It was observed that people with Alzheimer’s disease develop adverse events characteristic of osteoporosis more frequently in comparison with healthy people of the same age. Femur neck fractures are more frequent and their treatment and rehabilitation are more difficult.

Alzheimer’s disease and osteoporosis – correlation increasing the risk of life-threatening fractures?

Jerzy Bednarski¹, Karolina Gasińska¹, Mariola Rucińska², Karolina Turżakówna¹

1. Chair and Department of Rehabilitation and Orthopaedics, Medical University of Lublin, Jaczewskiego 8th Street, 20-090 Lublin, Poland
2. Chair and Department of Neurology, Medical University of Lublin, Jaczewskiego 8th Street, 20-090 Lublin, Poland

#Corresponding author: Jerzy Bednarski, Chair and Department of Rehabilitation and Orthopaedics, Medical University of Lublin, Jaczewskiego 8th Street, 20-090 Lublin, Poland Phone: +48 791592958, email: jerzybednarski@gmail.com

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ABSTRACT

Alzheimer’s disease (AD), as well as osteoporosis, appears after the age of 60. It was observed that people with Alzheimer’s disease develop adverse events characteristic for osteoporosis more often in comparison with healthy people of the same age. The aim of the study was to assess whether the two disease entities are interdependent and what factors are associated with this possible relationship. It has been confirmed by numerous reports that a decrease of bone mineral density (BMD), a recognized risk factor of life-threatening fractures, correlates with osteoporosis and Alzheimer’s disease. Loss of body weight and body mass index (BMI) and more frequent depression, which are also common in osteoporosis and AD, predispose to this risk. Discovery of correlation between Alzheimer’s disease and osteoporosis is important not only for understanding the pathogenesis, but also for the development of therapeutic methods in the treatment of both diseases. The papers mentioned above allow one to suppose that AD patients should be subjected to prophylactic measures for prevention of osteoporosis.
INTRODUCTION AND AIM OF THE PAPER

Alzheimer’s disease, as well as osteoporosis, appears after the age of 60. Percentage of ageing people incredible thus increasing the number of people suffering from these disease entities. It was observed that people with Alzheimer’s disease develop adverse events characteristic of osteoporosis [1] more frequently in comparison with healthy people of the same age. Femur neck fractures are more frequent and their treatment and rehabilitation are more difficult [2]. It has been proved that both disease entities decrease quality of life, lead to increase in frequency and length of hospitalizations and negatively influence health management by increasing the costs of hospitalization. Hence, studies on the two diseases are becoming more and more important in the context of an ageing society. Thus, the aim of this paper was to assess whether the two disease entities are interdependent and what factors are connected with this relationship.

OSTEOPOROSIS

Bone tissue is remodeled throughout life. Its peak bone mass (PBM) i.e. the biggest mass, which correlates with peak bone mineral density (BMD), is assessed around the age of 35. Unfortunately, in adulthood PBM may start to decrease. This process occurs when resorption prevails over bone formation. The loss occurs as a result of intense resorption which is not accompanied by proper deposition of new bone. Initially it occurs in cancellous bone and then changes develop in cortical bone. In adult people bone formation and resorption occur in parallel and annual bone loss is about 0.5% [3].

Faster changes occur in organisms of women at postmenopausal age. This is connected with estrogen deficiency which negatively influences osteoblasts responsible for anabolic processes – formation of bone matrix. As a result of estrogen deficiency osteoblasts’ lifespan decreases. Moreover, normally, estrogens inhibit osteoclastogenesis and stimulate osteoclasts apoptosis what leads to gradual loss of cortical bone thickness, bone trabeculae and decrease of bone mass density [4]. Accelerated bone resorption is accompanied by progressive negative calcium balance. Some women lose even 10% of skeleton mass which leads to a decrease in its mechanic durability and increases the risk of bone fractures [3]. It reduces skeleton’s durability and predisposes to low – energy fractures involving primarily vertebral bodies, distal part of the femur (such as femur neck fractures and transtrochanteric ones), distal parts of radius (the so called Colles’ fracture, Smith’s fracture) and proximal part of the humerus, however they may appear in every part of the skeleton [5, 6].

Such changes consisting of a decrease in bone mass and density and deterioration of the quality of bone tissue are the basis for osteoporosis. It is defined as a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bones leading to reduction of their durability and consequently to fractures caused by minor injuries (low-energy) [3].

Osteoporosis is recognized on the basis of bone mineral density measurement with the use of densitometric method (DXA). Basic radiological examinations are also useful. Additionally, computed tomography (CT) and magnetic resonance imaging (MRI) provide information which facilitate diagnosis. However, according to WHO directive, beginning of osteoporosis treatment should be connected with, among other things, measurement of BMD with bone densitometry DXA in femur neck (proximal part of the femur). Basic results are given in absolute values of g/cm². Densitometric apparatus are equipped with programs which compare the patient’s result with the norm in the form of percentages, T-score, Z-score. Z-score indicates how the result of the examined patient differs from BMD average at this age. T-score compares this result to BMD of a group at the age of 30-35, when human skeleton has its peak mass. On the basis of T-score WHO provides the following diagnostic categories:

T-score diagnosis

Norm +1,0 to -1,0
Osteopenia – 1,0 to -2,4
Osteoporosis < – 2,5
Advanced OP < - 2,5 and one or more fractures [5,6].

In children, the lower limit is 2SD below the value adequate for sex and age (Z-score), at levels lower than these values osteoporosis is diagnosed [5].

A newly introduced diagnostic method of osteoporosis is the FRAX® algorithm. It defines probability of fracture occurrence in the course of 10 years. It allows to suspect osteoporosis without the involvement of a physician. Conduction of specific diagnostics consists of an anonymous Internet survey in which a person answers 11 simple questions about numerous risk factors of the disease. The tool may increase its diagnostic power when the result of a densitometric examination is provided. The data are calculated according to algorithms devised for particular countries. They were developed on the basis of an analysis of 60 thousand men and women from Europe, North America, Asia and Australia. The algorithm is constantly developing on the basis of new data, including analysis of risk factors. So far neurologic diseases such as AD have not been taken into account [7].

ALZHEIMER’S DISEASE

Alzheimer’s disease belongs to a group of diseases of neurodegenerative character which are accompanied by dementia. Progressive and irreversible loss of cognitive functions and memory is characteristic
of this group of diseases. At the same time it is the most frequent affliction in elderly people. According to estimates, 35 million people suffer from dementia in the world, and by the year 2050 the number may increase even to 115 mln [8]. Alzheimer’s disease is characterized by a prevalence rate of 6% in the population over 65 years old, 40 % of whom are patients with a slight progress of the disease [9].

The course of Alzheimer’s disease is slow and a typical beginning is difficult to notice. Most often the first symptoms are memory disorders consisting in difficulties with remembering new information (wor
ding appear. Professional activities are performed slower, with difficulty, professional mistakes may occur. The next stage is loss of working capacity and problems with domestic activities [13].

The patient gradually becomes less critical and more indifferent about the disease. Also, gradual loss of all life skills may appear. They involve counting, shopping, preparing meals, answering the phone or taking care of one’s hygiene. In the final stage of the disease the patient may lose the ability to move independently or may become bedridden or lose sphincter muscle function. Additionally, muscular dystrophy, contractures of limbs and bedsores may occur [13].

Complications of Alzheimer’s disease may include separate mental disorders i.e. depression, mania and delusional complex. Serious concomitant diseases may include respiratory or urinary infections, thromboembolic complications and fractures which are connected with considerable disability and loss of independence [13].

COMMON FACTORS OF OSTEOPOROSIS AND ALZHEIMER’S DISEASE

Some research indicates that low BMD value is associate with increased risk of Alzheimer’s disease. Zhou et al. [2011] examined a group of 3263 patients aged at least 65. During 5-years-long observation AD developed in 132 patients. The authors confirmed that lowered BMD value measured with the use of DEXA (dual energy X-ray absorptiometry), increased bone loss index, smoking and everyday intake of alcohol were related to increased frequency of AD [14]. Other research, conducted by Loskutov et al. [2009], involved a group of 71 patients with diagnosed AD at an early stage. In the control group, there were 69 patients without symptoms of dementia. Measurements with the use of DEXA involved BMD of entire body. Average BMD value was lower in patients suffering from AD in comparison to the control group regardless of age, sex, physical activity, smoking, depression or levels of estrogen or apolipoprotein E4. Additionally, low BMD value was associated with brain atrophy, which was confirmed by measurements of total brain volume, and with a decline in cognitive functions, especially memory. These results suggest that bone loss occurring in AD may be caused by central nervous system disorder [15].

In the research of Tan et al. [2005] 987 patients took part, 610 of whom were women without cognitive disorders. BMD was measured in the femoral head, trochanter of femoral bone and groove for radial nerve. Observation of AD symptoms and multifactorial dementia testing was conducted for 8 years. It was shown that in women, who had the lowest BMD value in the femur head, AD and multifactorial dementia developed twice more frequently than in those with the highest BMD value. Analyses included age, sex, apolipoprotein E level, homocysteine level, use of hormone replacement therapy, smoking, past strokes and education level. Similar, although not statistically significant correlations, were observed.

In the development of the disease important factors include β-amyloid, tau proteins and alpha-synuclein – proteins of improper structure which deposit in brain tissue. β-amyloid, which deposits in extracellular space in the form of the so called senile plaques, is a certain stage of protein transformation in a healthy organism. It becomes harmful only when it is in excess and in the form especially prone to high concentration (the so-called hyperphosphorylated amyloid form). On the other hand, tau protein is one of the important regulators of microtubules forming cyto
skeleton. Presence and proper activity of tau protein is necessary for transportation of neurotransmitters and trophic factors along axons. The proteins are excessively deposited in nerve cells, thus creating clusters of improper fibres (neurofibrillary tangles of Alzheimer type). In Alzheimer’s disease, both of these proteins are of improper structure, develop in excess and cumulate in the form of pathological aggregates. This leads to damage of brain cells, connections between them (synapses) and in the end to the disappearance of neurons [10].

Diagnosis is based on clinical confirmation of dementia. It is advisable to confirm it with the use of diagnostic scales (for example, Brief Psychiatric Rating Scale - MMSE or the Blessed Dementia Scale) and by neuropsychological testing. Diagnosis may be supported by results of computed tomography indicating atrophy of the brain, especially progression of changes in subsequent CTs. Characteristic for Alzheimer’s disease are normal EEG (or non-specific changes) and a normal result of cerebrospinal fluid examination [11]. Moreover, significant are the NIN-CDSS-ADRDA and the DSM-IV-TR which, apart from neurological and mental disorders, do not involve other systemic changes [12].

Alzheimer’s main symptoms are: impaired memory, change of behavior and character traits, and in later stages of the disease loss of independence and impairment of everyday functioning which is associated with loss of mobility [11].

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between BMD of trochanter of femoral bone and AD prevalence. On the other hand, BMD of radial nerve groove did not correlate with AD and dementia. In men, the correlation between BMD and AD risk was reversed, however these results were not statistically significant in the case of BMD measurement in all 3 sites. Presented data indicate that sex hormones, especially estrogen, may have a role in AD development [16]. Sato et al. [1998] examined the value of BMD in the second metacarpal in 46 women at elderly age with diagnosed AD. BMD was significantly lower than in control group. In 26% of patients with AD, concentration of 25-hydroxyvitamin D(25-OHDD) in the blood serum was lowered (5-10 ng/mL), and in 54% of patients it indicated osteomalacia (<5 ng/mL). The calcium ion concentration was also lower than normal values. On the reverse, concentration of bone GLA protein and hydroxyproline in blood serum was clearly higher in the study group than in the control one. BMD showed positive correlation with 25-OHDD concentration and negative with parathormone (PTH). PTH concentration was higher in the study group than in the control one and negatively correlated with 25-OHDD. A lot of patients with AD were insufficiently exposed to the sun and consumed less than 100 IU of vitamin D per day. It was confirmed that vitamin D deficiency caused by insufficient exposition to the sun and malnutrition in combination with compensatory hyperparathyroidism significantly contributes to BMD reduction in patients with AD [17].

Low BMD value increases the risk of femur head fractures. This is confirmed by numerous papers, among others Zhao et al. [2012] [18], Sato et al. [2011] [19], Iwamoto et al. [2012] [20], Lai et al. [2013] [21], Tolppanen et al. [2013] [22], Bourdieu [2011] [23] and Rapp [2011] [24]. Zhao et al. analysed publications available in Medline, SciVerse Scopus and Cochrane Library databases. They had been published until January 2012 and concerned the relationship between hip BMD or hip fractures and AD prevalence. In their metaanalysis, the authors involved 9 studies. The results indicated that AD patients have an increased risk of hip fracture and lower BMD in comparison to healthy control group [18]. Sato et al. examined a group of 231 patients at elderly age with diagnosed Alzheimer’s disease. Some of the patients were administered 45 mg of menatetrenone (vitamin K) every day, the rest were given a placebo in combination with risedronic acid (pyrimidine bisphosphonate compound of third generation, bone resorption inhibitor) once a week. Administration of these substances was continued for 12 months. As the results showed, patients of both groups had increased osteocalcin and slight 25-OHDD deficiency with compensatory hyperparathyroidism. During the study, BMD increased by 5,7% in the study group and by 2,1% in the control one. In the control group there were 15 non-vertebral fractures, 10 of which were hip fractures, while in the study group there were 5 non-vertebral fractures, 2 of which were hip fractures. These results confirmed that AD patients with D and K hypovitaminosis have an increased risk of hip fractures. Drugs used in the research were well tolerated and showed few side effects. Additionally, they effectively reduced the risk of fractures in elderly AD patients [19]. Iwamoto et al. examined effectiveness of exposition to sunlight in decreasing the risk of fractures in patients with neurologic diseases including AD, Parkinson’s disease and strokes. This research confirmed that staying in the sun decreases D hypovitaminosis and increases BMD. Simultaneously, the risk of hip fracture decreased by 77% [20]. Tolppanem et al. conducted a cohort study in Finland in 2002-2009. It involved patients with diagnosed Alzheimer’s disease. It was shown that AD patients experienced hip fractures twice more often in comparison to healthy people. Age and sex were taken into account. Increase in the risk of fracture was higher in men than in women [22].

It has been proved that BMD index also correlates with BMI. Fawzy et al. [2011] examined 101 patients. BMD was measured with the use of DEXA method. They showed that 39 people had normal BMD and in 62 people it was lowered. Lowered BMD was found in 82,4% of patients with normal BMI, in 78,1% overweight patients and in 44,2% obese patients. Correlation between the two parameters was statistically significant. Low BMD value was found in 59,1% of women and 76,9% of men. Moreover, they proved that correlation between low BMI and advanced age is an important risk factor of BMD decrease [25]. Sato et al. [2005] studied the relationship between BMI value and Alzheimer’s disease. The study involved 100 women with AD (average age was 79,8). The control group comprised of 100 women without any cognitive disorders (average age was 80,6). Patients were divided into 2 groups according to the stages of dementia. The group with mild dementia comprised of patients with MMSE of 16 and more, whereas the group with severe dementia had a MMSE score of 15 or less. It was shown that BMI was significantly lower in women with the most severe AD. Low BMI may implicate the presence of general malnutrition, which results from vitamin D and K deficiency and osteopenia, in this group of patients [26]. Decrease of BMI value in AD patients was confirmed by Segers et al. [2012]. The authors assessed the influence of mirtazapine – antidepressant causing increase in body weight – on people with diagnosed AD. The aim of this research was to test the safety of use and potential usefulness of the drug in prevention of body weight loss in patients not only with AD, but also with AD accompanied by damage of cerebral vessels. Daily mirtazapine dose was 30 mg and was administered to 22 patients (average age 80,9, proportion of women 86,4%). Average body weight before the treatment was 52,4 kg and average BMI index was BMI 20,5 kg/m. 77,3% of the patients gained weight after 3 months (average gain ratio 1,93 kg or 3,9% of initial body weight) and 82,3% after 6 months (average gain
Research on osteoporosis found that WL correlates with condition of bone tissue. It is recognized as risk factor of life-threatening fractures [29]. The danger concerns mainly the femur which was proved by De Laet et al. on the basis of data analysis of about 60,000 patients it was declared that the risk define BMI loss. The highest increase in fracture risk is observed during BMI decrease from 25kg/m² to 20kg/m². Then the probability of hip fracture doubles and increases with ageing of not only men, but also women [30]. Similar conclusions may be drawn from the work of Johannsen et al. from 2014 [31], whereas Compton et al. proved that the probability of increase in the risk of spinal, wrist and hip fractures increases with BMI loss. They confirmed such correlation in postmenopausal women [32]. The results of above analyses indicate that common risk factors for osteoporosis and Alzheimer’s disease are loss of body weight and BMI.

Epidemiological research and clinical observations showed that there is a correlation between Alzheimer’s disease and depression. Depression is considered a risk factor and, at the same time, an AD symptom. Genetic and neurobiological mechanisms underlying those diseases have been described. With the use of fluorescence techniques, Wuwonqse et al. [2013] showed that synaptic functions were impaired in hippocampus neurons which were subjected to activity of Aβ oligomer and corticosterone (typical factors for AD and depression). Significant changes were found in proteins of presynaptic vesicles – synaptophysin and synaptotagmin. Probable mechanism of these changes were disorders in protein degradation connected with autophagy and ubiquitin- proteasome system. During ubiquitin-dependent protein degradation and preferential simulation of autophagy-lysosomal degradation path, scientists observed “up-regulation” phenomenon. They also discovered a neuroprotective role of various antidepressants. It was showed that imipramine and escitalopram were able to repair observed protein damages. Therefore, presented results suggest that synaptic degeneration is an important and common risk factor of Alzheimer’s disease and depression [33]. Nihonmatsu-Kikuchi et al. [2013] conducted post-mortem examinations of the brains of people with Major Depressive Disorders (MDD). They proved that MDD are connected with unknown type of myelin and myelination disorders in the frontal cortex [34]. Lebedev et al. [2013] studied changes in the cerebral cortex associated with depression and the use of antidepressants in people with mild AD and Lewy Body Dementia (LBD). Study group consisted of 74 patients. Montgomery-Asberg Depression Rating Scale (MADRS) was used to assess the degree of depression. The thickness of cerebral cortex was analysed with the use of the linear model. Decrease in the thickness connected with depression was discovered in prefrontal and temporal areas, whereas decrease connected with the use of antidepressants - in parahippocampal region. Results of this study indicate that depressive symptoms and mild dementia may develop as a result of neurodegeneration of the same neuronal paths. Moreover, modification of depression treatment with the use of antidepressants in patients with dementia is necessary. Development of depression in AD patients may have a genetic basis [35]. Teng et al. [2011] showed that increased risk of development of not only AD, but also depression, occur in children of AD patients. The scientists conducted a long-term study of families in which AD occurred. Depressive symptoms were assessed in offspring (30 people, average age 41,2). Average result of Hamilton Depression Rating (HDR) scale increased from 1,8 to 5,3 in the course of 20 years. Cognitive functions remained stable during this time. The research confirms that depression may be an early symptom of progressive dementia among family members in the group at increased risk of AD development [36].

Charles et al. [2012] conducted a research on correlation between depressive symptoms and BMD index. The study involved 97 police officers, 41 of whom were women aged 29 – 64. Depressive symptoms were measured with the use of CES-D scale. In order to measure BMD in hip, femoral bone, spine, wrist and entire body the authors used DEXA with standard procedures. The research showed that BMD index decreased along with escalation of depressive symptoms in all women. Such correlation was not observed in men [37]. Apart from that, a study of Hain [2011] confirmed BMD loss in hip of former prisoners of war with diagnosed PTSD (Posttraumatic Stress Disorder) [38]. In turn, Olkenon [2014] proved that depression in people exposed to chronic stress at work caused BMD reduction regardless of sex. Severity of depressive symptoms correlated with stress to which they were exposed at work [39]. Many other works...
of, among others, Robbins, Yazici, Spangler and Wu describing decrease of BMD index influenced by depression are available in the literature [40, 41, 42, 43]. Research shows that this disease may be treated as a risk factor of osteoporosis development.

CONCLUSIONS

Discovery of correlation between Alzheimer’s disease and osteoporosis is important not only for understanding the pathogenesis, but also for the development of therapeutic methods in the case of both diseases. Abovementioned research confirms that the risk of concurrence of these two entities is very high. BMD loss, decrease of body weight and BMI, and more frequent depression, which are common for AD and osteoporosis, predispose to this risk. Additional recognized factors include: lower exposition to sunlight, hormonal disorders and lower physical activity. The above indicates that AD patients should be subjected to measures of prophylactic character against osteoporosis. People with low – energy fractures, which are especially serious and life-threatening in Alzheimer’s disease, should be considered for such preventive interventions.

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BIBLIOGRAPHY


