Medicinski podmladak

Medical Youth

Mini review article

SCHIZOPHRENIA AND OSTEOPOROSIS

SHIZOFRENIJA I OSTEOPOROZA

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Abstract

Schizophrenia (SCH) is a complex mental disorder that affects about 1% of the population. SCH is characterized by positive symptoms, negative symptoms and cognitive impairment. SCH patients often require a long-term treatment with antipsychotics. Unfortunately, treatment with antipsychotics can often be followed with metabolic side effects, decrease of bone mineral density (BMD) and osteoporotic fractures. Osteoporosis is a degenerative disease characterized by decreased bone stiffness, as signified by low bone mineral density, vertebral or nonvertebral fragility fractures and disruption of bone microarchitecture. Decreased BMD and increased incidence of fractures are described in SCH patients treated for a long time with antipsychotics . On the other hand, deterioration of bones and metabolic disturbances are seen in SCH patients who have never received antipsychotics. It remains unclear if the observed changes of bones consequence of disease process itself or antipsychotics are responsible, together with characteristic life style of patients that usually include smoking, poor nutrition, sedentary and low vitamin D. The mechanisms of antipsychotic-induced osteoporosis are complex. The most possible one is hyperprolactinemia. Hyperprolactinemia might directly affect bone turnover by stimulating bone resorption relative to bone formation. Also, prolonged hyperprolactinemia may cause hypogonadotropic hypogonadism, resulting at the end in impaired suppression of sex hormones and ultimately in changes in bone metabolism. On the other hand, bone remodeling is also controlled by the hypothalamic-pituitary-adrenal (HPA) axis. Dysregulation of HPA axis activity is consistently described in SCH patients. Perinatal phencyclidine (PCP) administration to rodents represents an animal model of SCH. This model is suitable for the investigations if the changes of bones are a consequence of disease itself or applied antipsychotics. Furthermore, it can be used to clarify the mechanism of action of PCP and chronic treatment with antipsychotics on bone structure and body composition, in order to prevent the occurrence of osteoporosis.

Keywords:
schizophrenia,
antipsychotics,
bone mineral density,
osteoporosis,
hyperprolactinemia

The authors declare no conflicts of interest.

doi:10.5937/mp69-17304
Editorial board: podmladak.med.bg@gmail.com
e-ISSN: 2466-5525

Sažetak

Shizofrenija (engl. *schizophrenia*, SCH) je kompleksno mentalno oboljenje koji pogađa okto 1% populacije. Karakterišu ga pozitivni simptomi, negativni simptomi i kognitivna disfunkcija. Pacijenti sa shizofrenijom često zahtevaju dugotrajno lečenje antipsihoticima. Nažalost, tretman antipsihoticima često je povezan sa neželjenim metaboličkim efektima, smanjenom koštanom mineralnom gustinom (engl. *bone mineral density,* BMD) i osteoporotičnim prelomima. Osteoporoza je degenerativna bolest koju karakterišu smanjena čvrstina kostiju, značajno smanjena koštana mineralna gustina, fragilnost pršljenova i ostalih kostiju, prelomi i narušena koštana mikroarhitektura. Kod SCH pacijenata koji su na dugoročnoj terapiji antipsihoticima uočeni su smanjenje BMD i povećani rizik od preloma. Promene koštane mase i metaboličkih parametara su uočene i kod pacijenata koji nisu primali terapiju. Još uvek nije razjašnjeno da li su uočene promene karakteristika same bolesti ili način života obolelih (pušenje, sedentarni način života, ishrana, nedostatak vitamina D), udružen sa tretmanom antipsihoticima, dovodi do smanjenja koštane mase. Mehanizmi kojima antipsihotici uzrokuju osteoporozu izuzetno su kompleksni. Pretpostavlja se da je nastanak hiperprolaktinemije najverovatniji. Hiperprolaktinemija može direktno da utiče na metabolizam kostiju stimulisanjem resorpcije koštanog tkiva i remećenjem formiranja kostiju. Dugotrajna hiperprolaktinemija može da uzrokuje i hipogonadotropni hipogonadizam, sa posledičnim smanjenjem sekrecije polnih hormona koji značajno utiču na metabolizam kostiju. Homeostaza kostiju je takođe regulisana preko hipotalamo-hipofizno-adrenalne (HPA) osovine. Disregulacija HPA osovine često se opisuje kod obolelih od shizofrenije. Perinatalna primena fenciklidina (engl. *phencyclidine*, PCP) kod pacova predstavlja animalni model SCH. Ovaj model je pogodan za ispitivanje da li su promene na kostima posledica same bolesti ili primenjenih antipsihotika. Štaviše, može se koristiti za rasvetljavanje mehanizma delovanja fenciklidina i hroničnog tretmana antipsihoticima na koštanu strukturu i telesni sastav, a u cilju prevencije nastanka osteoporoze.

Ključne reči:
shizofrenija,
antipsihotici,
koštana mineralna gustina,
osteoporoza,
hiperprolaktinemija

Introduction

Schizophrenia (SCH) is a complex, life-long psychiatric disorder. About 1% of the global population is affected by this disease (1). Many genetic, epigenetic and environmental factors are suggested to be involved in the disruption of brain development in SCH. SCH is manifested by diverse psychopathology: positive symptoms (delusions, hallucinations), negative symptoms (impaired motivation, reduction in spontaneous speech, social withdrawal) and cognitive impairment (problems with working memory, attention and executive functions). SCH is manifested by phases of acute psychosis where mainly positive symptoms predominate, followed by the periods of remission, where negative symptoms are more conspicuous. Its onset occurs typically in late adolescence or early adulthood and is characterized by a high rate of morbidity and mortality (2,3).

Long-term treatment of SCH patients includes antipsychotics that are classified as typical or first generation (e.g. haloperidol) and atypical or second generation antipsychotics (e.g. clozapine, olanzapine and risperidone). Antipsychotic effects occur due to the blockade of neurotransmission between the dopaminergic neurons of the ventral tegmental area and the neurons in the limbic and cortical forebrain. Typical antipsychotics primarily inhibit dopaminergic pathways and dopamine blockade in the basal ganglia is related to the occurrence of extrapyramidal side effects. Symptoms include dystonia, akathisia, bradykinesia and tremor. Elderly patients may be at increased risk for hip fractures as a result of drug associated movement disorders. About 30 percent of patients develop tardive dyskinesia, a choreoathetotic movement disorder, usually after several years of treatment (4). Atypical antipsychotics, that have both anti-dopaminergic and anti-serotonergic activity, are very efficient and cause fewer extrapyramidal side effects (5). However, the use of atypical antipsychotics is often followed by metabolic disturbances especially obesity (6), type 2 diabetes and dyslipidemia (7).

Clozapine, an atypical antipsychotic, acts as an antagonist on a unique profile of monoaminergic receptors. The highest affinity of this drug is for dopamine D4 (8), α1- adrenergic, histaminergic H1 and muscarinic receptors (9). Clozapine has a moderate affinity for dopamine D2 (8), dopamine D1 (10), α2-adrenergic (9) and serotonergic 5-HT3 (11) receptors. This broad receptor coverage makes clozapine uniquely superior in treatment resistant schizophrenia, compared to other atypical antipsychotics from a clinical perspective, and from a research perspective undoubtedly makes the drug a useful tool to promote our knowledge of complex pharmacotherapy that incorporates multiple interacting receptor systems.

The appreciation of bone health has lagged behind in comparison to the significant recognition and treatment of obesity and metabolic disturbances in SCH patients. Osteoporosis is a metabolic disease characterized by decrease of bone strength including lowering of bone

mineral density (BMD) and impairments of bone quality. Changes of bone microarchitecture, that are present as a consequence, are the basis for the greater probability of low trauma bone fractures (12). Osteopenia, a precursor of this disease, is present if the BMD is lower than expected for a given age but no fracture has occurred, or the BMD is < 2.5 standard deviations (SD) below the mean. Osteoporosis is a major public health concern worldwide, affecting about 200 million people and resulting in increased morbidity and mortality and decreased quality of life (13). Osteoporosis has a complex pathogenesis and multifactorial etiology. Risk factors include menopause, low peak bone mass, age, smoking, calcium and vitamin D deficiency, sedentary life-style, alcohol consumption and therapeutic use of glucocorticoids (14).

DXA (dual energy X-ray absorptiometry) is currently considered as the widest and most precised method used for assessing BMD (15). The most clinically relevant DXA measurements are those taken at the lumbar spine and proximal femur, because of their correlation with spine and hip fractures (16). BMD may be expressed as absolute raw levels (g/cm^2). However, it is clinically more relevant to measure it, in relation to two sets of values generated by the DXA scanner (17,18):

- t-scores, comparing the individual's BMD with standardized peak bone mass for gender-specific groups of young healthy adults between 20-30 years;
- z-scores, comparing the individual's BMD with the average for his/her age/gender/ethnic group.

According to the WHO (World Health Organization) criteria (19), osteoporosis can be operationally defined as a t-score of 2.5 SD or more below the mean value, for peak bone mass in young healthy adults, as determined by DXA. Osteopenia is defined as a BMD of more than 1 SD below this value (15,16,18).

High incidence of osteoporosis and osteoporotic fractures in SCH patients have been first described about 30 years ago (20,21). Nowadays, many investigations have confirmed relation between osteoporosis and SCH. Decreased BMD and increased occurrence of fractures are described in SCH patients treated for a long time with antipsychotics (22). On the other hand, deterioration of bones and metabolic disturbances are seen in SCH patients who have never received antipsychotics (23). It remains unclear if the observed changes of bones consequence of disease process itself or antipsychotics are responsible, together with characteristic life style of patients that usually include smoking, poor nutrition, sedentary and low vitamin D. Several studies were directed to the investigations, whether sex is a factor that has influence on the intensity of bone deterioration in SCH patients. Men were found to be more vulnerable to osteopenia and osteoporosis than women. Also, gender differences were found to be a determining factor for the manifestation of the antipsychotic effects on bones, in patients suffering from SCH (24).

Antipsychotic Medication, Prolactin and Osteoporosis

The mechanisms of development of osteoporosis due to antipsychotics are very complex. The hyperprolactinemia that arises, in response to antipsychotic treatment, is considered the most significant cause of bone loss that occurs in SCH patients. Prolactin is a hormone released by pituitary lactotrophs. Hyperprolactinemia develops as a response of the blockade of D2 receptors on lactotrophs (25). Dopamine is secreted in periventricular zone of hypothalamus and transported by the portal vessels to the anterior part of the pituitary gland were it binds to D2 receptors on the membrane of lactotrophs. This binding initiates a signaling cascade that leads to the inhibition of prolactin gene transcription and results in the decrease of synthesis and secretion of prolactin (12). In clinical practice, hyperprolactinemia is defined as a plasma prolactin level of > 20 ng/mL for men and > 25 ng/mL for women (26).

The use of antipsychotics is the most common cause of pharmacological hyperprolactinemia, and the majority of antipsychotic agents cause this disturbance (27). On the basis of their effectiveness in elevation of prolactin in blood, antipsychotics are divided into two groups: prolactin-sparing (PS) and prolactin-raising (PR) antipsychotics (28). Antipsychotics with a limited effect on prolactin levels are called PS antipsychotics. Examples include some atypical antipsychotics such as olanzapine, clozapine and quetiapine whose D2 antagonistic effects are not long lasting and not followed by long–term hyperprolactinemia. PR antipsychotics have potent D2 antagonist effect and their use is accompanied by long-term prolactin release (29).

There are two potential mechanisms by which hyperprolactinemia induced by antipsychotics may influence bone homeostasis. First, hyperprolactinemia can directly stimulate bone resorption and thus increase bone turnover (30,31). There is increasing evidence on the molecular level that prolactin receptors exists on human osteoblasts and prolactin has been shown to decrease osteoblast cell numbers due to reduced proliferation (30,32). Second, long-lasting hyperprolactinemia may produce hypogonadotropic hypogonadism (33). That can be the cause of the changes in bone metabolism (34). Low production of gonadal hormones or hypogonadism, in both sexes, favors abnormal bone metabolism and osteoporosis, similar to that associated with postmenopausal osteoporosis. Also, estrogen and testosterone withdrawal leads to an increase in osteoclast activity, not compensated by a concomitant increase in osteoblast activity (35,36).

However, although it is known that prolonged hyperprolactinemia can affect bone turnover, the relative contribution of the changes of this hormone, provoked by antipsychotics, to the bone mineral loss in SCH patients is still unclear. Several studies have reported the findings of significantly increased prolactin levels together with a

decrease of BMD and presence of osteoporosis after the long-term use of antipsychotics (37,38). Recent meta-analysis of Stubbs et al. (39) have analyzed 19 studies and more than 3000 SCH patients. The authors found that every second person suffering from SCH have decreased bone mass and that osteoporosis is present two and a half times more frequently in SCH patients than in controls. Interestingly, the correlations between incidence of osteoporosis and hyperprolactinemia caused by PR antipsychotics, smoking, duration of illness or body mass index were not seen. Chen et al. (24) have also suggested that contribution of PR antipsychotics and related hyperprolactinemia to the bone loss in SCH patients cannot be clarified on the basis of previous studies, mainly due to the cross-sectional study design or lack of adequate control groups.

Critical literature review done by De Hert et al. (40) summarized the most recent evidence, concerning the relationship between antipsychotic-induced hyperprolactinemia and bone health outcomes. This review included studies that enrolled non-elderly adults (< 65 years old) having been diagnosed with schizophrenia. The authors observed some methodological shortcomings of existing studies, including the lack of prospective data and the focus on measurements of BMD, instead of bone turnover markers, which exclude definitive conclusions regarding the relationship between PR antipsychotics and BMD loss in patients with SCH. Several studies (41-43) have found important gender differences in the prevalence of low BMD. The repeated founding was that prolactin responses to antipsychotic medication are greater in females than in males. The explanation lies in the ability of estrogens to bind to the receptors in hypothalamus, causing decrease of dopamine release, subsequent increase of the number of pituitary lactotrophs and elevation of serum prolactin levels (17). However, despite the higher prevalence and severity of hyperprolactinemia in women, and contrary to the general trend in which women are at a higher risk of osteoporosis compared to men (44), certain studies revealed that hyperprolactinemia with associated hypogonadism may have a more profound impact on BMD in male, compared to female patients (41,42).

Beneficial effects of PS antipsychotics (43), as well as increased incidence of hip fractures in patients treating with PR antipsychotics (45) were seen in both genders. Lin et al. (46) have demonstrated dose-dependent protective effect of clozapine regarding bone mineral density in women with schizophrenia. It is interesting that hyperprolactinemia is registered more frequently in women taking PR antipsychotics (42,47) but men are those that are more prone to osteopenia and osteoporosis than women (39). The explanation for this could be found in the investigation of Lee et al. (48) who suggested that negative symptoms but not hyperprolactinemia caused by antipsychotics, could be responsible for the findings of decreased BMD in male SCH patients.

Therefore, the relationship between hyperprolactinemia and osteoporosis remains controversial, and further research is warranted.

The Disturbances of Hypothalamic-Pituitary-Adrenal (HPA) Axis Activity and Osteoporosis

The hypothalamic-pituitary-adrenal (HPA) axis is one of the most important neuroendocrine regulatory systems involved in the adaptive responses of the mammalian organism to external and internal threatening stimuli (49).

Hypothalamus over the HPA axis influences the balance of bone remodeling. Result of the activation of the HPA axis is secretion of glucocorticoid hormone (GC). This hormone achieves its effects by binding to the specific glucocorticoid receptors (50). Direct binding of GC to the receptors on osteoclasts inhibits apoptosis of these cells. Also, GC binds to the receptors on osteoblasts causing disturbances in their differentiation, activity and survival. The apoptosis of osteoblasts and osteocytes is stimulated and formation of new bone suppressed (51). Cortisol is the main GC hormone in humans, while corticosterone is the major form in rodents. Chronic stress can stimulate bone loss through the activation of HPA axis and sympathetic nervous system, suppression of the sex and growth hormones and increase of pro-inflammatory cytokines (52).

Dysregulation of HPA axis activity is consistently described in SCH patients (53-55) and hypercortisolemia is another factor that could be responsible for more frequent osteopenia and osteoporosis, in patients suffering from SCH (56). A systematic review of HPA axis function in SCH, done by Bradley and Dinan (53), has concluded that SCH patients periodically have increased cortisol secretions. These elevations are present almost regularly in drug-naive schizophrenia patients, with the first episode of illness and without any influence of antipsychotic medication. However, increased cortisol levels are also seen in some chronic patients with more stable clinical features. Many factors, including different symptoms of the disease, use of drugs and influence of diverse environmental factors, can modulate HPA axis function. Patients with SCH frequently display an impaired HPA axis response following an acute stress (57,58). Antipsychotic drugs could have influence on the levels of cortisol (59). Observed cortisol changes in patients with psychosis have been associated with both first and second generation antipsychotics. However, most studies indicate that second generation antipsychotics are more effective in reducing cortisol levels, than those belonging to the first generation (60-62). The study of Cohrs et al. (63) has investigated the cortisol levels in healthy volunteers receiving typical or atypical antipsychotics. Atypical drugs, namely quetiapine and risperidone, caused decrease of cortisol levels, while typical antipsychotic haloperidol had no effect. It is suggested that different affinity and occupancy of D2 and 5-HT receptor subtypes are responsible for the effects of second generation antipsychotics on cortisol levels (64).

Recently, animal and human studies have

demonstrated the link between chronic psychological stress and osteoporosis (65,66).

Animal Studies

In order to increase knowledge about the neurobiological basis of complex psychiatric disorders such as schizophrenia, as well as to reveal new drugs with greater therapeutic efficiency, predictive animal models are developed. Animal models of schizophrenia can be classified into four categories that are different in the mechanism of induction: developmental, drug-induced, lesion or genetic manipulation models (67). One of the actual pharmacological animal models of this disease is perinatal phencyclidine (PCP) administration to rodents (68,69).

Latest investigations have pointed out that dysfunction of the glutamatergic system can be the first pathophysiological alteration observed in SCH (70,71). Pharmacological evidence for the role of glutamate in SCH focus on findings that blockade of the N-methyl-D-aspartate (NMDA) receptor by non-competitive antagonists, such as ketamine or PCP, can produce a wide range of effects in healthy human volunteers that are similar to those seen in SCH and can exacerbate psychosis in SCH patients. PCP may induce positive symptoms (agitation, audiovisual hallucinations, paranoid delusions), negative symptoms (blunting of affect, apathy) as well as, cognitive disorders (72,73).

Typical and atypical antipsychotics are efficient in reducing effects of PCP and this is important for the confirmation of predictive validity of this animal model (74). Influence of antipsychotics on bone in animals have been investigated in several studies. Kunimatsu et al. (75) have shown that long-term treatments with typical antipsychotics haloperidol or chlorpromazine is followed by a loss of trabecular bone of the femur in female rats. On the other hand, Costa et al. (76) have found that clozapine applied to growing male rats for 6 weeks decreases BMD while haloperidol does not show this effect. Possible explanation for this findings the authors have seen in the direct action of clozapine on the osteoblasts that results in a decrease of their proliferation and differentiation.

However, especially important are the investigations of the effects of antipsychotics on bone in experimental animal models of SCH, although there are very few of them. Results of recent study have demonstrated that perinatal PCP treatment used for modeling of SCH is followed by a decrease of BMD in male rats that can be prevented by atypical antipsychotic risperidone (77). The first study that investigated the chronic effects of haloperidol and clozapine on bone mass and body composition in PCP animal model of schizophrenia (78) has demonstrated that perinatal PCP treatment causes a significant reduction of bone mass and decline in bone quality both in male and female rats indicating that disease *per se* could be responsible for observed bone deterioration. Haloperidol had harmful effects, while clozapine was even protective for bones. The effects of haloperidol on bones were more pronounced in male rats. However, treatment with clozapine caused significant changes of biochemical and metabolic parameters that were mainly sex specific (78).

Conclusion

The relative contribution of antipsychotic-induced hyperprolactinemia to bone mineral loss in SCH patients remains unclear, although long-standing hyperprolactinemia can have an impact on the rate of bone metabolism and, in association with hypogonadism, may lead to decreased bone density, both in female and male subjects. Methodological shortcomings of existing studies, including the lack of prospective data and the focus on the measurements of BMD instead of bone turnover markers, preclude definitive conclusions regarding the relationship between PR antipsychotics and BMD loss in patients with SCH. Therefore, more well conducted prospective trials of these biomarkers are necessary to establish precise relationship between antipsychotics, prolactin levels and osteoporosis/osteoporotic risk (40). Also, some prevention strategies and intervention methods, such as to help the schizophrenia patients to change their lifestyle, improve diet and exercise, promote physical activity and prevent the risk of falls, could be considered to be taken (79).

Animal models are very important since they enable accurate control of different factors that are difficult to be controlled in humans. Also, a better and more complete understanding of glucocorticoid signaling during disease will aid in the improvement of current therapies and hopefully lead to the enhanced clinical outcomes of patients.

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