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Osteoporosis and fracture risk in people with schizophrenia

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Abstract

Purpose of review—Excessive bone mineral density (BMD) loss has been associated with schizophrenia, but its mechanisms and clinical implications are less clear. The aim of this review was to summarize the risk of osteoporosis and bone fractures in schizophrenia patients. Moreover, we aimed to examine the impact of antipsychotic-induced hyperprolactinemia on bone metabolism.

Recent findings—Fifteen of 16 studies (93.8%) reported lower BMD or higher prevalence of osteoporosis in at least one region, or in at least one subgroup of schizophrenia patients compared with controls, but results were inconsistent across measured areas. Higher fracture risk was associated with schizophrenia in 2/2 studies (independently: $n = 1$), and 3/4 studies with antipsychotics. Reasons for this difference include insufficient exercise, poor nutrition, smoking, alcohol use, and low vitamin D levels. Altogether, 9/15 (60.0%) studies examining the relationship between antipsychotic-induced hyperprolactinemia and BMD loss found some effects of

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hyperprolactinemia. However, results were mixed, samples and effects were small, and only two studies were prospective.

Summary—Schizophrenia is associated with reduced BMD and fracture risk. Prevention, early detection, and intervention are required. The relative contributions of antipsychotic-related hyperprolactinemia and unhealthy lifestyle behaviors remain unclear, needing to be assessed in well designed, prospective studies, including bone turnover markers as intermediary endpoints.

Keywords

bone mineral density; fracture; osteoporosis; prolactin; schizophrenia

INTRODUCTION

Schizophrenia is a severe and predominantly chronic-relapsing disorder that is associated with marked functional impairments [1]. Furthermore, schizophrenia has been associated with a greater prevalence of health problems, including obesity, diabetes, metabolic syndrome, cardiovascular diseases, HIV infection, hepatitis, altered pain sensitivity, obstetric complications, dental problems, polydipsia, sexual dysfunction, and osteoporosis, than in the general population [2,3■,4]. Of these medical comorbidities, osteoporosis has received attention recently. Osteoporosis, characterized by abnormally low bone mineral density (BMD), is an important comorbidity in schizophrenia, as it can be related to the mental illness or developed due to a third, medical condition, unhealthy lifestyle behaviors or, possibly, the prolactin-elevating effects of antipsychotics [5].

Although lower BMD among schizophrenia patients was noted earlier [6,7], insufficient attention has been paid to this phenomenon. Moreover, the mechanisms, prevention, and clinical management of osteoporosis in schizophrenia patients have been only insufficiently defined. Over the past 5 years, there have been several reviews in this area [8-11], including a thorough review by Graham *et al.* [9]. However, the debate has mainly focused on the effects of antipsychotic-related hyperprolactinemia on BMD. By contrast, no review has specifically focused on the relationship between BMD and schizophrenia since 2007 [12].

METHODS

In this study, we will review first the definition, measurement, risk factors, and causes of osteoporosis. We will then examine the recent evidence regarding BMD and fracture risk in schizophrenia and examine the impact of antipsychotics on bone metabolism. To this end, we conducted a systematic review, searching PubMed from its inception until April 2012, using the following key words and their synonyms: ‘schizophrenia’, ‘bone’, ‘osteoporosis’, and ‘fracture’. Finally, focusing on the most recent and qualitatively best evidence, we will make recommendations for the clinical evaluation and management of osteoporosis in patients with schizophrenia.

RESULTS

In the sections below, we summarize the definition and measurement of osteoporosis as well as its risk factors and causes. In addition, we review the studies that have investigated the association of BMD or fracture risk with schizophrenia, antipsychotic treatment, and prolactin levels.

OSTEOPOROSIS DEFINITION AND MEASUREMENT

Osteoporosis is defined as 'a systemic skeletal disease characterized by low bone density and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture' [13]. Osteoporosis is often described as a 'silent disease', meaning that it commonly is not characterized by overt symptoms, despite being a strong predictor of fractures. Osteoporosis can lead to spinal fractures, hip fractures, and other potentially life-threatening complications [14]. It can impair activities of daily life and is also associated with increased mortality [15].

The standard method for assessing BMD is dual-energy X-ray absorptiometry (DEXA) [16]. BMD (g/cm^2) is usually expressed as a population standard based *t*-score and a *z*-score according to the following formula:

1. *t*-score = (BMD of the patient − young adult mean BMD)/standard deviation of the BMD of a young adult;
2. *z*-score = (BMD of the patient − mean BMD of the age and sex-matched group)/ standard deviation of the BMD of an age and sex-matched group.

On the basis of this convention, the *t*-score is used for assessing the patients' bone density compared with standardized peak bone mass and for making a diagnosis of osteoporosis, whereas the *z*-score is used when comparing the patient with an age and sex-matched general population. According to the WHO definition, a *t*-score of less than −1 to greater than −2.5 is categorized as osteopenia, and a *t*-score of −2.5 or less is categorized as osteoporosis [13]. There are also several nonstandard methods to measure BMD. These include single-energy X-ray absorptiometry (SXA), peripheral dual-energy X-ray absorptiometry (pDXA), dual-photon absorptiometry (DPA), quantitative computed tomography (QCT), and quantitative ultrasound (QUS). QUS is widely used because of the low cost and lack of ionizing radiation. Different from other methods using X-ray, QUS measures broadband ultrasound attenuation (BUA), speed of sound (SOS), and so on, but often results are converted into *t*-scores or *z*-scores [17].

Bone is a dynamic tissue. Throughout life, bone tissue is continually being formed and resorbed. This process is called remodeling, which is under the control of many factors, including sex hormones. In postmenopausal type I osteoporosis, the decline of estrogen levels in women leads to the acceleration of BMD loss, which results from loss of estrogen's bone protective effects [18]. Thus, stable BMD depends on the balance of bone resorption and formation. A number of sensitive and valid bone turnover markers (BTMs) are available that can help measure a patient's bone resorption and bone formation status, and some of them are utilized in clinical practice (Table 1) [16,19,20■].

RISK FACTORS FOR AND CAUSES OF OSTEOPOROSIS

Since bone mineralization, formation, and resorption are under the control of multiple physiological processes, many conditions, medications, and lifestyle behaviors have been associated with decreased BMD. Common medical conditions include hypogonadism, hyperthyroidism, hyperparathyroidism, chronic renal failure, and hypercortisolemia. The list of medications that can decrease BMD include corticosteroids, anticoagulants, thyroid hormones, and methotrexate. Poor nutrition, lack of exercise, smoking, excessive use of alcohol or caffeine, insufficient sun exposure, low calcium intake, and low vitamin D or vitamin K levels are among the most important lifestyle factors that contribute to bone demineralization (Table 2) [18,21-30].

BONE MINERAL DENSITY IN SCHIZOPHRENIA

For quite some time after Baastrup *et al.* [6] in 1980 reported decreased BMD in schizophrenia, only little attention was paid to this phenomenon. However, after the introduction of second-generation antipsychotics, which generally affect prolactin levels less than high potency first-generation antipsychotics, more studies focused on this topic. Across 16 studies comparing BMD in schizophrenia patients and healthy controls, 11 used a control group (patients = 1967, controls = 8127, mean age 51.3 years, 49.8% men) and five used reference data as a comparator (patients = 452, mean age 48.0 years, 47.3% men) (Table 3) [6,7,31■,32-44]. Nine studies used DEXA to assess BMD, and five studies used QUS. Among 11 studies using a control group, 10 (90.9%) found lower BMD in schizophrenia compared with healthy controls in at least one region or at least one patient subgroup. All five studies using reference data found lower BMD in schizophrenia. The magnitude of the differences varied. Some studies reported lower BMD in only one or few of many other measures; some reported that lower BMD was found in most measures.

Four studies also utilized BTMs to assess the bone metabolism status in patients, each finding significant differences from healthy controls, or abnormality, including the one study [33] which did not find significant BMD differences, probably due to the small sample.

FRACTURE RISK IN SCHIZOPHRENIA

Only few studies ($N = 4$) have focused on fracture risk in schizophrenia. In a Canadian population-based, administrative database, persons with osteoporotic fractures ($n = 15\,792$) were compared with controls matched for age, sex, ethnicity, and comorbidity ($n = 47\,289$) [45]. Whereas antipsychotics did not significantly increase the risk of osteoporotic fractures, schizophrenia diagnosis did [odds ratio (OR) 2.17, 95% confidence interval (CI) 1.75–2.69]. Somewhat opposing results were obtained in a case–control study using the General Practice Research Database in the UK, which compared 16 341 hip fracture cases with 29 889 matched controls [46]. In this study, hip fracture was associated with schizophrenia (OR 1.73; 95% CI 1.32–2.28), as well as with mostly prolactin-raising first-generation antipsychotics (OR 2.6; 95% CI 2.43–2.78). However, in a multivariate analysis, prolactin-raising antipsychotics were independently associated with hip fracture, whereas this was not the case for schizophrenia. In a Danish case–control study (fracture cases = 373 124 655, controls = 962), focusing on the use of psychotropic medications, antipsychotic use was associated with a small but significant increase in overall fracture risk (OR around 1.2) [47]. Similarly, another case-control study from the UK ($n = 44\,500$) found that both current and prior antipsychotic use and duration of antipsychotic use were associated with a small significant increase (OR 1.3, 1.3, $r^2 = 0.88$, respectively) of hip/femur fractures after adjustment for possible confounders [48].

Taken together, these results seem to suggest that antipsychotics contribute to a small increase in the risk of fractures. However, results are restricted to database and case–control studies, whereas more definitive, prospective, long-term studies that directly assess relevant confounding variables are missing.

LIFESTYLE AND LOW BONE MINERAL DENSITY IN SCHIZOPHRENIA

Since poor lifestyle behaviors can lower BMD (Table 2), the greater prevalence and intensity of sedentary lifestyle, staying indoors, and poor diet in schizophrenia [3■], which can be related to negative symptoms and poor functioning, may predispose patients to low BMD and fracture risk. In fact, a recent review demonstrated low levels of physical activity in schizophrenia patients and a significant relationship with negative symptoms [49].

Smoking is an established risk factor for osteoporosis and osteoporotic fracture [50]. A metaanalysis, including 42 studies across 20 nations, confirmed high smoking rates in schizophrenia, finding a weighted average OR for current smoking of 5.9 (95% CI 4.9–5.7) [51]. Mechanisms include alterations in calciotropic hormone metabolism, intestinal calcium absorption, sex hormone regulation, adrenal cortical hormone metabolism, and the various receptor activators [52].

Excessive alcohol intake is common in schizophrenia. Lifetime alcohol abuse is found in 14.5% of schizophrenia patients, with a rate for alcohol dependence of 14.2% [53]. Alcohol's negative impact on BMD results from direct or indirect adverse effects on bone-forming cells, calcium-regulating hormones, and growth factors [54]. Malnutrition or inappropriate amounts or composition of food intake is also found in schizophrenia. In a study of 25 schizophrenia patients, 25(OH)vitamin D levels were significantly lower than in healthy controls (23.6 ± 2.8 vs. 71.9 ± 8.3; $P = 0.001$) [33]. In an Austrian study, 25-hydroxy-vitamin D3 deficiency was found in as many as 50.9% of men and in 52.9% of women with schizophrenia [43]. Vitamin D deficiency reflects both lack of vitamin D intake and/or synthesis, being related to poor diet or insufficient sun exposure. Moreover, polydipsia, which is sometimes observed in schizophrenia, can also lead to low BMD, presumably through excessive urinary calcium loss [55].

An individual's peak bone mass is typically achieved by age 30, and thereafter BMD decreases. Therefore, it is crucial to achieve high peak bone mass through appropriate exercise and nutrition during adolescence and young adulthood. However, unhealthy lifestyle behaviors can already occur in younger patients. Decreased BMD, measured via QUS in 133 women with schizophrenia, was prominent not only in older but also in younger patients (20–24 and 25–29 years old) with shorter illness and antipsychotic medication exposure [44].

ANTIPSYCHOTIC-INDUCED HYPERPROLACTINEMIA AND BONE METABOLISM

Antipsychotics can inhibit the hypothalamopituitary-gonadal axis and this is partly responsible for low BMD in schizophrenia. Elevated serum prolactin can suppress secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus. In turn, low GnRH results in a reduced secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary gland, reducing levels of estradiol, progesterone, and testosterone, leading to abnormal bone metabolism similar to type I osteoporosis [11,41,56].

The hypothesis that antipsychotic-induced hyperprolactinemia lowers BMD is derived from early observations and has been consistently replicated in patients with usually severe hyperprolactinemia due to medical reasons, such as prolactin-secreting pituitary tumors, which were associated with low testosterone levels and/or significant BMD reductions [57-59]. Moreover, bone loss was also related to the duration of the hyperprolactinemia [57]. Therefore, it is reasonable to assume that antipsychotic-induced hyperprolactinemia can have the same effect, at least, when reaching a certain physiological threshold that induces hypogonadism. Animal studies support the negative effect of antipsychotics on bone density and formation. A note of caution is required, because this mechanism is not consistent with the hypothesis mentioned above [60,61], antipsychotic half-lives are much shorter in rodents, and rodent prolactin physiology also differs from humans.

Results from human studies (Table 4 [38,40-43,56,62■,63-70]) have been inconsistent, possibly due to methodological limitations, the predominantly cross-sectional study design, and small sample sizes. Across 15 studies we identified examining prolactin effect on bone,

13 were cross-sectional (n = 1062, mean age 54.2 years, 43.5% men) and only two were prospective (n = 52, mean age 36.3 years, 0% men) (Table 4). The 13 cross-sectional studies examined the effect of hyperprolactinemia on bone by correlating BMD or BTM levels with prolactin values, comparing groups with higher vs. lower serum prolactin, high vs. normal prolactin groups, or longer exposure vs. shorter exposure to prolactin-raising antipsychotics; investigating the correlation between prolactin levels and BMD; or comparing prolactin levels between low vs. normal-BMD patient groups. Overall, 8/13 (61.5%) studies found some relationship between hyperprolactinemia and low BMD. Whereas these data seem to point in one direction, the results are less convincing because, even among studies reporting significant associations, this was frequently only one finding among several negative results. These cross-sectional studies contain considerable limitations for a conclusive examination of the prolactin effect on BMD since it may take years for BMD loss to manifest after disruption of normal bone metabolism.

Recent studies have examined the long-term effects of excessive prolactin secretion. For example, Kishimoto *et al.* [41] found a significant negative correlation between the duration of anti-psychotic treatment and the z-score in hyperprolactinemic patients ($r^2 = 0.07$, $P < 0.05$). On the contrary, Hummer *et al.* [43] also found a trend-level negative correlation between duration of treatment and z-score ($r^2 = 0.06$, $P < 0.08$) in male patients, but this finding was mainly due to one extreme outlier with a long duration of treatment, and the statistical trend disappeared after excluding this patient.

Given the difficulties of directly assessing the effect of prolactin on BMD, utilization of BTMs that predict future bone density loss and fractures [16] and that may be more sensitive markers of shortterm bone metabolism disruption is a reasonable alternative strategy. Across four cross-sectional studies (n = 521), only one showed an association between prolactin/prolactin-raising antipsychotics and BTM. However, in two small prospective studies (n = 52, mean age 36.3, 0% men), both found a significant negative prolactin effect on BTM after just 1 year.

RECOMMENDATIONS FOR THE MEASUREMENT, PREVENTION, AND TREATMENT OF OSTEOPOROSIS

Low BMD is prevalent in schizophrenia patients. Prevention, early detection, and intervention are required. Proper diet, exercise, and sufficient sun exposure should be encouraged in all patients. Given uncertain prolactin effects on bone metabolism, no specific recommendation can be made at this point. However, other prolactin-related side effects, such as sexual dysfunction, reproductive system dysfunction, a questionable risk increase of breast cancer, and so on [71], should be screened for, and hyperprolactinemia that leads to physical symptoms should be corrected via use of or switch to prolactin-sparing antipsychotics including olanzapine and, especially, quetiapine, clozapine, and aripiprazole [71,72]. Aripiprazole is known to decrease prolactin levels, even in combination with prolactin-raising antipsychotics [73,74]. Finally, standard therapy for osteoporosis, such as bisphosphonates and selective estrogen receptor modulators [24,75,76■], should be considered for patients with osteoporosis.

CONCLUSION

Osteoporotic fractures have considerable adverse effects on general health, subjective well being, the ability to engage in healthy lifestyle behaviors, and increased healthcare costs. A higher prevalence of osteoporosis or lower BMD is widely reported in schizophrenia, and needs to be recognized as an important comorbidity. Prevention, early detection, and intervention are required. Although the effect of antipsychotic-induced hyperprolactinemia

seems be one contributing factor for low BMD, others, especially those related to poor lifestyle behaviors, may have an even bigger impact. Moreover, since osteoporosis develops over time, sufficiently large, longitudinal studies are required to examine contributors of accelerated BMD loss. To date, there is only limited evidence for the osteoporosis-producing effects of antipsychotics. Better designed studies, including studies utilizing BTM, may further clarify the relationship between antipsychotics and bone metabolism. Until such data are available, the main clinical focus should be on promoting healthy diet and exercise as well as adequate sun exposure. However, if hyperprolactinemia develops, hypogonadism needs to be ruled out via assessment of menses or sex hormone levels, or a change of antipsychotic treatment to a less prolactin-elevating agent should be considered, especially when sexual and/or reproductive system dysfunction is present.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 442).

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KEY POINTS

- A higher prevalence of osteoporosis compared with the general population is reported in patients with schizophrenia.
- Unhealthy lifestyle behaviors, such as little or no exercise, alcoholism, smoking, undernutrition, and unhealthy diet with deficiencies of calcium and vitamin D contribute to low bone mineral density and elevated fracture risk in schizophrenia.
- Antipsychotic-induced hyperprolactinemia has been suggested as one of the mechanisms of low bone mineral density in schizophrenia, but the results are mixed and firm conclusions cannot be drawn at this point.
- In order to better examine the relationship between antipsychotics and low bone mineral density, well designed, longitudinal studies are needed, and measurement of bone turnover markers may be helpful.
- Until the relationship between hyperprolactinemia and osteoporosis has been better clarified, the main clinical focus should be on prevention and early intervention through promoting healthy diet, exercise, and adequate sun exposure, although hypogonadism associated with hyperprolactinemia should prompt actions to reduce serum prolactin.

Table 1

Bone turnover markers [16,19,20□]

Bone formation markers	Bone resorption markers
Osteocalcin (OC)	Deoxypyridinoline (DPD)
Bone alkaline phosphatase (BALP)	Amino-terminal cross-linking telopeptide of type I collagen (NTX)
Carboxy-terminal propeptide of type I procollagen (PICP)	Carboxy-terminal cross-linking telopeptide of type I collagen (CTX)
	Pyridinoline (PYD)
Amino-terminal propeptide of type I collagen (PINP)	Tartrate-resistant acid phosphatase (TRACP)

Table 2

Risk factors for osteoporosis [18,21–30]

Genetic factors	**Age (>50), family history of osteoporosis, sex (female), white race**
Physical factors	Low BMI, slight body build
Lifestyle	Excessive use of alcohol, excessive consumption of caffeine, sedentary lifestyle (no or little exercise), inadequate diet (calcium deficiency, excessive salt consumption, vitamin D deficiency, vitamin K deficiency), smoking, too little sun exposure
Endocrine conditions	Diabetes mellitus, hypercortisolemia (e.g. Cushing's disease), hyperparathyroidism, hyperprolactinemia, hyperthyroidism, hypogonadism
Ovarian disorder/condition	Amenorrhea, early menopause, late menarche, ovariectomy
Gastrointestinal conditions	Gastrectomy, inflammatory intestinal disease, malabsorption syndrome
Connective tissue diseases	Ehlers-Danlos syndrome, Marfan's syndrome, osteogenesis imperfecta, rheumatoid arthritis
Bone marrow diseases	Anemia, leukemia, lymphoma, plasma cell dyscrasia, systemic mastocytosis
Miscellaneous diseases	Anorexia nervosa or bulimia nervosa, cadmium poisoning, chronic neurological disease, malignant tumor, renal failure
Medications	Anticoagulants, antiepileptics, aromatase inhibitors, corticosteroids (prednisone and prednisone-like substances), gonadotropin-releasing (GnRH) analogs, high-dose heparin, immunosuppressants (calmodulin/calcineurin phosphatase inhibitors), methotrexate, proton pump inhibitors, thyroid hormones

Table 3

Bone mineral density/bone turnover marker in schizophrenia compared with healthy control (reference data after 2005)

Study	Country	Patient inclusion criteria	Patient (*n*)	Healthy control	Control (*n*)	Mean age	Male %	BMD measurement	Results
Study using control group: *N*=11									
Sugawara *et al.*, 2012 [31■]	Japan	Diagnosed as SCZ or SCZAD at 3 psychiatric hospitals in northern Japanese region	362	Healthy population from same region	832	54.7	42.3	QUS	Male OSI
									20–49 yo: SCZ=HC
									≥50 yo: HC>SCZ (*P*<0.05)
									Female OSI
									20–59 yo: SCZ=HC
									≥60 yo: HC>SCZ (P<0.05)
Jung *et al.*, 2011 [32]	South Korea	Inpatients with schizophrenia aged ≥50 yo	229	No medical and psychiatric illness aged ≥50 yo	125	58.6	43.2	DEXA	Osteoporosis prevalence: SCZ>HC (*P*=0.0043)
									FN: HC>SCZ (*P*<0.005)
									FW: HC>SCZ (*P*<0.05)
									Trochanter: HC>SCZ (*P*<0.005)
Doknic *et al.*, 2011 [33]	Serbia	Stable outpatients in real-life conditions without psychiatric comorbidity	26	Sex, age, BMI, and education matched	35	31.8	37.8	DEXA	LS: SCZ=HC
									FN: SCZ=HC
									OC: SCZ=HC
									CTX: SCZ>HC (*P*=0.023)
Partti *et al.*, 2010 [34]	Finland	Population-based sample with primary psychotic disorder	48	Population-based sample	6241	52.0	50.0	QUS	BUA: population sample >SCZ (P<0.001)
									SoS: population sample >SCZ (*P*<0.001)
Renn *et al.*, 2009 [35]	Taiwan	Chronic schizophrenia aged ≥20 yo	965	Community population living in the same district aged ≥20 yo	405	50.2	59	QUS	BUA: HC>SCZ (*P*<0.01)

Study	Country	Patient inclusion criteria	Patient (*n*)	Healthy control	Control (*n*)	Mean age	Male %	BMD measurement	Results
Rey-Sánchez *et al.*, 2009 [36]	Spain	Under treatment on antipsychotics ≥5 years	73	Age, weight, height, and gonadal status matched	73	61.0	66	QUS	Female
									SoS: HC>SCZ (P<0.05)
									TRAP: SCZ>HC (P<0.0001)
									Male
									SoS: SCZ>HC (P<0.05)
									TRAP: SCZ=HC
Bergemann *et al.*, 2008 [37]	Germany	Premenopausal female schizophrenia (59 received BMD measurement)	72	Age, sex-matched healthy control	71	33.8	0	DEXA	FN: SCZ=HC
									LS: SCZ=HC
									PYD: SCZ>HC (P<0.001)
									DPD: SCZ>HC (P=0.001)
									OC: SCZ>HC (P<0.001)
Jung *et al.*, 2006 [38]	South Korea	Inpatient who had taken haloperidol monotherapy for ≥2 years	51	Similar age	57	39.0	59.2	DEXA	LS: HC>SCZ (P<0.05)
									FN: HC>SCZ (P<0.005)
									FW: HC>SCZ (P<0.005)
									Trochanter: HC>SCZ (P<0.005)
Bilici *et al.*, 2002 [39]	Turkey	Patients on classical or atypical antipsychotics for average of 14 months	75	No significant difference in age and sex	20	29.9	50.1	DEXA	L1: HC=atypical >classical
									L2: HC=atypical >classical
									L3: HC=atypical >classical
									L4: HC=atypical >classical
Keely *et al.*,	Canada	Male patients who had taken	16	Age, sex matched	16	41.0	100	DEXA	LS: HC>SCZ

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Study	Country	Patient inclusion criteria	Patient (*n*)	Healthy control	Control (*n*)	Mean age	Male %	BMD measurement	Results
1997 [40]		neuroleptic medication for 1–30 years							
									Trochanter: HC>SCZ
									Ward's triangle: HC>SCZ
									FN: SCA=HC
Baastrup *et al.*, 1980 [6]	Denmark	Patients treated with antipsychotics, whose serum creatinine is ≤13mg/l	50	People with a normal creatinine value, and having no digestive or renal diseases	252	39.8	52.0	Photon-absorptio-metry	BMC: HC>SCZ (86% of normal value; $P<0.001$)
Subtotal *N*=11			1967		8127	51.3	49.8		BMD lower in SCZ at least in one region, or in one subgroup: positive=10/11
									BTM abnormality in SCZ at least in one marker, or in one subgroup: positive=3/3
Studies using *reference* data: *N*=5									
Kishimoto *et al.*, 2008 [41]	Japan	Male inpatients with schizophrenia	74	Age, sex-matched reference data	NA	58.9	100	DEXA	BMD:
									30–39 yo: SCZ=HC
									40–49 yo: HC >SCZ ($P<0.05$)
									50–54 yo: SCZ=HC
									50–79 yo: HC >SCZ ($P<0.05$)
Howes *et al.*, 2005 [42]	UK	Consecutive outpatient clinic attendees	102	Reference value of the same age, sex, and ethnicity	NA	46.0	47	DEXA	Female
									LS, FN, hip: SCZ=HC
									OC, DPD: normal range
									Male
									LS: HC>SCZ in black men

Study	Country	Patient inclusion criteria	Patient (*n*)	Healthy control	Control (*n*)	Mean age	Male %	BMD measurement	Results
									FN, hip: SCZ=HC
									OC: exceeded upper limit
									DPD: normal range
Hummer *et al.*, 2005 [43]	Austria	In and outpatients with SCZ treated with antipsychotics ≥1 year	75	Age, sex-matched reference data	NA	34.8	76.0	DEXA	Male BMD: HC >SCZ (P<0.001)
									Female BMD: SCZ=HC
Kishimoto *et al.*, 2005 [44]	Japan	Inpatients with SCZ or SCZAD	133	Age, sex-matched reference data	NA	55.4	0	QUS	Stiffness:
									20–24, 35–44, >55 yo: HC>SCZ (P<0.01)
									25–29, 50–54 yo: HC>SCZ (P<0.05)
									30–34, 45–49 yo: HC=SCZ
Halbreich *et al.*, 1995 [7]	USA	Acutely ill psychiatric patients admitted to psychiatric ward	68 (40 SCZ or SCZAD, 28 with other Dx)	National standard reference data (which was found to be equivalent to local healthy people)	NA	39.4	51.5	DPA	Male
									LS: HC>SCZ (P=0.0001)
									FN: HC>SCZ (P<0.0001)
									Female
									LS: HC>SCZ (P<0.0001)
									FN: SCZ=HC
Subtotal N=5			452		NA	48.0	47.3		BMD lower in SCZ at least in one region, or in one subgroup: positive=5/5
									BTM abnormality in SCZ at least in one marker, or in one subgroup: positive=1/1
ITotal N=16			Patient total n=2419		Control total n=8127	51.2	49.7		BMD lower in SCZ at least in one region, or in one subgroup:

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Study	Country	Patient inclusion criteria	Patient (*n*)	Healthy control	Control (*n*)	Mean age	Male %	BMD measurement	Results
									positive=15/16
									BTM abnormality in SCZ at least in one marker, or in one subgroup: positive=4/4

BMC, bone mineral content; BMD, bone mineral density; BTM, bone turnover marker; BUA, broadband ultrasound attenuation; DPA, dual-photon absorptiometry; Dx, diagnosis; FN, femoral neck; FW, femoral Ward's triangle; LS, lumbar spine; NA, not applicable; OSI, osteosono-assessment index; PYD, pyridinoline; SCZ, schizophrenia; SCZAD, schizoaffective disorder; SoS, speed of sound; yo, years old.

Table 4

Studies investigating antipsychotic/prolactin effects on bone density/turnover in patients with schizophrenia

Study	Patient (*n*)	Sex (% male)	Mean age	Antipsychotics	Study design	BMD measurement	Comparison btw./ group definition	PRL levels	BMD comparison	BTM comparison
Cross-sectional studies using comparison group: *N*=9										
Lin *et al.*, 2011 [62■]	48	0	41.8	CLO, CPZ, HAL, RIS, PALI, sulpiride	Demographically and clinically matched SCZ on CLO vs. PRL-raising AP were compared.	DEXA	CLO vs. PRL-raising	PRL-raising>CLO (109.0±65.6 vs. 19.2±10.0 ng/ml)	Rate of patients with *t*<−1: PRL-raising >CLO (45.8 vs. 16.7%)	AP: PRL-raising= CLO
								HyperPRL (>25 ng/ml): PRL-raising>CLO (95.8 vs. 20.8%)		
Lee *et al.*, 2010 [63]	45	100	49.5	RIS, OLA, CLO	BMD, PRL, hormones measured and compared between medications.	DEXA	RIS vs. OLA, CLO	RIS>OLA, CLO (33.3±17.1, 21.8±17.6, 10.5±9.4)	*z*: RIS=OLA=CLO	CTX: RIS=OLA= CLO
									z: association between negative symptoms and *z* (P<0.05)	
Kishimoto *et al.*, 2008 [41]	74	100	58.9	Mixed	BMD, PRL, sex hormones, 1,25-dihydroxy-vitamin D3 and number of steps were measured.	DEXA	High PRL vs. normal PRL (high PRL defined as >12.78ng/ml)	High PRL > normal PRL (30.7±13.5 vs. 8.7±2.9 ng/ml; P<0.01)	*z* score: high-PRL= normal-PRL	NR
									Association between duration of illness and *z*, duration of treatment and *z* in high PRL group (r^2=0.07, P<0.05)	
Jung *et al.*, 2006 [38]	51[a]	59.3	39.0	HAL	Low BMD group and normal BMD group were compared.	DEXA	SCZ with BMD loss (*t*<−1.0) vs. normal BMD (*t*≥−1.0)	Female: low t>normal *t* (72.5±49.7 vs. 42.1± 31.2 ng/ml; P=0.043)	[female BMD: HC>SCZ]	NR
								Male: low *t*=normal *t*	[male BMD: SCZ=HC]	
O'Keane and Meaney, 2005 [64]	38	0	31.8	PRL-raising, OLA	BMD, PRL, Sex hormones were compared between PRLraising vs. OLZ.	DEXA	PRL-raising vs. OLA	PRL-raising>OLA (1692±1109 vs. 446±333IU/l; P<0.001)	Rate of patients with *t*<−1: PRL-raising >OLA (P<0.001)	NR
								Association between PRL and E2, testosterone, FTI, FSH (P<0.05 for all values)	Association between PRL and lumbar BMD (P=0.003), SHBG and hip BMD, lumbar BMD (P=0.01, P=0.01)	
Howes *et al.*, 2005 [42]	102	53	46	FGA, SGA	BMD, PRL, BTM were measured.	DEXA	PRL-raising vs. PRL-sparing	PRL-raising>PRL-sparing (802±1092 vs. 565±688mIU/l)	*z*: PRL-raising= PRL-sparing	NR
Hummer *et al.*, 2005 [43]	75	76	34.8	PRL-increasing, others, combination	BMD, PRL, 25-hydroxyvitamin D3 and sex hormones were measured.	DEXA	Pts on PRL-raising <6 months vs. pts on PRL-raising ≥6 months	Female: 44% were higher than normal range	*z*: PRL-raising <6 months= PRL-raising	NR

Study	Patient (*n*)	Sex (% male)	Mean age	Antipsychotics	Study design	BMD measurement	Comparison btw./ group definition	PRL levels	BMD comparison	BTM comparison
									≥6 months	
								Male: 22.9% were higher than normal range	Association between *z* and negative symptoms (r^2=0.08, *P*<0.03), *z* and PANSS (r^2=0.10, *P*<0.02), *z* and BMI (male: r^2=0.35, *P*<0.01; female: ^{r2}=0.32, P<0.05)	
Meaney *et al.*, 2004 [65]	55	55	50.6	FGA, SGA, combination	BMD, PRL, sex hormones were measured.	DEXA	High dose vs. low dose (high dose defined as >300mg CPZ equivalent)	High dose>low dose (81% vs. 45%; prevalence of hyperPRL; P<0.01)	Rate of patients with *t*<−1: high dose>low dose (*P*=0.01)	NR
									Association between FTI and *z* (r^2=0.25, *P*=0.01), antipsychotic dose and *z* (r^2=0.25, *P*=0.01)	
Becker *et al.*, 2003 [66]	26	0	38	RIS, OLA	BMD, SoS, BTM, PRL and sex hormones were compared between RIS vs. OLA.	DEXA and QUS	RIS vs. OLA	RIS>OLZ (123±144 vs. 25.9±25.7 ng/ml; *P*<0.05)	*z* (DEXA): RIS=OLA	DPD: RIS=OLA
									z (SoS): OLA>RIS (*P*<0.05)	
Subtotal *N*=9	514	56.5	44.5					Higher PRL in lower BMD group: positive 1/1	PRL effect on BMD: positive 5/8	PRL effect on BTM: positive 0/3
Cross-sectional studies with no comparison group: *N*=4										
Sugawara *et al.*, 2011 [67]	114	43.0	42.6	Mixed	BMD, PRL, sex hormones were measured.	QUS	NA	Male mean: 27.8± 25.4 ng/ml	No correlation between PRL and OSI	NR
								Female mean: 51.4± 45.2ng/ml		
Liu-Seifert *et al.*, 2004 [68]	402	NR	NR	PRL-raising FGA, RIS	BMD, PRL, OC were measured.	QUS	NA	Measured but not reported	Association between low t and elevated PRL in males	Association between elevated OC and PRL in females (*P*=0.03) and males (*P*=0.05)
Abraham *et al.*, 2003 [69]	16	69	43	FGA, RIS, CLO	BMD, PRL, sex hormones were measured	DEXA	NA	Mean: 39.9 ng/ml	Negative association between PRL and BMD (femoral neck: *P*<0.01, trochanter: *P*<0.01, Ward's triangle: *P*<0.05)	NR
Keely *et al.*, 1997 [40]	16a	100	41.3	FGA	BMD, PRL, sex hormones were measured	DEXA	NA	Mean: 8.9±1.5μg/l	No correlation between PRL and BMD, or FTI	NR
Subtotal *N*=4	548	52.1	42.5						PRL effect on BMD:	PRL effect on BTM:

Study	Patient (*n*)	Sex (% male)	Mean age	Antipsychotics	Study design	BMD measurement	Comparison btw./ group definition	PRL levels	BMD comparison	BTM comparison
									positive 2/4	positive 1/1
Longitudinal studies: *N*=2										
Abraham *et al*., 2003 [70]	14	0	36.3	RIS, OLZ	1-yr follow up. BMD, BTM were followed and compared by higher and lower PRL group.	DEXA	High-PRL vs. low-PRL (median split)	High-PRL>low-PRL (88.8±34.7 vs. 21.1±15.7ng/ml)	*z* change: high-PRL= low-PRL	OC: high-PRL ↑; low-PRL ↓ (group-by-time interaction: P<0.003) NTX: high-PRL ↑; low-PRL ↓ (groupby-time interaction: *P*<0.01)
Meaney and O'Keane, 2007 [56]	38	0	NR	FGA or SGA monotherapy	1-yr follow-up. Interventions to improve BMD were done. BMD, BTM, PRL, hormones were compared by PRLraising vs. PRL-sparing group.	DEXA	PRL-raising vs. PRL-sparing	PRL-raising>PRL-sparing (1636 IU/l vs. 377 IU/l, P<0.001)	*z* increase in nonintervention group: PRL-sparing>PRL-raising (*P*=0.017)	AP: PRL-sparing ↑ (*P*=0.05), PRL-raising →
									z increase in intervention group: PRL-raising= PRL-sparing	DPD: PRL-sparing →; PRL-raising →
Subtotal *N*=2	52	0	36.3						PRL effect on BMD: positive 1/2	PRL effect on BTM: positive 2/2
Total *N*=15	1114	51.5	43.9					Higher PRL in lower BMD group: positive 1/1	PRL effect on BMD: positive 8/14	PRL effect on BTM: positive 3/6

↑, increase; ↓, decrease; →, no change; AP, alkaline phosphatase; BMD, bone mineral density; BTM, bone turnover marker; BUA, broad ultrasound attenuation; CLO, clozapine; CPZ, chlorpromazine; CTX, cross-linked C-terminal telopeptide of type I collagen; DEXA, dual-energy X-ray absorptiometry; DPD, deoxypyridinoline; FGA, first-generation antipsychotics; FTI, free testosterone index; HAL, haloperidol; HC, healthy control; NA, not applicable; NR, none reported; NTX, urinary N-telopeptide; OC, osteocalcin; OLA, olanzapine; PALI, paliperidone; PRL, prolactin; PYD, pyridinoline; QUS, quantitative ultrasound; RIS, risperidone; SCZ, patients with schizophrenia; SGA, second-generation antipsychotics; SHBG, sex hormone-binding globulin; SoS, speed of sound; *t*, *t*-score; *z*, *z*-score.

[a]Subpopulation was extracted.