Serum Prolactin and Bone Mineral Density in Schizophrenia: A Systematic Review

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The relationship between serum prolactin and bone mineral density (BMD) in schizophrenia is unclear. We conducted a literature review of databases from inception until December 2018 for cross-sectional, case-control, prospective and retrospective studies analyzing correlations between serum prolactin and BMD measured using dual energy X-ray absorptiometry or quantitative ultrasound at any skeletal site in people with schizophrenia. Data was summarized with a best evidence synthesis. This review identified 15 studies (1 longitudinal study, 10 cross-sectional and 4 case-control studies; 1,360 individuals with a psychotic disorder; mean age 45.1 ± 9.4 [standard deviation] years, female 742 [54.6%], mean illness duration 17.7 ± 11.3 years) assessing the relationship between serum prolactin and BMD in schizophrenia. There was a statistically significant inverse correlation between serum prolactin and BMD identified in eight of the studies (53% of all studies), suggesting mixed evidence for an association between serum prolactin and BMD. Of those studies which identified a significant inverse correlation between serum prolactin and BMD (n = 5), 152 (52.1%) of patients were treated with prolactin raising antipsychotics, compared to 197 (48.1%) of patients in those studies which did not identify a significant correlation between prolactin and BMD. Available studies cannot resolve the link between excess prolactin and reduced BMD in schizophrenia. Future studies should be longitudinal in design and combine measures of serum prolactin along with other risk factors for reduced BMD such as smoking and vitamin D and sex hormone levels in assessing the relationship between prolactin and BMD in schizophrenia.

KEY WORDS: Psychotic disorders; Hyperprolactinemia; Hormones; Fracture; Bone density.

INTRODUCTION

Osteoporosis is a progressive disease characterised by a marked bone loss, disruption in the microstructure of bone tissue, and deterioration of the skeletal structure.[1] Worldwide, 200 million people are estimated to have osteoporosis.[2] Osteoporosis and low bone mineral density (BMD) are associated with an increased fracture risk.[1] The fragility factors resulting from reduced BMD and osteoporosis significantly impair quality of life and are associated with increased morbidity and mortality.[3]

People with schizophrenia are two and a half times more likely to have osteoporosis[4] and have a 70% increased fracture risk compared to healthy general population controls.[5] However, risk factors for osteoporosis and fractures in psychotic disorders are not well defined. In a meta-analysis of BMD in established psychosis, hyperprolactinemia (β = −0.0102; 95% confidence interval [CI], −0.0135 to −0.0068; $p < 0.0001$) and smoking (β = −0.0099; 95% CI, −0.0185 to −0.0012; $p = 0.02$) were significant moderators of low bone mass at the lumbar spine.[6] Whilst this meta-analysis was helpful, we restricted our inclusion criteria to those studies which provided BMD measures at the lumbar spine or hip region. In doing so, there are several studies evaluating the effects of prolactin on BMD in psychotic disorders, which were excluded.

High rates of hyperprolactinaemia are found in the early stages of psychotic disorders; with 43% with hyperprolactinaemia at time of first contact for psychosis, and 27% at 12 months follow up.[7] Prevalence rates for hyperprolactinaemia with antipsychotic use in multi episode schizophrenia across various clinical trials range from 28% to 69%.[8] Epidemiological studies have reported conflicting effects of hyperprolactinaemia on fracture risk in schizophrenia, with some reporting an increased risk with prolactin raising (PRL-R) antipsychotics compared to prolactin spearing (PRL-S),[9,10] while others have not identified a differentiating effect by PRL-R or PRL-S antipsychotics on the fracture risk.[11-13] A Norwegian population nationwide population cohort study over a six-year period, identified 39,938 people who experienced a hip fracture. This study found that an increased risk of hip fracture was associated with any antipsychotic exposure (standardized incidence ratio [SIR] = 2.1; 95% CI, 1.9−2.1), first-generation antipsychotics (FGAs; SIR = 2.0; 95% CI, 1.8−2.2), second-generation antipsychotics (SGAs; SIR = 2.2; 95% CI, 1.9−2.4), prolactin-sparing antipsychotics (SIR = 2.4; 95% CI, 1.8−3.1) and prolactin-elevating antipsychotics (SIR = 2.0; 95% CI, 1.9−2.2).[14]

A previous narrative review indicated that associations between antipsychotic induced prolactin and reduced BMD in schizophrenia remains inconclusive, though with some evidence to support a stronger association in older men and postmenopausal women.[15] In a meta-analysis of 7 studies[16-22] by Tseng *et al.*,[23] 304 people with schizophrenia in receipt of PRL-R antipsychotics, and 212 treated with PRL-S antipsychotics were identified.[23] The BMD in those treated with PRL-R antipsychotics was significantly lower than in those receiving PRL-S (effect size = −0.410, 95% CI¼, −0.703 to −0.117, *p* = 0.006). However, in meta-regression analysis, serum prolactin levels were not a moderator of reduced BMD (*p* = 0.456; though only 5 studies with serum prolactin measures were included).

To clarify the relationship between serum prolactin levels and BMD in schizophrenia we performed a systematic review of studies examining for correlations between serum prolactin and BMD in psychotic disorders. A previous review provided data on the proportion of studies reporting associations between prolactin, hyperprolactinaemia or use of PRL-R antipsychotics and osteoporosis, but did not specify studies which reported associations between serum prolactin levels and reduced BMD.[24]

METHODS

This systematic review adhered to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines[25] and PRISMA statement.[26]

Inclusion and Exclusion Criteria

Included in the review were: (1) observational studies of cross sectional, case-control, prospective, and retrospective design were included, involving adults (aged 18 years or more) with a diagnosis of schizophrenia or schizoaffective disorder or a related psychotic disorder, according to Diagnostic and Statistical Manual of Mental Disorder (DSM)[27] or International Classification of Diseases (ICD) classification[28]; (2) Studies measuring and reporting BMD via dual energy X-ray absorptiometry (DXA) and/or quantitative ultrasound (QUS) scanning and serum prolactin levels a patient group with a confirmed diagnosis of schizophrenia or other psychotic disorder were included; (3) studies published in peer-reviewed journals and with no language restrictions.

Studies were excluded if they did not provide sufficient data: (1) to ascertain BMD values; or (2) serum prolactin levels; or (3) the study assessed the association between serum prolactin and BMD but did not provide prolactin and/or BMD values; and (4) if they were review articles or case reports.

Information Sources and Searches

Literature search and study selection

Two independent authors (JL and ABS) systematically searched, Medline, PubMed, Scopus, Embase, and PsycINFO from database inception until December 2018 using the following search terms: (osteoporosis or osteopenia or osteo* or BMD or DXA or DEXA) and (schizophrenia or schizo* or psychosis or antipsychotics) and prolactin, with removal of duplicate articles. The electronic search was supplemented by a manual review of reference lists from eligible publications. The corresponding authors of research groups were contacted where additional information was necessary.

Study Selection

Two authors (JL and ABS) independently searched through titles, abstracts and full-text articles for review. The two authors applied the eligibility criteria, and a list of full text articles was developed through consensus. Articles deemed viable were cross-checked by both authors and an independent author (BS) to ensure that they met the inclusion criteria.

The two reviewers then considered the full text of these articles, and a final list of included articles was reached through consensus.

We included studies which assessed the relationship between serum prolactin levels and BMD and provided comparisons by correlational analysis between BMD and prolactin levels in patients with schizophrenia or other psychotic disorders.

Outcome Measures

We performed a search for studies having examined associations between prolactin and BMD in psychotic disorders.

The primary outcome was relationship between serum prolactin and BMD captured by DXA scans or QUS in schizophrenia. The more portable nature of QUS scanners may make it an appropriate method of evaluating BMD in large populations.[29] QUS provides a different measure of bone structure to DXA scans, but with close relationship in measurements between both tools.[30,31]

The data were collected as T scores, which compare the measured BMD with the mean for a young adult of that gender, or z scores, which compare the measured BMD with that of an age- and gender matched mean value. For studies which reported both T and z scores, we used the T score as recommended by the World Health Organization to better predict risk of fracture.[32,33] We used z scores when it was the only measure reported. We included BMD measurements expressed as absolute raw levels (g/cm^2), when this was the only BMD measure compared to serum prolactin levels.

We extracted data on sample size, and serum prolactin levels (mIU/L). We measured serum prolactin levels in mIU/L, but have also presented data in ng/ml, calculated on the basis of 1 ng/ml equaling 21.2 mIU/L.[8]

We extracted data on PRL-R and PRL-S antipsychotics. Antipsychotics with a PRL-R effect included amisulpride, risperidone, paliperidone and FGAs, with the PRL-S anti-psychotics including olanzapine, quetiapine and aripi-prazole.

For studies, which used the same sample group of patients at a different point in time, we used data from the study with the largest data set.

Data Extraction

Two authors (ABS and JL) extracted data from the relevant studies. Additionally, we extracted further data where possible to assess the study-level factors associated with BMD, in patients. The data collected from each article included: study design, geographical location, study setting, method of BMD assessment, skeletal site for BMD assessment, and details of study participants (sample size, number of cases [and controls], mean age, and sex), mean serum orolactin concentrations of the study sample, number with hyperprolactinaemia, proportion treated with PRL-R and PRL-S antipsychotics, first episode psychosis (yes or no), psychotic disorder type (schizophrenia, schizoaffective disorder, psychosis or other [specified]) and duration of illness.

The data were collected in a predetermined database.

Data Analysis

We assessed correlations between serum prolactin levels and BMD levels. In our study negative correlation indicates that higher serum prolactin associates with reduced BMD.

Information on all reported significant and non-significant correlates of serum prolactin levels and BMD in psychotic disorders were collated (as defined by primary author's papers). To assess the effect and direction of the relationship between serum prolactin and BMD, we sought to standardize the statements about statistical significance in line with guidance from the Canadian Agency for Drugs and Technology in Health (https://www.cadth.ca/interventions-directed-professionals).[34]

For this study the categories were defined as the following: 0% of studies found a significant association between serum prolactin levels and BMD = no evidence for an association; 1% to 33% of studies found a significant association = largely no evidence for an association; 34% to 66% of studies found a significant association = mixed evidence for an association; more than 67% of studies found a significant association = good to strong evidence of an association.
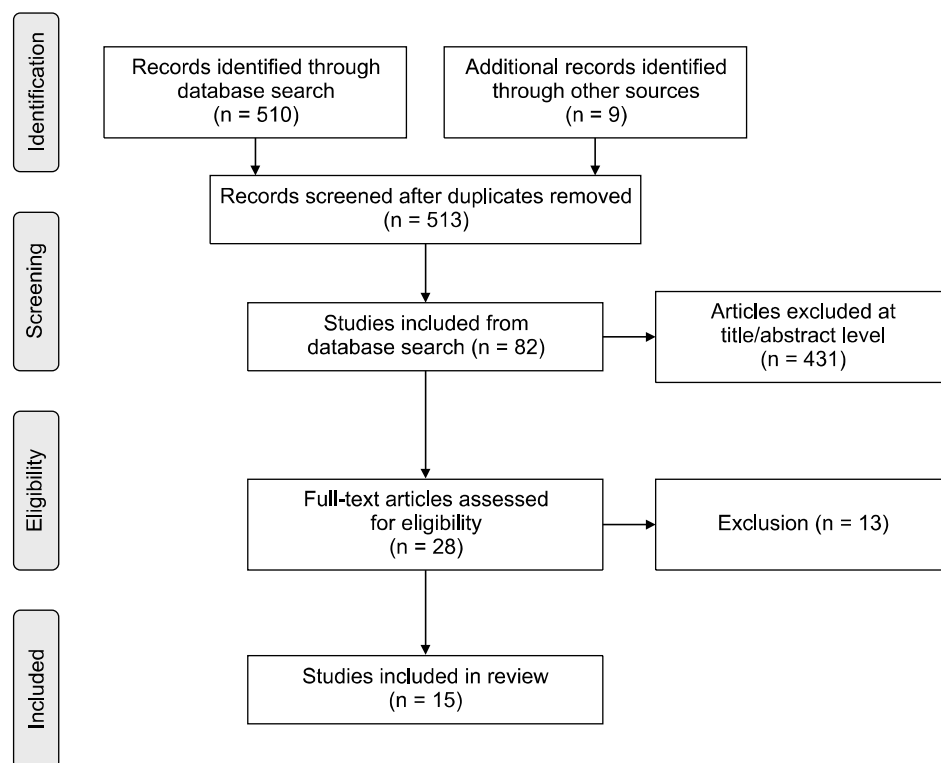
Fig. 1. Flowchart of the article selection process in a systematic review of associations between serum prolactin and bone mineral density in psychotic disorders.

We analyzed the relationship between PRL-R and PRL-S antipsychotics and BMD, and correlations between serum prolactin and BMD.

Data Synthesis

The review is presented in a best evidence synthesis.

RESULTS

The systematic review identified 519 studies and after the removal of duplicates and screening, 15 studies[16,18,22,35-46] met our inclusion criteria for assessing the relationship between serum prolactin and BMD (Fig. 1). Full details of the included studies are shown in Table 1.

Across the 15 studies, there were 1,360 individuals with a psychotic disorder (100% with a schizophrenia diagnosis). The mean age was 45.1 years (standard deviation [SD], 9.4 years) (range, 34−61 years), 742 (54.6%) were female, with a mean illness duration of 17.7 years (SD, 11.3 years) (range, 1−35 years). There was 1 longitudinal study (total cases, 163), 10 cross-sectional studies (n = 959) and 4 case-control studies (total cases, 238). Five of the studies were conducted in inpatient settings, 1 in an outpatient setting and two in a mix of in- and out-

patient settings. Seven of the studies were conducted in Asia, four in Europe and one from each of North America, South America, the Middle East, and Australia.

The mean serum prolactin level across all studies was 773.5 IU/L (SD, 317.5 IU/L) (range, 244.0−1,628 IU/L).

All of the included studies measured BMD. Twelve studies measured BMD using DXA (n = 1,080), and three used QUS (n = 280) to measure BMD. Eight studies used T scores to quantify BMD, while 5 used z scores, and 2 studies measured BMD in g/cm^2 (n = 1 study measured g/cm^2 only). Eleven of the studies provided BMD measures at the spine or hip. And six measured BMD at the hand/radius (n = 4) or calcaneus (n = 2).

Correlates of Prolactin and BMD

There was a statistically significant inverse correlation between higher serum prolactin and BMD identified in eight of the studies.[18,22,35,37,40,42,44,46] The remaining 7 studies showed no significant correlation between serum prolactin and BMD.[16,36,38,39,41,43,45]

Fifty-three percent of studies identified a significant inverse correlation between serum prolactin and BMD in psychotic disorders, suggesting mixed evidence for an association between serum prolactin and BMD.

Table 1. Characteristics of included studies

Study	Design	Setting	Country	Sex (n), M:F	Age (yr)	Duration of illness (yr)	Mesurement	Locations	Score	Serum PRL (mIU/L)	HPL (%)	Antipsychotics (n)	PRL-R	PRL-S
Abraham et al., 2003[46]	Long,	NA	USA	11:5	43 ± 11.6	22.2 ± 10.4	DXA	Spine (L1−L4), hip (neck, Troch, Ward's)	BMD	845.9 ± 801.4		16	10 (62.5)	6 (37.5)
Becker et al., 2003[18]	CS	OP	Israel	0:26			DXA, QUS	Bone speed of sound (phalanx, radius)	Z	Risperidone: 2,068.0 ± 3,052.0 Olanzapine: 549.1 ± 544.8	46.2	26	12 (46.2)	14 (53.8)
Bergemann et al., 2008[36]	CC	Hosp	Germany	0:72	33.8 ± 6.5	8.1 ± 6.3	DXA	Spine (L1−L4), hip (neck)	T	1,628.0 ± 1,212.0	100	68		
Bulut et al., 2016[37]	CC	OP	Turkey	42:0	37.9 ± 10.5	9.19 ± 8.3	DXA	Spine (L1−L4), hip (neck, Troch, Ward's)	BMD, T	448.2 ± 369.3	42.9	42	23 (54.8)	19 (45.2)
Howes et al., 2005[38]	CS	OP	UK	48:54	46 ± 13.1		DXA	Spine, hip, neck	Z	698.7 ± 915.9	56.4	102	57 (56.4)	44 (43.6)
Hummer et al., 2005[39]	CS	Mixed	Austria	57:18	34.8 ± 6.2	9.8 ± 7.4	DXA	Spine (L1−L4), hip (neck, Troch, interTroch, Ward's)	T, Z	730.2	28.0	72	14 (18.7)	58 (77.3)
Jung et al., 2006[40]	CS	Hosp	South Korea	30:21	39 ± 5.3		DXA	Spine (L1−L4), hip (neck, Troch, interTroch)	BMD, T	883.5 ± 598.1	60.8	51	100 (100)	
Kishimoto et al., 2008[41]	CS	Hosp	Japan	74:0	58.9 ± 12.2	34.6 ± 13.0	DXA	Radius (ditsal one-third)	Z	587.8 ± 255.3	86.5	74	57 (77.0)	17 (23.0)
Lee et al., 2010[16]	CS	Mixed	South Korea	45:0	49.5 ± 11.1	24.7 ± 9.3	DXA	Spine (L1−L4), hip (neck, Troch, interTroch)	Z	517.3 ± 383.3	48.9	45	20 (44.4)	25 (55.6)
Liang et al., 2016[42]	CS	Hosp	China	0:219	60.4 ± 7.0	30.0 ± 10.0	DXA	Spine (L1−L4), hip (neck))	T	682.3 ± 443.6				
Lin et al., 2015[22]	CS	Mixed	Taiwan	80:115	42.9 ± 9.7	20.0 ± 9.4	DXA	Spine (L2−L4)	T, Z	835.3 ± 829.1	51.8	195	56 (35.7)	101 (64.3)
Renn et al., 2010[43]	CS	Mixed	Taiwan	48:45	47.5 ± 18.7		QUS	Calcaneus		939.0 ± 124.5				
Rey-Sánchez et al., 2009[44]	CC	NA	Spain	48:25	61.2 ± 14.3		QUS	Phalanges II−V	T, Z	244.0 ± 191.1				
Sugawara et al., 2011[45]	CS	NA	Japan	49:65	42.6 ± 12.8		QUS	Radius (ditsal one-third)	Z	875.6 ± 839.5		114	49 (72.1)	19 (27.9)
Wang et al., 2014[35]	Long,	Hosp	China	86:77	34.5 ± 10.7	0.65 ± 0.45	DXA	Spine (L1−L4)	BMD	913.5 ± 503.7				

Values are presented number only, mean ± standard deviation, percent only, or number (%).
All included cases had a diagnosis of schizophrenia.
M, male; F, female; PRL, prolactin; HPL, hyperprolactinaemia; PRL-R, PRL raising; PRL-S, PRL sparing; Long,, longitudinal; CS, cross sectional; CC, case control; NA, not available; OP, outpatient/community; Hosp, hospital; Mixed, hospital and community based; DXA, dual energy X-ray absorptiometry; QUS, quantitative ultrasound; Troch, trochanter; BMD, bone mineral density; Z, Z score; T, T score.

Studies with significant correlation between serum prolactin and reduced BMD (n = 8) and those with absence of a significant correlation between the measures (n = 7) did not differ in mean age, mean duration of illness or in the method of measurement or quantification of BMD (Tables 2 and 3).

Ten of the included studies documented the proportion of patients treated with PRL-R or PRL-S antipsychotics. Of those studies which identified a significant inverse correlation between serum prolactin and BMD (n = 5),[18,22,37,40,46,47] 152 (52.1%) of patients were treated with PRL-R antipsychotics, compared to 197 (48.1%) of patients in those studies which did not identify a significant correlation between prolactin and BMD.[16,38,39,41,45]

Narrative Results

Only one of the included studies was of longitudinal design. This prospective study from Wang *et al.*[35] in 163 people with first episode psychosis found that the reduction in BMD at 12 months in those treated with FGAs was significantly negatively correlated with serum prolactin levels. However, there was no correlation between prolactin and BMD in the SGA group.

Five cross sectional studies identified significant correlations between serum prolactin levels and low BMD in schizophrenia. In the largest cross sectional study, 219 Chinese, postmenopausal female inpatients with schizophrenia (mean age [SD], 60.4 years [7.0 years]) were found to have a significant inverse correlation between serum prolactin and BMD.[42] They further identified a relationship between duration of antipsychotic use and reduced BMD. A cross sectional study of 51 patients with schizophrenia (30 males and 21 females; mean age, 39.0

years) treated with haloperidol monotherapy for 2 years or more found no evidence of an overall association between serum prolactin and BMD loss (t scores) or actual bone density (g/cm^2).[40] However, 94.4% (17/18) of the female patients with BMD loss had hyperprolactinaemia, of whom 7 showed concurrent hypoestrogenism, and serum prolactin levels were significantly higher in female patients with BMD loss (low t score) as compared to those with normal BMD (normal t score) (72.5 ± 49.7 ng/ml vs. 42.1 ± 31.2 ng/ml; p = 0.043).[40]

Inconsistent findings have been reported in the literature in relation to gender in the context of prolactin's effect on BMD. No associations were found between serum prolactin and BMD in women in 4 studies.[18,19,21,36] In the cross sectional study of Rey-Sánchez *et al.*,[44] 48 male (mean age, 61.9 years) and 25 postmenopausal female (mean age, 59.8 years) patients with chronic schizophrenia were assessed. There was significant negative correlation between bone mass and prolactin levels in fe-

Table 2. Comparison between studies with positive (n = 8) and negative (n = 7) correlation between serum prolactin and bone mineral density

	Positive/negative correlation studies (n)	Prolactin (ng/ml)*	T value	p value
Mean number of cases	No (7)	82.1 ± 22.8	−0.502	0.624
	Yes (8)	98.1 ± 81.2		
Mean age	No (7)	44.7 ± 8.7	−0.158	0.877
	Yes (7)	45.6 ± 10.8		
Duration of illness	No (4)	19.3 ± 12.6	−0.257	0.803
	Yes (5)	16.4 ± 11.5		

*Mean ± standard deviation.

Table 3. Comparison between methods and quantification of BMD measurement and positive/negative correlation between serum prolactin and BMD

Measurement	Studies with positive correlation, n (%)	χ^2 value	p value
Bone scan			
QUS			
No	2 (66.7)		
Yes	1 (33.3)		
DXA		0.603	0.446
No	5 (41.7)		
Yes	7 (58.3)		
Bone region			
Spine/hip			
No	4 (40.0)		
Yes	6 (60.0)	1.339	0.512
Hand/radius			
No	2 (50.0)		
Yes	2 (50.0)		
BMD measurement			
T score			
No	3 (37.5)		
Yes	5 (62.5)		
Z score			
No	4 (80.0)		
Yes	1 (20.0)		
BMD (g/cm^2)		4.252	0.119
No	0 (0)		
Yes	2 (100)		

BMD, bone mineral density; QUS, quantitative ultrasound; DXA, dual energy X-ray absorptiometry.

male, but not in male patients treated with FGAs. Contrasting findings were seen in a later study of 195 people with schizophrenia (80 males and 115 females),[22] in which hyperprolactinaemia was associated with a lower DXA t score in men, but not in women.

Two cross sectional studies of male only patients, did not identify significant correlations between serum prolactin and reduced BMD.[16,41] The study from Kishimoto *et al*.[41] identified a relationship between duration of antipsychotic treatment and reduced BMD in the subset of patients with high hyperprolactinaemia.

Only one study identified consistent associations between prolactin concentration and reduced BMD at multiple bone sites.[46] This study of 16 people with schizophrenia found statistically significant correlations between increased serum prolactin and were reduced BMD at the femoral neck ($p < 0.01$), trochanter ($p < 0.01$), Ward's triangle ($p < 0.05$) and total BMD ($p < 0.05$). Lumbar spine BMD was not correlated with prolactin levels.

DISCUSSION

In this systematic review of serum prolactin and BMD in psychotic disorders, the evidence for an association with reduced BMD in psychosis remains mixed. Large scale epidemiological studies have indicated an association between the use of PRL-R antipsychotics and fractures, though the exact relationship between raised serum prolactin and effects on BMD remains elusive. Epidemiological studies have reported conflicting effects of hyperprolactinaemia on fracture risk in schizophrenia, with some reporting an increased risk with PRL-R antipsychotics compared to PRL-S antipsychotics,[9,10] while others have not identified a differentiating effect by PRL-R or PRL-S antipsychotics on the fracture risk.[11-13] The meta-analysis from Tseng *et al*.[23] found evidence of reduced BMD in those treated with PRL-R antipsychotic compared to PRL-S antipsychotics.

From the evidence in this review, it is not possible to conclude that contemporaneous serum prolactin levels alone are consistently associated with reduced BMD in psychotic disorders. It may be the case that other features such as hypogonadism[48] are required to increase the risk for reduced BMD with elevated serum prolactin levels.[49] Other risk factors associated with reductions in BMD such

as vitamin D deficiency,[50-52] obesity,[53,54] and smoking[55,56] are prevalent in psychotic disorders, and may further contribute to low BMD.

The paucity of longitudinal studies is a limitation. All but one of the studies[35] were cross-sectional in design, and this longitudinal study was to only one to investigate the association between serum prolactin and BMD in first episode schizophrenia. This study identified an inverse correlation between serum prolactin levels and reduced BMD in those treated with FGAs raising the possibility of a relationship between sustained excess prolactin and reductions in BMD.[35]

Given the high rates of hyperprolactinaemia seen in the early stages of psychosis,[7] and that hyperprolactinaemia and elevated prolactin secretion occurs more frequently in antipsychotic naïve schizophrenia patients than controls,[57] more prospective studies in early psychosis populations may help clarify the relationship between prolactin and BMD identify risk factors without the confounding influence of antipsychotic medication.

Data in the majority of primary studies was not presented in a format that allowed a more complete data extraction of variables such as stage of illness, or duration of treatment. Further, the lack of longitudinal information on the relationship between serum prolactin levels, and lifetime antipsychotic use is a limitation in our ability to examine the enduring effects of raised prolactin levels and antipsychotic use on BMD.

Four of the included studies measured BMD using QUS (including one which used both DXA and QUS). The QUS is increasingly recognized as a valid alternative to DXA,[58] but conclusive evidence supporting this is lacking- specifically that it lacks sensitivity and specificity when compared with DXA and so it cannot be used as a direct alternative to DXA scanning.[59] However, we did not identify a significantly increased number of studies with significant correlations between serum prolactin and reduced BMD in studies using DXA scanning compared to those using QUS.

The mean age of this patient group was 45 years with little inclusion of older patients, which is not representative of the general patient population. However, the mean age in our study was higher than that identified in a previous review and meta-analyses of the relationship between schizophrenia and skeletal site specific reduced BMD (average age, 34 years) in schizophrenia[6] and is

similar to the average age in the meta-analysis of Tseng *et al.*[23)] in which PRL-R antipsychotic use was associated with reduced BMD.

CONCLUSION

Further work is required to elucidate the nature of the relationship between serum prolactin excess and BMD in psychotic disorders. There is mixed evidence to date to support a significant relationship between contemporaneous raised prolactin and reductions in BMD. It is likely that other factors such as hypogonadism relating to excess prolactin and other risk factors such as smoking and vitamin D deficiency contribute to the reductions in BMD seen in psychotic disorders. Studies that include all these considerations should be able to evaluate the differential weight of factors contributing to BMD reductions in schizophrenia and other psychotic disorders.

■ **Conflicts of Interest**

Fiona Gaughran has received honoraria for advisory work and lectures or CME activity support from Roche, BMS, Lundbeck, Otsuka, Janssen and Sunovion, is a collaborator on a NHS Innovations project co-funded by Janssen and has a family member with professional links to Lilly and GSK, including shares. All other authors declare they have no conflict of interest.

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