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Effects of Antipsychotics on Bone Mineral Density in Patients with Schizophrenia: Gender Differences

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Low bone mineral density (BMD) and osteoporosis are common in patients with schizophrenia and detrimental to illness prognosis and life quality. Although the pathogenesis is not fully clear, series of studies have revealed factors related to low BMD such as life style, psychotic symptoms, medication use and the activity of bone absorption markers. It has been known that antipsychotic-induced hyperprolactinemia plays a critical role on decreased BMD. However, it remains uncertain whether the risk factors differ between men and women. According to the effect on prolactin, antipsychotics can be classified into two groups: prolactin-sparing (PS) and prolactin-raising (PR). Our previous study has demonstrated that clozapine which is among the PS antipsychotics is beneficial for BMD when compared with PR antipsychotics in women with chronic schizophrenia. We have also found that risks factors associated with low BMD are different between men and women, suggesting that gender-specific risk factors should be considered for intervention of bone loss in patients with schizophrenia. This article reviews the effects of antipsychotics use on BMD with particular discussion for the differences on gender and age, which implicate the alterations of sex and other related hormones. In addition, currently reported protective and risk factors, as well as the effects of medication use on BMD including the combination of antipsychotics and other psychotropic agents and other potential medications are also reviewed.

KEY WORDS: Schizophrenia; Bone density; Gender effects; Antipsychotics agents; Hyperprolactinemia.

INTRODUCTION

Prevalence of Osteoporosis and Osteopenia in Patients with Schizophrenia

The effects on life quality and prognosis of lower bone mineral density (BMD) and osteoporosis as to bone fracture[1,2] among schizophrenia patients receiving antipsychotics had earned attention gradually during this decade.[3] Patients with schizophrenia have 54% increased risk of mortality after a major fracture than control group.[4] Besides, the vital impact of hip fractures in schizophrenia patient is stated, which would cause worsening mental state and ambulatory,[5] higher rate of postoperative infection and a risk of contra-lateral fractures.[6,7] Osteoporosis is defined as "a systemic skeletal disease characterized by low bone density and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture."[8] The standard method assessing BMD is dual-energy X-ray absorptiometry (DEXA), that DEXA of the femur may represent actual bone strength.[9] According to the World Health Organization (WHO) definition, osteoporosis stands for the condition of patient's femoral neck BMD was 2.5 standard deviations (SDs) below the mean of a young and healthy population (T-score), matched for gender and ethnic group. Z-score was defined similarly to T-score, but the mean BMD was from an age-matched adult reference population.[10] Low BMD, or osteopenia, was defined as a BMD value more than 1 SD but <2.5 SDs.[11] Previous studies indicated that 32-65% of patients treated with antipsychotics suffer from osteopenia, which may lead to osteoporosis[12,13] A recent meta-analysis on decreased BMD in schizophrenia patients revealed that the overall pooled prevalence of osteopenia was 40.0% and osteoporosis was 13.2%.[6] The prevalence rates of osteopenia and osteoporosis differ from ages and genders. A report of 965 chronic schizophrenia patients indicated that 44% men and 48.9% women have osteopenia while 9.2% men and 21% women

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have osteoporosis.[14] The above evidences pointed out that schizophrenia patient had significantly increased risk of low BMD comparing with healthy controls.[4,6,12-14] The underlying mechanisms, risk/protective factors, gender differences and medication effects need to be discussed.

The Effects of Hyperprolactinemia and Hypogonadism on Bone Metabolism

Dopamine is synthesized in the tubero-infundibular neurons of the hypothalamus. It is transported to the pituitary by the portal hypophyseal circulation. Most antipsychotics, as D2 receptor antagonists, bind to the D2 receptors of lactotroph cell in the pituitary would lead to the release of prolactin[15] and subsequent hyperprolactinemia, a sustained prolactin elevation above normal laboratory level. The usual normal prolactin levels in peripheral blood are below 530 mIU/L (25 ng/ml) in women and 424 mIU/L (20 ng/ml) in men.[16] The BMD is decreased by 15-30% in hyperprolactinemia women compared with control groups.[17] Nevertheless, high levels of prolactin inhibit the release of gonadotropin releasing hormone (GnRH) from the hypothalamus, resulting in impaired secretion of the luteinizing hormone and follicle-stimulating hormone, which consecutively lower the gonadal hormone secretion.[18] Studies suggest that high prolactin levels affect bone metabolism by reducing sex hormone levels.[19,20] Estrogen promotes osteocytes and osteoblasts directly and has inhibitory effect on osteoclasts.[21] It also affects the synthesis of 25-OH-vitamin D and the absorption of calcium in the intestine.[12,22] Therefore, withdrawal of estrogen leads to an enhancement of osteoclast activity which is not completely compensated by a collateral increase in osteoblast activity,[23] meanwhile, the decrease of progesterone no longer facilitate bone formation by stimulating osteoblast.[24] Furthermore, prolactin has been observed to directly decrease osteoblast cell numbers by reduced proliferation, thus providing a "direct effect" mechanism explaining the reduction of BMD.[25]

Other Risk Factors for Decreased BMD in Patients with Schizophrenia

WHO recognized several factors associated with decreased BMD, including smoking,[26] lower body mass index (BMI),[12] although recent evidence showed that obesity is a risk factor of low BMD,[27] lack of exercise,[28] alcohol consumption,[29] glucocorticoid use,[30] family history,[31] prior fracture[32] and poor nutrition.[33,34] Among the above reported factors, a review article found only 2 significant correlations: decreased BMD and lower BMI, BMD at the 4th lumbar spine and smoking.[35] Nevertheless, prospective studies that focus on schizophrenia are needed to verify the contribution of each risk factor as well as the interaction among different factors.

Beside the above mentioned risk factors, schizophrenia patients are at higher risk for decreased BMD and fractures for the disorder *per se* and its related health problems.[4,36] Risk factors of decreased BMD specific to schizophrenia include lower levels of physical activity[37] and sedentary lifestyle, vulnerability to metabolic syndrome[27,38] and diabetes mellitus,[39] polydipsia which is related to excessive calcium loss,[40] vitamin D deficiency resulting from inadequate diet and insufficient sun exposure,[41,42] high smoking prevalence rate with greater frequency of heavy smoker than control group[43,44] which dysregulated calciotropic as well as sex hormone and imbalanced the receptor activator of nuclear factor-kappaB ligand (RANKL)-RANK-osteoprotegerin (OPG) system,[45] and excessive alcohol intake.[46,47] Among the aforementioned factors, both pathological alcohol drinking and diabetes may also increase the risk of falling and subsequent fracture.[48] The motor incoordination commonly seen in patients with schizophrenia[49] could also lead to the increased risks of falling and fracture.

Schizophrenia itself may also be an independent determinant of osteoporosis. A cross-sectional study in 28 women and 20 men with schizophrenia compared with 6,100 control population found that schizophrenia was an independent risk factor of osteoporosis in women but not in men after controlling other risk factors including vitamin D status, and medications.[50] However, the finding might be limited by its relatively small sample size of male schizophrenia patients.

Different Measurements, Definition of Bone Mineral Density/DEXA Z Score than T Score

According to the National Institutes of Health Consensus Development Panel on Osteoporosis in 2001, osteoporosis is defined as "a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture."[51] Since the introduction of DEXA in the late 1980s, acquisition time was dramatically shortened and the accuracy and precision of BMD measurement improved.[52] In 1994, the mean BMD of a young and healthy population was recommended by the WHO as a comparison in diagnosing osteoporosis. T scores were derived from the comparison with the healthy adult population. Osteopenia was defined by an absolute BMD value, T score, between -2.5 and -1,[53] and osteo-

porosis was defined by a T score of −2.5 or lower.[54] Later, the International Society for Clinical Densitometry (ISCD) suggested physicians to use Z-score, rather than T-score, for diagnosing low bone mass in children, premenopausal women, and men younger than 50 years.[11,55-57] Z score is of help for determining whether bone mineral loss results from aging.[58] Nevertheless, Z-scores are currently lack of sufficient reliability due to the lack of standardization of definition and calculation techniques as well as developing an ethnicity-matched reference population.[57,59]

GENDER DIFFERENCES

Gender Difference about Effects of Hormone on Bone Metabolism

Men have a higher level of peak bone density than women among aged 20-29 years that prevents the exacerbation of osteopenia or osteoporosis.[60,61] Testosterone exerts effect on increment and perseveration on bone trabecular number and is fundamental in bone maturation,[62] thereby is negatively correlated with osteoporosis in men.[12] However, BMD is related more to estradiol than to testosterone in elderly men.[62-66] Testosterone is also associated with the level of 25-hydroxylation of vitamin D that is related to Leydig cells recently found to be involved in bone-testis endocrine loop.[67] Simultaneous reduction of sex hormones and vitamin D was associated with 4-fold risk of a major osteoporotic fracture.[68] In both men and women, bio-available testosterone plays a role in preventing low BMD via converting into estradiol by aromatase.[69-71] However, in patients with hypogonadism, testosterone replacement alone did not improve BMD greatly[72] and the effect of testosterone was uncertain.[69] Research regarding estrogen receptor and aromatase deficiency suggests that estrogen plays important role in BMD in men.[73,74] Lower level of estradiol was associated with an increased risk of fracture in men.[69]

Women's BMD is highest in their early to the mid-30s, which declines in greater extend in the first 3 to 5 years of menopause. In premenopausal women, the findings of sex hormones effect on BMD were inconsistent. A study showed that androgen level was positively related to BMD among premenopausal women.[75] Serum bioavailable testosterone was also found to be a significant independent predictor for BMD of premenstrual women in another study.[76] A review article indicated that combined estrogen and testosterone therapy increased BMD in premenopausal women to a greater degree than estrogen therapy alone.[77] Whether estrogen plays a more important role than testosterone on BMD in premenstrual women remains inconclusive due to limited reports. The post-menopausal effect on schizophrenic women and the effect of prophylactic hormone replacement therapy would be discussed later.

Gender Difference of Antipsychotic Effect on Bone Mineral Density

Antipsychotic drugs can be categorized into 2 groups: prolactin-sparing (PS) group, including olanzapine, quetiapine, aripiprazole, ziprasidone and clozapine, and prolactin-raising (PR) group, including all first-generation antipsychotics, amisulpride, risperidone and paliperidone.[78] Table 1 summarized articles that discussed gender difference of antipsychotic effect on BMD as well as comparison of antipsychotics agent and hyperprolactinemia with decreased BMD. A cross-sectional study in 195 Taiwanese schizophrenia patients pointed out that both women and men taking PS antipsychotics have higher BMD than those taking other antipsychotics (including PR antipsychotics and combination of PS and PR antipsychotics).[79] A study in 16,341 hip fracture patients based on the General Practice Research Database found the association between PR antipsychotics use and hip fractures in both gender.[2]

A literature review pointed out that the prevalence of hyperprolactinemia is the highest in women using risperidone and amisulpride (around 80-90%) than other antipsychotic drugs. Amisulpride caused hyperprolactinemia in almost all cases and the prolactin level was significantly higher in female than male patients. The dose of antipsychotic drugs was not correlated with the prolactin level.[80] The prolactin levels did not differ between the pre- and post-menopausal women.[24] A large point-prevalence study in 402 schizophrenia patients also revealed that hyperprolactinemia was more common among females than male patients taking risperidone (88% vs. 47.6%, respectively; p=0.0001).[81] Another review[82] of 5 clinical studies indicated that haloperidol- or risperidone-induced hyperprolactinemia appeared to be abrupt and persistent, and the magnitude of hyperprolactinemia was greater in females than males.

Although some study suggested that there was no gender difference for the effect of PR antipsychotics on prolactin levels,[12] in a meta-analysis by Stubbs *et al*.,[6] the result of a total of 3,038 schizophrenia patients from nineteen studies pointed out that men were more vulnerable to osteoporosis and osteopenia than women. Another cross-

Table 1. A summary of the antipsychotic effects on prolactin and bone density in men and women

Reference number	Design and setting	Schizophrenia participants n, age (yr)		Type of antipsychotic treatment % PR antipsychotics		Number (%) of patients with hyperprolactinemia		Type of bone scan and measurement	Number (%) of patients with schizophrenia with osteoporosis and osteopenia	
		Male	Female	Male	Female	Male	Female		Male	Female
12	Cross-sectional study	30, 43.5±13.4	25, 59±5.5	Miscellaneous, hyperPL vs. non-hyperPL=602 vs. 267 mg/day of chlorpromazine equivalents		18 (60)	16 (64)	DXA, L1-L4 & Femur t-score	Decreased BMD 17 (57)	Decreased BMD 8 (32)
41		12, 31.3±1.3	14, 31.3±1.3	Both treated with risperidone consta		8 (66.7)	14 (100)	DXA, Lumbar spine & Femoral head t-score	Not categorized	
42		57, 33.6±5.4	18, 38.3±7.4	17.5 3.6 treated with PR & PS	22.2 5.6 treated with PR & PS	12 (22.9)	8 (44.4)	DXA, L1-L4 & Femur t-score	Osteoporosis: total 6 (10.5) Osteopenia: total 26 (45.6)	Osteoporosis: total 1 (5.6) Osteopenia: total 6 (33.3)
86		30, 39.9±5.1	21, 37.8±5.5	Both treated with haloperidol 12 (40)		17 (81)	DXA, L1-L4 & Femur t-score	Decreased BMD 15 (50)	Decreased BMD 18 (85.7)†	86
82		255, 40.8±10.0	147, 44.5±11.4	Not categorized		110 (43)	90 (31)	QUS Calcaneus	Osteoporosis: total 8 (1.9) Osteopenia: total 102 (25.4)	
80		80, 42.4±9.0	115, 43.3±10.2	25 20 treated with PR & PS	31.3 19.1 treated with PR & PS	38 (47.5)	63 (54.8)	DXA, L2-L4 t-score	Decreased BMD 27 (33.8)†	Decreased BMD 28 (24.3)
84	Cross-sectional study	45, 49.5±11.1	Nil	44.4 treated with risperidone 33.3 treated with olanzapine 22.2 treated with clozapine	Nil	15 (75) in risperidone 6 (40) in olanzapine 1 (10) in clozapine		DXA, L1-L4 z-score	Osteoporosis: total 3 risperidone (20) Osteopenia: total 3 risperidone, 7 olanzapine, 1 clozapine (20, 46.6, 10)	
20	Longitudinal study	74, 58.9±12.2	Nil	77	Nil	54 (94.7) in PR 10 (58.8) in PS		DXA radius t-score & z-score	Osteoporosis: total 20/74 (27) Osteopenia: total 28/74 (38.7)*	
128	Longitudinal study	Nil	38, Pre-menopausal	Nil	62.5 Not intervention of exercise, Calcium ... etc. : 8/20	Not mentioned		DXA, L1-L4 & hip t-score & z-score	Decreased BMD: 8/8 (100)	
13	Cross-sectional study	Nil	38, 32.8±6.8PR 29.5±5.7PS	Nil	68.4	25 (96) in PR 4 (33) in PS		DXA, L1-L4 & Femur z-score	Osteoporosis: total 7^{PR} (27)† Osteopenia: total 10^{PR}, 2^{PS} (28.4, 17)	
91	Cross-sectional study	Nil	14, 36.3±9.4	Nil	42.9	6 (100) in PR 1 (12.5) in PS		DXA, L1-L4 & hip z-score	Not mentioned	

*Significance of association between duration of hyperprolactinemia and decreased BMD; †significance of association between hyperprolactinemia and decreased BMD.
BMD, bone mineral density; PR, prolactin-raising; PS, prolactin-sparing; PL, prolactin; DXA, dual-energy X-ray absorptiometry; QUS, quantitative ultrasound.

sectional study in 195 Taiwanese schizophrenia patients found that men taking PR antipsychotics tended to have lower BMD than women.[79] Male patients with schizophrenia taking antipsychotics for at least 1 year suffered from a lower BMD than did women.[42] Furthermore, a longitudinal study of 74 schizophrenia men suggested that the duration of hyperprolactinemia was correlated with the reduction in BMD, whereas the level of prolactin did not directly reflect the extent of BMD loss.[20] This conclusion was supported by another prospective study showing that BMD is negatively correlated with longer time periods (more than 12 months) of hyperprolactinemia or affected by prolactin at only much higher levels.[13] A cross-sectional study followed 45 male patients with schizophrenia who had been receiving antipsychotic monotherapy (risperidone, olanzapine or clozapine) for long-term (more than 20 years).[83] The results showed that those patients' BMD were not associated with both their sex hormone level and prolactin level. The study further proposed that the pathophysiology of the decreased BMD among schizophrenic male patient might be different from that of female patients. It also suggested that the effect of negative symptoms might be greater than antipsychotics use on BMD in schizophrenia patients.

A cross-sectional study of 229 schizophrenia patients (93 postmenopausal women and 136 men) who were older than 50 year-old found that postmenopausal women had a significantly higher prevalence of osteoporosis than men (48.4% vs. 25.7%).[44] An earlier study conducted by the same author proposed that PR antipsychotics-induced hyperprolactinemia was associated with decreased BMD among premenopausal female schizophrenic patients.[84] Another cross-sectional study of 71 schizophrenia women showed that bone turnover acceleration was found in all female patients including pre- and post- menopausal women; nevertheless,[85] in a longitudinal study, only postmenopausal women were found to have decreased BMD compared to premenopausal women.[86] A large scale cross-sectional study involving 6,820 postmenopausal women with schizophrenia suggested that both schizophrenia *per se* and treatment with atypical antipsychotics were independent risk factors for osteoporotic bone changes.[87] Nonetheless, a longitudinal study for old men >52 year-old and postmenopausal women of schizophrenia with long-term (>10 years) PR antipsychotics treatment showed that only the dose of antipsychotics (shown in chlorpromazine equivalence index) was associated with decreased BMD in multivariate analysis.[12]

Dose Dependent or Course Dependent

A previous study showed that decreased BMD was related to the duration of hyperprolactinemia.[88] Sustained hyperprolactinemia was found to have an impact on the rate of bone metabolism.[89] Researchers had no consensus yet about the effect of antipsychotic dose on prolactin level. A common finding is that lowering the dose of antipsychotics may decrease the prolactin level in subjects with hyperprolactinemia.[12,90] Furthermore, antipsychotic-induced hyperprolactinemia is not related to the duration of antipsychotic treatment.[91] Besides, there were evidences for both approving[20] and opposing[22,92] the negative effect of the duration of antipsychotic use on BMD. Together, the association of decreased BMD between antipsychotic dose and duration has not yet been conclusive.[36]

Gender Difference on Bone Mineral Density of Other Psychotropic Agents

Many psychotropic drugs have been reported to be associated with the development of BMD loss, including lithium, selective serotonin reuptake inhibitors (SSRIs) and anticonvulsants.[11] Earlier studies suggested no effect of lithium on bone structure,[93] whereas recent evidences showed protective effect of lithium on BMD.[94] A cross-sectional study suggested that women taking lithium of therapeutic dose had higher estradiol levels which were correlated with spinal BMD, although the psychiatric illness and combined medications were not controlled in the study.[94]

SSRIs but not tricyclic antidepressants was found to have negative effect on BMD.[87] Chronic administration of SSRIs may increase the risk of osteoporotic fractures.[90] A recent review demonstrated that SSRIs negatively affected bone growth by interfering 5-HT transporter in bone cells that leads to bone demineralization and subsequent reduced BMD, and the effect was dose-dependent.[95] Although studies about the effect of SSRIs on BMD are lacking in schizophrenia patients, SSRIs are indicated to cause decreased BMD in patients with generalized anxiety disorder, especially in those female patients who are older and post-menopausal.[96]

Anticonvulsants such as carbamazepine and valproic acid which were frequently used as mood stabilizers may also lead to decreased BMD in bipolar disorders. The decrease of BMD was found to be related to the diminished level of 25-hydroxy vitamin D, and this effect was related to duration of anticonvulsants treatment.[97] A meta-analysis consisted of more than 907,000 men and women in-

dicated that the use of beta-blocker was associated with 17% reduction in the risk of any fracture.[98] However, currently there is no reported study about the effect of beta-blocker on BMD in schizophrenia patients.

Biochemical Bone Markers and Other Hormonal Effects

The subtle change of BMD is hardly to detect by radiologic exam particularly within 3 to 4 years of bone resorption. Nonetheless, biochemical bone markers can serve as more sensitive tests that the change of bone metabolism can be evaluated in a much shorter time (about 2 to 4 weeks) after treatment.[99] Various biochemical bone markers have been reported including bone-specific alkaline phosphatase (BAP), osteoclacin (OC), C-terminal or N-terminal propeptides of type I procollagen (PICP or PINP), deoxypyridinoline (DPD), type I collagen releases carboxy-terminally cross-linked telopeptides and amino-terminally cross-linked telopeptides (CTX and NTX), tartrate-resistant acid phosphatase 5b (TRAP5b), bone sialoprotein (BSP), osteopontin (OPN), carboxy-terminal cross-linking telopeptide of type I collagen (ICTP).[100] Among those bone markers, BAP and OC are mostly recommended as bone formation markers; and DPD, CTX and NTX as well as collagen fragments as ICTP are regarded as bone resorption markers.[101] However, ICTP has a low specificity in reflecting bone absorption, since it may also be correlated with decomposition of other tissue result from physical changes.[102,103]

Bone turnover markers, including bone formation and bone resorption markers, reflect the bone physiological fluctuations that may be involved in the relationship between antipsychotics use and BMD change.[36] Consequently, bone markers may be potentially useful predictor for osteoporosis induced by antipsychotic use. A bone resorption marker TRACP-5b was found negatively related to both testosterone level in men and estradiol level in women with schizophrenia.[104] Moreover, the TRACP-5b level was positively correlated with prolactin levels in female patients but not in males.

Leptin, a 16 kDa protein synthesized by adipose tissue, may inhibit bone formation through both peripheral and central ways.[105] Leptin acts as a negative feedback signal against absorption of fat. It is also found in lower level in central nervous system of obese people who may induce leptin resistance.[106] Meanwhile, obesity, partially related to the side effects of medication and negative symptoms, is very common among patients with schizophrenia.[107] Obesity that leads to the resistance to the effects of leptin therefore serves as a protective factor, compensating the low BMD related to hypogonadism and hypercortisolism commonly seen in schizophrenia patients treated with antipsychotics.[108,109] Furthermore, it is suggested that leptin could modulate the mesolimbic dopamine system[110] and was thus inversely associated with the severity of positive symptoms in schizophrenia patients.[111] A meta-analysis of 28 studies indicated that olanzapine, clozapine and quetiapine may raise leptin levels in patients with schizophrenia. The study suggested that the leptin levels were positively correlated with BMI in the consequence of leptin resistance result from antipsychotics related weight gain and metabolic syndrome.[106] There was no gender difference on antipsychotic-induced changes in leptin levels from this meta-analysis. Further studies are needed to clarify the effects of gender on leptin in patients with schizophrenia particularly those with obesity or higher BMD that is more common in postmenopausal women and older men.

Age Differences on BMD

The cross-sectional study that involved 327 schizophrenia patients implied that 79.9% of those schizophrenia patients older than 50-year-old had decreased BMD (45.0% and 34.9% for osteopenia and osteoporosis, respectively).[44] The prevalence of decreased BMD, including osteopenia and osteoporosis, in older schizophrenia patients is higher than that of schizophrenia patients with overall age (53.2%).[6] The prevalence of osteoporosis in elderly patients with schizophrenia is about 2 times as that of healthy individuals of the same age (34.9% vs. 18.4%). Among patients treated with PR antipsychotics, aging has been reported to be a risk factor of osteopenia for both genders.[112] Another research showed that the difference in BMD between schizophrenia patients and controls was not significant until their 30s, and the difference became detectable in their 40s or older respectively.[20]

A study in Japan with 362 patients diagnosed as schizophrenia or schizoaffective disorder found that the decrease in BMD was found in men of age 40 years or older and in women of age 60 years or older.[113] In both genders of schizophrenic patients in the study, the older group (aged 50 years and older) has significantly lower BMD than the younger group. A more interesting finding of the study was that the effect of age on BMD was more prominent in schizophrenia male than female patients: the rate of age-related BMD loss of male schizophrenia patients was greater than that of male control group, whereas the decline rates of BMD with age were not different between female schizophrenia patients and female control group.

The main cause of the gender difference might possibly be that the effect of menopause on bone loss exceeded those of other risk factors including antipsychotics use or the disease itself.[113]

In postmenopausal women, both menopause and hyperprolactinemia lead to hypogonadism that accelerate the decrease of BMD.[12,114] The bioavailable estradiol is of particular importance to skeletal health and correlated with BMD change. Evidences support the supplement of exogenous estrogen for the prevention of osteoporotic fractures.[69] Testosterone, on the other hand, could also maintain BMD and prevent osteoporotic fracture in postmenopausal women with low estradiol levels.[115] Nevertheless, although endogenous testosterone also serves as a protective factor for BMD in postmenopausal women, estrogen seems to play a more important role.[116] A recent cross-sectional study in postmenopausal women also indicated that serum testosterone itself did not affect BMD; the effects of testosterone on BMD are dependent of estrogen levels.[75] It is likely that the effect of estrogen on BMD is greater than that of testosterone in postmenopausal women.

Some reports revealed that children and adolescents taking antipsychotics also experienced substantial problems of decreased BMD, although those patients were young and only had modest (varying between two- to four-fold) increase of prolactin levels than normal levels.[117] The effect of PR antipsychotics on prolactin level may be independent of age, in other words, PR antipsychotics may affect prolactin level in patient at all age.[82] Although the peak bone mass is mainly determined by genetic factors, up to 20% of the variance results from environmental or hormonal factors during puberty.[118] The exact effect of hyperprolactinemia on BMD during puberty, a vital period of bone development during which 60% of bone growth occurs, is unknown; it should be deliberate when treating patients with PR antipsychotics during the adolescent period.[13]

PROTECTIVE FACTORS FOR BMD

There are many factors that have shown protective effect on BMD. Vitamin D is one of the protective factors for BMD.[119] Pro-vitamin D in the body reacts to ultraviolet light which cannot be replaced by indoor light[12] on the surface of the skin and is converted to vitamin D.[22] Sufficient calcium intake (1,200-1,500 mg/day) is also vital for the prevention and treatment of osteoporosis.[120] Dopamine agonist may also serve as a protecting factor to restore normal menstrual function and increase BMD among the hyperprolactinemic women with amenorrhea.[121] Exercise is among the well-known protective factors for BMD. In detail, light exercise can stimulate the growth of bone cells[79] while weight-bearing exercise may work against bone demineralization.[122] It is well-known that long term use of many psychotropic drugs, such as amitriptyline, mirtazapine and the second-generation antipsychotics including clozapine, olanzapine, quetiapine and risperidone may cause weight gain.[123,124] Since modest increase in BMI can enhance BMD,[125] weight gain that results from medication effect may possibly act as a protecting role against BMD loss especially for patients receiving PR antipsychotics.[41] Besides, a study of chronic schizophrenia women indicated that clozapine may protect BMD by activating N-methyl-D-aspartate receptors on osteoblast with dose-related effect.[126] Recent study about the receptor activator of NF-κB ligand (RANKL) showed that quetiapine can inhibit RANKL-induced osteoclast differentiation and decrease cancer-associated bone resorption.[127] Another animal study in 2011 also pointed out the effect of phenothiazines such as chlorpromazine, trifluoperazine, and promethazine inhibited inhibit RANKL-induced osteoclastogenesis through anti-CaM action (CaM, calmodulin, a intracellular calcium-receptive protein actions).[128]

As aforementioned, resistance to leptin may be a protecting factor against the decrease of BMD. This hypothesis was supported by an animal study in which the mice with leptin or leptin receptor deficiency could maintain high BMD despite of hypogonadism, suggesting that the high BMD was the consequence of the paucity of leptin signaling, not of obesity.[108] Interventions to improve the bone density, such as calcium or vitamin D supplement, octacalcium phosphate (a precursor of bone apatite crystals) and exercise were demonstrated to be helpful for enhancing BMD in schizophrenia women taking either PS or PR antipsychotics; however, the effect of these interventions in improving BMD was found significant only in women who were treated with PS antipsychotics.[129]

For disease-specific factors, positive symptom that may lead to increased psychomotor activity was reported to be a protecting factor of BMD in women with schizophrenia.[130] For male schizophrenia patients, the score of Global Assessment of Functioning (GAF) was found to be correlated with the exercise capacity that might be a positive predictor of BMD.[131]

SUMMARY

Osteoporosis and the subsequent comorbidities lead to poor outcome and quality of life in patients with schizophrenia, particularly those taking antipsychotic drugs. Decreased BMD was found in more than half of all schizophrenia patients, and its prevalence was significantly higher than normal population. The effect of hyperprolactinemia on BMD is inconclusive. Antipsychotics-induced hyperprolactinemia is more common in female schizophrenia patients. However, current evidences show that postmenopausal women and older men were more vulnerable to hyperprolactinemia-related low BMD than premenopausal women and younger men. In addition to antipsychotic drugs and possibly associated hyperprolactinemia effects, there are many other factors that can affect BMD in patients with schizophrenia, including medications such as lithium, SSRIs and anticonvulsants, sex hormones, body weight, life style, negative symptoms, inadequate nutrition…etc. This review discussed the gender differences about the effect of these risk factors on BMD in patients with schizophrenia.

On the issue of the effect of PR antipsychotics-related hyperprolactinemia on BMD, evidences from previous studies were inconclusive. The inconsistent findings among studies might partially result from the cross-sectional study design and lack of adequate control groups. Certain questions remain unanswered by present literatures. This review on BMD in patients with schizophrenia is limited by the insufficient prospective studies on the topic of gender differences. Prospective studies with larger sample size and adequate controls are required in the future for elucidating the unsolved issues. This review points out that gender differences exist in various aspects regarding the decreased BMD in patients with schizophrenia. Physicians should pay attention to gender differences in treating low BMD in order to formulate specific prevention and therapeutic strategies for different populations.

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