease facing the aging population because of its association with fracture of the hip, vertebrae and distal radius. The disease provoke a significant economic burden and major public health problem of an elderly. The life-time risk of hip fracture in white women is approximately 15% which is equal to the combined risk of breast, uterine, and ovarian cancer.

Despite its deleterious effect on women's health, knowledge of the epidemiology of osteoporosis in Korea is only beginning. 1970 in Korea has nown as the crossover period between the chronic and an infectious diseases. As the result, the infant mortality declined and an elderly population in Korea increased significantly in the past decade. The average life expectancy of women in Korea is now about 75 years. Thus, the majority of Korean women will spend approximately one-third of their life in the postmenopause state. Therefore, better understanding of bone metabolism and fracture incidence in Korean population is a great interest for the medical community as well as for public health. Currently, no population based epidemiologic data are available to support the incidence of osteoporotic fractures in Korea. However, available data suggest that significant declining of bone mineral density (BMD [g/cm^2]) has been occurring in Korean women after menopause. In same population, peak BMD was observed around 33-39 years of age and continue to decline thereafter. An accelerated bone losses occur after the menopause and the average loss is approximately 13% within 15 years from the menopause. The incidence of fracture was highly correlated with an age and bone mineral density.

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The mean age of menopause in Korean women was 47 years and this age appears to getting younger when analyzed by the birth cohort. An earlier menopausal age and increase life expectancy place Korean women at increase risk for osteoporosis and bone fracture. Korean or Asian women are no longer protected from the risk of bone fracture. Therefore, an early prevention or intervention schemes are essential before the outbreak of osteoporosis and/or fracture occurs in Korean or Asian women.

Introduction

Many prospective studies indicate that the risk of fragility fractures increases progressively and continuously as bone mineral density declines (1−3). It is well documented that bone density in Asian women is lower than that of Caucasian women. Despite a low bone density, the prevalence of bone fracture in Asian population is lower than the Caucasian rates (4−6). The low fracture incidence described in Asian populations are perhaps related to either under reporting of cases or less bone loss during postmenopausal period. We postulated that less bone loss during postmenopausal period in Asian populations are responsible for the low fracture incidence. Therefore, in order to demonstrate our hypothesis of less bone loss in Korean women during postmenopausal period we will describe, 1) general physical and metabolic characteristics in over 6700 female subjects from Cheil general hospital; 2) the pattern of BMD change during the pre− and postmenopausal period from the same cohort.

Characteristics of Climacteric Korean Women

The mean age of the study subjects were 51.4±6.9 years and ranges from 20 to 94 years; the mean menopause age was 47± 5.5 years and ranges from 20 to 60 years. A handful of young women who experienced an early menopause was not the case of natural menopause but disease related phenomenon. Twenty-three percent of the subjects received a grade school edcuation, 24% with Junior high school, 38% with high school and 8% with a college level education. Furthermore, 3% of the women were nulliparity, 5.5% have one child, 36.7% have a two, 29% have a three, 16.2% have a four, and approximately 10% have more than 5 children. The mean height and weight was 1.57±0.05m and 57.3±7.3kg respectively. The mean body mass index (BMI, kg/m^2) was 23.2±2.8. The demographic and physical parameters of our hospital population shows heterogeneity and no sign of disparity from the general population (7).

The patients presented with a variety of climacteric symptoms. These symptoms include; hot flushes, night sweats, insomnia, palpitations, headaches, panic attacks, mood changes, anxiety, irritability, poor memory, poor concentration, loss of confidence, indecisiveness, depression, tiredness/loss of energy, genital track atrophy, dyspareunia, loss of libido, increased urinary frequency, increased urgency, nocturia, dysuria, dry thin skin, dry hair, formication, aches and pains in joints. Lumbago was the most frequently complained

symptoms in Korean women and the most severe cases were observed 7 years after the menopause. The most frequently complained symptoms within a three years of postmenopause was both hot flush and sweating. The other symptoms were not related to the duration of years since the menopause (7).

The clinical and laboratory characteristics were frequently used as the predictors and/or markers for the osteoporosis. Thus, in this section, we will describe the characteristics of the bone markers and lipid profiles related to the aging process.

Bone markers and lipid profiles measurement

Osteoporotic syndromes are characterized by a wide spectrum of bone turnover, ranging from accelerated to reduced remodeling rates. Thus, we measured both bone markers and the lipid profiles in over 6700 women enrolled in Cheil general hospital since 1985 〈Table 1〉. Serum alkaline phosphatase and osteocalcin(bone Gla-protein) was measured because it thought to play a role in mineralization for bone formation. Urinary calcium and creatinine was measured to evaluate the rate of bone resorption. Follicle stimulating hormone (FSH) was also assayed in this study to evaluate its relationships with the bone markers and the lipid profiles. As shown in Table 1, wide ranges of the lipid profiles and bone markers were observed in our study subjects. FSH was positive and significantly correlated with age ($r=0.31$, $p<0.00001$), alkaline phosphatase ($r=0.15$, $p<0.0001$), osteocalcin ($r=0.23$, $p<0.0001$) and all four parameters of the lipid profiles (i.e., Cholesterol, HDL, LDL, and triglyceride). Osteocalcin was positively correlated with age ($r=0.15$, $p<0.0001$) and alkaline phosphatase ($r=0.23$, $p<0.0001$), but negatively with BMI ($r=-0.05$, $p<0.001$). BMD was inversely correlated with age ($r=-0.32$, $p<0.0001$), osteocalcin ($r=-0.32$, $p<0.0001$), FSH ($r=-0.26$, $p<0.0001$), and alka-

〈Table 1〉 Bone markers and lipid parameters

	mean ± SD	Range
Height(m)	1.57± 0.05	1.3 − 2.0
Weight(kg)	57.3 ± 7.3	33 − 92
ALP(I.U.)	74.0 ± 30	15 − 837
Cholestrol(mg%)	207.8 ± 38.2	54 − 482
Triglyceride(mg%)	127.2 ± 75.5	5 − 786
LDL-cholesterol(mg%)	122.7 ± 29	50 − 289
VLDL-cholesterol(mg%)	15.8 ± 12.1	0.3 − 150.5
HDL-cholesterol(mg%)	66.3 ± 18.6	6.3 − 193.3
Apolipoprotein(a) (mg%)	334 ±286.4	2.0 −1932
Osteocalcin(ng/ml)	4.7 ± 1.9	1 − 9.9
Urinary Ca/Cr 100mg	16.3 ± 27.4	0.52−1192
FSH(I.U.)	57.6 ± 22	10 − 99

ALP : alkaline phosphatase
FSH : Follicle Stimulating Hormone

line phosphatase ($r=-0.29$, $p<0.0001$), but positively with BMI ($r=0.20$, $p<0.001$). No correlation was observed with any of the lipid profiles. Our observations clearly indicate that bone turnover rates are increased but bone density is decreased function of an age. The lipid profiles, exception of the HDL-cholesterol levels was increased with an age. The study population consisted of both pre-and postmenopausal women with a wide age range. Perhaps these characteristics of the population results a wide variability in the study parameters.

It has been debated whether there is a significant bone loss in women before menopause. Therefore, we examined the same parameters after stratifying the subjects according to the menopausal status(ie., pre- and postmenopause). The present review addresses this issue and discusses an important findings from our cross-sectional study. Although there was a trend for cholesterol, triglyceride and low density lipoprotein to be elevated in the postmenopausal, but no significant differences were detected when compared to the premenopausal condition 〈Table 2〉. On the other hand, bone markers for bone formation and resorption was significantly elevated in postmenopausal. Osteocalcin level increased approximately 20 percent and alkaline phosphatase as much as 50% between the two time period. Significantly decreased BMD level was observed between the two condition 〈Figure 1〉. These phenomena suggest that rapid bone loss process undertaken in postmenopausal state.

Bone density measurement

Many techniques have been developed to measure the bone mass including single photon absorptiometry (SPA), dual photon absorptiometry (DPA), dual energy x-ray absorptiometry (DEXA), and quantitative computed tomography (QCT). These are the four most frequently used instruments in Korea.

〈Table 2〉 Bone markers and lipid parameters before and after menopause.

	Premenopause	Postmenopause	p
Height(m)	157.7 ± 0.8	157.7- 0.4	ns
Weight(kg)	58.7 ± 1.2	56.3- 0.7	ns
ALP(I.U.)	62.0 ± 2.5	92.0-12.9	ns
Cholestrol(mg%)	199.8 ± 5.5	199.7- 3.8	ns
Triglyceride(mg%)	102.3 ±10.0	118.0- 8.8	ns
LDL-cholesterol(mg%)	119.0 ± 4.2	121.6- 2.8	ns
VLDL-cholesterol(mg%)	9.9 ± 1.5	12.1- 1.4	ns
HDL-cholesterol(mg%)	71.3 ± 3.0	66.8- 2.0	ns
Apolipoprotein(a) (mg%)	37.1 ± 5.1	31.4- 3.0	ns
Osteocalcin(ng /ml)	3.8 ± 0.2	4.5- 0.2	<0.05
Urinary Ca /Cr 100mg	10.6 ± 1.0	17.7- 1.7	<0.01
FSH(I.U.)	30.0 ± 4.0	61.0- 3.8	<0.0001

ALP : alkaline phosphatase
FSH : Follicle Stimulating Hormone

In our studies, bone mineral density of the lumbar spine was measured by DEXA and DPA in both normal and patients enrolled our hospital for various reasons. The subjects age was inversely correlated with BMD ($r=-0.32$, $p<0.0001$) and directly correlated with osteocalcin level ($r=0.15$, $p<0.0001$). The highest level of lumbar spine BMD was observed between age 33-39 years. The BMD declined significantly thereafter and more than 13% loss occur within 15 years from the menopause 〈Figure 2〉. Our observation shows 9% decline of BMD between the pre- and postmenopause condition 〈Figure 1〉. Although the level of BMD loss is less severe in Korean women, the magnitude of the loss is very similar to the reports in Caucasian women (8). Furthermore, we examined the relationship between BMD and the frequency of bone fractures by the face-to-face interview method. BMD was significantly associated with fracture incidence. As shown in 〈Figure 3〉, the mean BMD level was significantly reduced in the subjects with more bone fractures. Although the compliance rate to the interview was only 50%, the relationship was very strong and convincing. Moreover, osteocalcin level was not associated with the frequency of the fracture. In many studies, including some in Asian women, BMD has been found to correlate with BMI as well as the fracture incidence (9). Thus, we examined the relationship between the fracture incidence and body mass index and bone mineral density. BMI was not associated with the fracture incidence but positively correlated with BMD($r=0.26$, $p<0.0001$) independent of age. Our study revealed that BMI is a good predictor for BMD but no relationship to the fracture incidence.

Hormones in the Treatment of Climacteric Symptoms and Prevention of Osteoporosis

The relatively slow subsequent age-related bone loss occurs in both men and women, but women are additionally exposed to accelerated bone losses after the menopause. Since Albright's suggestion of bone loss could be minimized by estrogen replacement, estrogen and estrogen/progestine combined therapy are commonly prescribed in the perimenopausal period for relief of the symptoms of ovarian failure and prevention for osteoporotic fractures (10). Hormone replacement therapy is widely accepted and advocated by the clinicians in Korea to treat the climacteric symptoms and women are profoundly benefited from the therapy (11). The bone mineral density was significantly increased 1 year after the therapy and the increment was even greater 3 years after (12). Moreover, the HRT also had a beneficial effects on the lipid profiles. We measured the lipid profiles sequentially from 2, 6 and 12 months after the therapy. In this prospective study, we observed dramatic declining of the putative risk factors for cardiovascular disease, ie., cholesterol, LDL and Lipoprotein (a) [Lp (a)]. On the other hand, the protective factor for cardiovascular disease such as HDL-cholesterol was significantly increased after the therapy 〈Table 3〉. Detailed results of the study will be shown in the next section of the

Figure 1. The level of BMD (g/ cm²) between pre- and postmenopause

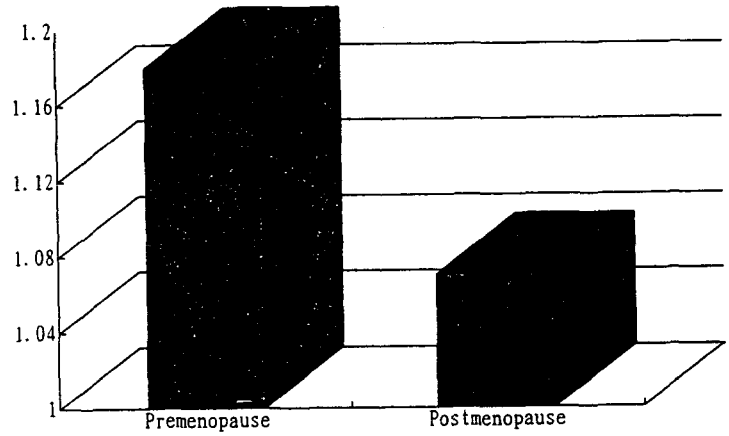


Figure 2. The Relationship between Age and BMD

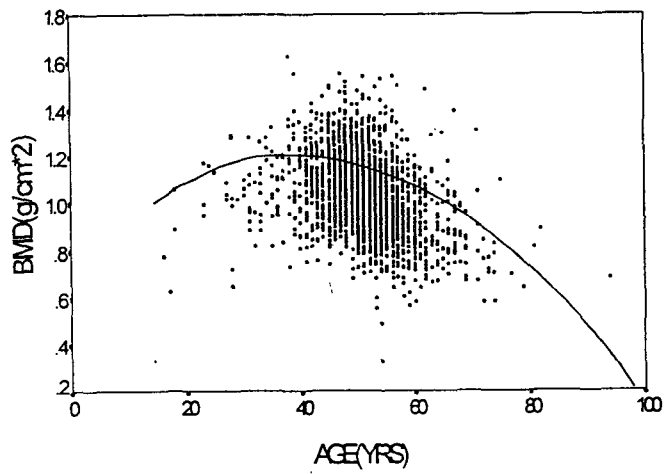
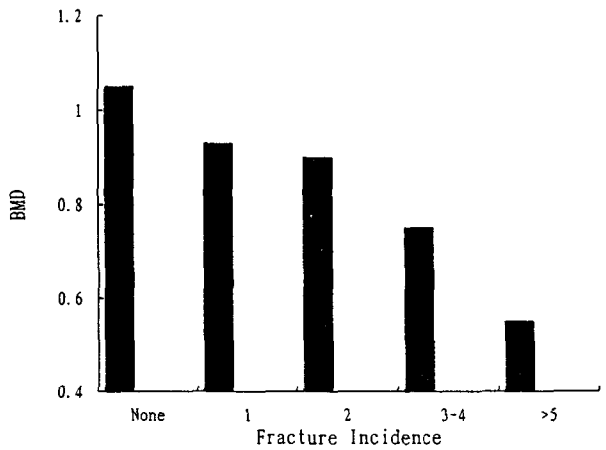


Figure 3. The Relationship of fracture incidence and BMD



regimens of hormone replacement therapy. Despite its wide acceptance and beneficial effects of the hormonal replacement therapy for the treatment of perimenopausal climacteric symptoms and prevention of bone loss, the therapy accounted a significant economic burden to the society.

The most recent health survey in Korea indicated that approximately 32 million US dollars were spend for the treatment of climacteric symptoms and prevent osteoporosis each year (12). In addition to an economical burden, the side effects from a long-term use of therapy has been a major issue in the other countries as well as in Korea. An increased in the risk of endometrial, ovarian, breast cancers were reported from the subjects who received HRT. The results are controversial, but existing epidemiological data indicate that an adverse effects are substantially dependent on dose an duration of the therapy. A moderate, perhaps twofold, increase in the incidence of breast cancer has been found in several recent studies, notably among long-term and/or current users of potent estrogen; there is no evidence that progestin counteract this adverse effect. A biologically plausible in protective effect of progestin has been documented in only a few studies(13-15).

These reports are significantly affecting the application of HRT in Korea. To compensate such problems we proposed the prospective epidemiological study to evaluate the relationship between HRT therapy and

〈Table 3〉 Effects of the Lipid Profiles after the HRT

	△Cholesterol	△Triglyceride	△HDL-Chol	△LDL-Chol	△VLDL-chol	△Lp(a)
2 months treatment (%/ 2m, n=2,008)						
A(n=360)	− 5.1±0.9	34.3±7.3	6.2±2.4	−11.6± 1.3	36.0±15.1	−19.1±6.8
B(n=494)	− 6.3±1.1	11.9±4.2	3.1±1.6	−10.6± 1.0	0.6± 6.1	−20.5±3.4
C(n=818)	−15.3±0.6	1.1±5.4	−17.3±1.1	−4.1 ± 4.6	0.4± 8.7	− 8.8±2.1
D(n=248)	−10.7±1.3	15.5±5.8	1.2±3.2	−12.9± 1.9	− 3.7± 7.5	−16.6±5.5
E(n=88)	−14.4±1.7	−30.1±4.3	−24.3±2.1	11.3±16.0	−22.5± 8.5	− 6.0±6.9
6 months treatment (%/ 6m, n=1,719)						
A(n=327)	− 3.6±1.4	36.1±7.0	14.6±3.7	−12.4± 2.1	10.1± 8.4	−29.3±5.5
B(n=416)	− 5.0±1.5	8.7±3.6	9.1±6.6	−11.1± 1.3	2.1± 8.9	−19.3±4.2
C(n=678)	−15.7±7.1	− 3.3±5.1	−18.0±1.5	− 4.8± 7.4	31.3±37.7	− 0.9±9.7
D(n=222)	−10.2±1.6	23.5±7.9	1.5±4.2	−14.0± 2.3	− 3.0± 9.4	−28.4±5.5
E(n=76)	−11.2±2.2	−24.5±4.2	−17.0±3.1	7.4±12.0	− 2.8±11.7	− 2.8±8.0
12 months treatment (%/ 12m, n=1,494)						
A(n=311)	− 0.9±1.8	34.5±8.5	15.1±4.3	− 6.6± 2.1	28.2±12.7	−16.0±10.0
B(n=375)	− 3.0±1.4	6.6±4.1	6.1±2.7	− 5.2± 1.7	11.2± 7.6	−10.3± 7.0
C(n=560)	− 5.3±5.5	− 4.3±6.4	−12.4±2.1	2.6±13.2	15.9± 8.5	3.7±10.0
D(n=184)	− 7.3±1.8	16.6±9.3	3.9±4.7	−12.4± 2.7	4.6±10.1	−17.6± 6.0
E(n=64)	−11.2±2.9	−26.5±5.6	−20.3±3.9	22.3±23.1	−14.0±12.7	3.7±10.3

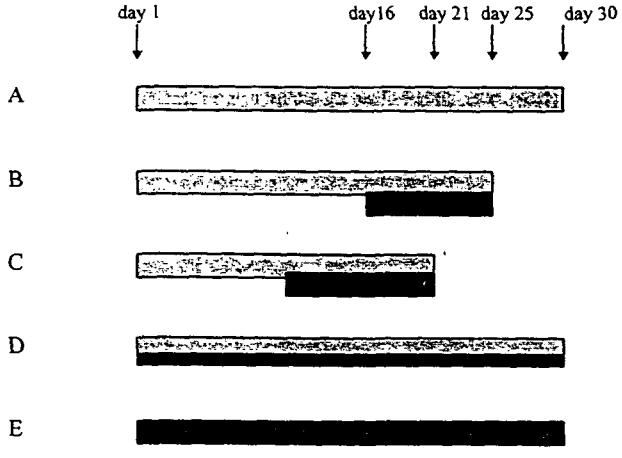
*All data are expressed as Mean±S.E.

breast, and endometrial cancers. In the main time, we have been carefully selecting the regimens and the treatment strategies for the patients. In this section, we will review an effect of the regimens that has been applied to our population to treat climacteric symptoms and prevent osteoporosis.

Regimens of hormone replacement therapy

Our subjects were treated by one of the five regimens showing in 〈Figure 4〉. The lipid profiles and the bone markers were serially measured at 2, 6 and 12 months after the treatment 〈Table 3〉. The HRT revealed a significant beneficial effects on the lipid profiles. However, the magnitude of the benefit was somewhat different according to the type of regimens. The subjects who received either C, D, or E had the most improvement in lowering cholesterol level whereas the A and B regimens shows significant effects in increasing HDL-cholesterol levels. Furthermore, all regimens exception of type C revealed a similar effects in lowering Lp(a) levels. No cumulative effects of the duration of treatment was observed in this study. Indeed our study shows an immediate effect of the therapy on the lipid metabolism. A significant beneficial effects of the HRT on the bone markers were observed in the all groups. Bone mineral density, alkaline phosphatase, and osteocalcin was significantly improved by the therapy 〈Table 4〉 (16). Although there were some differences in the beneficial effects in the lipid metabolism, the bone markers were significantly improved by all types of regimens.

Figure 4. HRT regimens used to treat osteoporotic patients



A : CEE(Premarine) of 0.625 mg /day was administered everyday ;
B : CEE 0.625 mg /day was administered for 25 days and MPA 5 mg was added in the last 10 days ;
C : Estradiol valerate 2 mg /day was administered for 21 days and Norgestrel 0.5mg was added in the last 10 days ;
D : Both CEE 0.625 mg /day and MPA 2.5mg /day was administered for 30 days ;
E : Tibolone(Livial) 2.5mg /day was administered everyday ;

〈Table 4〉 Effects of the Bone markers 1 year after the HRT

	(%/yr)#	△BMD(Lunar, %/yr)* △BGP(%/yr)#	△BMD(Hologic, %/yr)*	△ALK
Group A	2.0±0.7(149)	3.5±0.5(67)	−16.7±5.2(201)	−30.6±6.6(117)
Group B	2.1±0.2(269)	3.2±0.5(120)	−11.4±5.6(281)	− 5.1±8.8(125)
Group C	3.5±0.2(356)	4.0±0.4(124)	−18.0±3.3(422)	−15.1±5.5(136)
Group D	5.7±0.6(55)	4.8±0.6(46)	−33.1±2.1(90)	−24.7±5.1(89)
Group E	3.4±1.2(5)	3.9±0.7(75)	−19.5±3.1(73)	−24.5±5.3(76)
None	−1.0±0.4(131)		27.6±5.5(64)	

*: expressed as Mean±S.E. #: expressed as Mean±S.D.
( ): patient number, BMD: Bone Mineral Dencity,
ALK: Alkaline Phosphatase, BGP: Bone Gla Protein(=Osteocalcin)

Comments

Osteoporosis is a major financial and public health problem in the Western society and such problem is also burgeoning in Asia. There are several reasons to assume that osteoporosis as a disease will remain a major problem in Korea: (1) the population is aging, and many people will live long enough to develop a bone mineral density lower than the fracture threshold; (2) the prophylactic with HRT is limited by lower compliance at older age.

A deficit of estrogen secretion after the menopause causes diminution of the bone mineral density of the various sites. Researchers have shown that peak bone mass at skeletal maturity may be the single most important factor in the development of osteoporosis. There is strong evidence linking bone fractures and osteoporosis with low bone mass(17, 18). Asians appear to have lower bone mass than Caucasians, on average, although the difference is reduced after adjusting for body size (19, 20). In spite of low bone mass in Asians, several studies indicate that the incidence of hip fractures in Japan is actually lower than among Caucasians (21, 22). Although the overall incidence of bone fracture is lower in Asians when compare to the other ethnic groups, the rates were similar when adjusting for bone mineral density. Thus, it appears likely that factors other than bone mass may explain the observed differences in osteoporosis and the fracture rates. For example, the amount of bone loss rather than the peak bone mass might be related to the rate of osteporosis or fractures. The amount of bone loss may be influenced by the vairous factors such as genetic, nutrition, life-style and an environment.

Numerous previous reports indicate that genetic, nutrition, life-style and evironment factors could significantly affect the amount of bone loss and the peak bone mass. The role of genetic factors is poorly understood, but its importance is suggested by the observations that blacks have greater bone mass than do whites. Inadequate calcium intake and consumption of alcohol that is though to have an adverse effect by decreasing bone formation by depressing osteoblast activity. High intake of animal pro-

tein and sodium may have deleterious calciuric effects on the skeleton. Caffeine may also adversely affect the skeleton. Two life-style risk factors for inadequate peak bone mass and osteoporosis are limited physical exercise and cigarette smoking. Certainly, these factors are frequently observed in Westernized life-styles. Despite the fact that Korea continue their westernization and industrialization, the fracture rates in Korean women are still low. However, Koreans would be expected to have a higher fracture rates in the future, because of an earlier menopausal age in younger generation than older generation. In other word, Korean women are living longer and reach menopause in younger age resulting a longer life after menopause. Therefore, longer exposure to the westernized life style and longer duration after menopause certainly places Korean women at increased risk for the disorder.

At present, no satisfactory way to replace lost bone exists, thus the ideal treatment for osteoporosis is prevention and which must begin early in life. Adequate intake of calcium, vitamin D, and protein and appropriate exercise cannot be overemphasized and its affects should be considered. Moreover, our studies clearly demonstrated beneficial effects of the HRT on the bone density and an improvement of the lipid profiles. Therefore, we thought the risk of osteoporotic fractures can be reduced substantially, at least during ongoing, treatment starting early after menopause. It is now accepted that HRT use is associated with a reduced risk of cardiovascular disease in postmenopausal women. Although the side effects of the therapy is the major concern of the medical community, a 25 to 50% reduction in cardiovascular morbidity and mortality as well as the positive beneficial effects on BMD might outweigh any conceivable adverse effect of HRT(23, 24).

The most promising approach in the primary prevention of osteoporosis is to help each person achieve as high a peak skeletal mass and bone density as genetically possible prior to skeletal maturity. And the second approach is minimizing bone loss after menopause which can be accomplished via HRT. Although some adverse effects has been reported, the efficacy of hormonal replacement therapy has been reported from a numerous previous studies. If no preventive therapy is considered, the cost of osteoporosis will dramatically increase in the years to come and this phenomenon is no exception to Korea as well as in Asian countries.

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