

**RESEARCH ARTICLE**

**The Use of Bone Tissue Non-Steroid Anabolizers in Treatment of Osteoporosis**

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**ABSTRACT:**

Pathogenesis of OP in aged women is complicated enough and depends on many exogenous and endogenous factors. Ageing process is accompanied by involutive processes almost in all tissues and systems of the body. All these age-related changes lead to lesions of hormonal status, reproductive/regenerative system, especially in combination with negative endogenous factors. In this study we presented data about optimization of the treatment of osteoporosis in elderly people with cognitive disorders using anabolizers of bone tissue based on entomological hormones of drone brood. Our studies showed that it is possible not only to stop osteoporosis but also to reduce its severity as well as reduce the risks of fractures and cognitive disorders.

**KEYWORDS:** personified approach, bone mineral density, cognitive disorders, "Osteomed Forte", densitometry, drone brood.

## INTRODUCTION:

Osteoporosis is human disease that is characterized by substantive decrease of bone mineral density (BMD) and bone mass, deterioration of architectonic of the body tissues. As a result, bone structures loss their strength and become fragile that multiplies the risk of pathologic fractures. These processes may be accelerated by climax, a number of chronic diseases, inadequate diet, endocrine system diseases, physical activity decay, etc. In spite of great successes in diagnostics and treatment of osteoporosis (OP), the importance of this problem is constantly growing. It is due to the growth of average life expectancy almost in all countries of the world. So, in 2000 there were about 400 million people over 65 years worldwide. By 2025, this age group will increase to 800 million people. The ageing process and osteoporosis are closely related to each other. Health and normal bone status are supported in the body through sufficient intake of calcium, vitamin D3, and other nutrients. Furthermore, normal function of endocrine system is also necessary. OP may sneak up early and imperceptibly. Already at the age of 35 – 40 begins gradual and natural excretion of calcium (Ca) from bones that with concomitant diseases can lead to OP. The greater age, the more frequent is incidence of OP and bone fractures.

Currently, treatment of osteoporosis in most world countries is reduced to target therapy (as in oncology) in order to find a cancerous cell and destroy it by any means! In osteoporosis, such a cell is osteoclast that destroys (resorbs) the bone. The number of osteoclasts may multiply in osteoporosis, therefore, the whole therapy is aimed to inhibiting osteoclasts' function by any means (i.e. killing, hardening, lulling, etc.). This trend in therapy of osteoporosis resulted in creation of an entire industry that developed numerous pharmaceuticals called antiresorbents. Bisphosphonates became a "Golden standard" in OP treatment (Fosamax, Bonviva, Etidronate, Alendronate, etc.). Manufacturing companies received billions of dollars in profits but the urgency of the problem of osteoporosis is still growing.

Recent studies revealed that there is a close signal exchange between osteoclasts (OC) and osteoblasts (OB) so that raise in OC activity leads to increase of OB activity.

So, exosomal miR-214-3p OC stimulates the OB activity! Therefore, antiresorbents should not be prescribed for treatment of osteoporosis. First of all, they are extremely undesirable for patients with senile osteoporosis, because it is inhuman to kill bone cells in patients at the age as their bone cells are ageing and dying without it in huge amounts. Based on the said above, during the last 10 years we carried out a planned withdrawal of antiresorptive therapy and gradual

transition to an anabolic therapy aimed to the support of all bone cells, including OCs as well as OBs.

## THEORETICAL OVERVIEW:

The world medical practice has a large experience in estrogen replacement therapy. However, its wide use results in increase of the risk of mammary cancer. Therefore, since administration of natural hormones – estrogens and androgens—has a number of disadvantages, it was suggested the use of herbal hormones. For instance, Citracal plus Vitamin D plus Genistein manufactured by Bayer USA includes genistein – soya hormones as substrate for synthesis of endogenous hormones by the body. We, Parapharm Company and Penza Postgraduate Medical Institute under Ministry of Health of Russia, developed new technologies in OP therapy with use of entomological hormones—drone brood hormones—as donators of sex hormones. We created 3 new biologically active supplements for personified approach in OP treatment: "Osteomed", "Osteo-Vit D3", and "Osteomed Forte". (They were be granted with 40 patents, including in Japan, New Zealand, Australia, Germany, Ukraine, etc.)<sup>[1,2,3]</sup>.

The ways to optimize the OP therapy at the present stage:

1. Improvement of the diagnostics of OP. Our studies showed that bone quality, severity of OP, and effectiveness of treatment can be determined only with considering morphometric parameters<sup>[1,2,3]</sup>. Without it, it is difficult to determine the diagnosis of the disease and the effectiveness of medicine.
2. Accounting for comorbidity. As a rule, OP is comorbid disease accompanied by other sever diseases of heart, joints, blood vessels, endocrine diseases, arterial hypertension, and others. Often such patients have to attend several doctors and to take a lot of pharmaceuticals that frequently leads to iatrogenic pathology and development of special, previously uncommon and hard curable or incurable pathologies<sup>[4,5,6]</sup>. However, doctors of a narrow profile often turn a blind eye to comorbidity while preferring to treat only "their" profile disease and leaving their colleagues—therapists and others – to treat all concomitant diseases. Such an approach inherently results in failures in diagnostics as well as in therapy of OP. Therefore, when comorbidity is present, it is necessary to understand and calculate the rating of each disease and its role in pathology in order to make the correct diagnosis. To make a correct diagnosis, it is required to determine an underlying disease, background diseases, complications and concomitant pathologies. That is, first of all, it is necessary to determine among this "bunch of diseases" which disease is the most dangerous to the patient's life, lowers his work ability, and thus requires high priority treatment.

Therefore, the task of every doctor is to clarify a clinical Figure as a whole, “to treat the disease, not the patient”. Such an approach lowers the likelihood of severe adverse effects. When choosing pharmaceuticals a doctor should take into account their compatibility with each other in treatment of several pathologies simultaneously.

3. Scientific approach. Taking into account the latest achievements of the science, it is important to understand the interaction consistency of OB–OC parts of system in forming a single structure as a whole. For older people it is important the support of all bone cells, and not pharmaceutically induced imbalance of their functioning.
4. Personified approach in OP treatment. Even today a practitioner can succeed when taking into account the role of concomitant and predisposing factors, such as: age, unbalanced nutrition, absence of teeth, and gastrointestinal disorders that lead to decreased tolerance of dairy products and reduced calcium absorption. Hormonal status disorders, insufficient exposure to sunlight result in vitamin D deficiency, etc. Underestimation of these factors creates the situation in which maintaining normal calcium level in blood is possible only due to the enhanced resorption of bone tissue that lead to OP as well as to bone fractures.
5. It is important to distinguish senile OP that is diagnosed in elderly people at the age of 70 and older. This is an involutive process caused by ageing process, decreased absorption of calcium in intestines, reduced synthesis of vitamin D, increase in number of osteoclasts (resorption cells), and inhibition of osteoblasts (skeleton forming growth cells). To diagnose primary involutive OP it is necessary to exclude diseases that cause secondary osteoporotic process. However, if the comorbidity index is high, it makes no sense to differentiate whether this is a secondary or involutive OP. The approach to the treatment of OP in patients at the age of 70 and over is almost the same.
6. And last but not least. The main and only condition of success in treatment and prevention of OP is the patient’s own persistent and significant effort. This condition is indispensable. Fortunately, the human body is so perfect that it can almost always improve its health. Only necessary efforts increase with ageing and deepening of diseases.

The objectives of the study were to explore age-related clinical status of a present-day patient with OP taking into account comorbidity and cognitive disorders, and to evaluate the possibility of replacing antiresorptive pharmaceuticals with anabolic support using supplements of the group “Osteomed”.

## MATERIALS AND METHODS:

The study was open, prospective and randomized. It was carried out in accordance with “Rules for conducting evaluation of clinical trials” (OST No.42 dated 12.29.1998) and Order No.103 dated 3.24.2000 “About conducting clinical trials”. The study was conducted from 2006 to 2017 on the base of “Center for Osteoporosis” under Penza Postgraduate Medical Institute. The comorbidity survey included 510 women at the age of 60-94 years. Inclusion criteria were: female sex, bone mineral density (BMD) less than  $-2.5$  CO, and symptoms of cognitive disorders. Exclusion criteria: endocrine diseases (diabetes mellitus); gastrointestinal pathologies (malabsorption syndrome, conditions after intestinal resection); rheumatoid arthritis. Determination of BMD was carried out by X-ray absorptiometry method. The survey included physical, clinical, and laboratory examinations of patients. Hormonal examination was carried out by immune chemiluminescence method on device Immulite 2000. Severity of OP was evaluated according to the classification of the WHO. Criteria of the effectiveness of the therapy were: ability of a pharmaceutical to increase BMD, to close or reduce in size cavity formations in bones, to increase muscle strength; reducing incidence of falls; absence of new bone fractures, enhancement of physical activity, decrease in incidence and severity of cognitive disorders (CD).

There were examined 510 patients, the most of whom were diagnosed with various diseases together with OP. In the study researchers paid special attention to the presence of cognitive disorders (CD) comorbid with OP since specialists in treatment of OP pay little attention to them. Russian ambulatory neurological and psychiatric practice shows that about 70% of elderly patients have CDs of various degree of severity – from decrease of their cognitive abilities to partial or complete loss of self-dependence. Occurrence of such disorders indicates a lesion of cerebral neurons<sup>[7,8]</sup>. Among cognitive disorders the most frequently were observed: progressing memory disorders, especially of recent events, to a lesser degree – of distant events; intellect decline; thinking disorders in form of difficulties with information assessment, abilities to summarize data and to draw conclusions; decreased concentration of attention when patients are difficult to maintain active mental activity; problems with expression of patient’s own thoughts or understanding someone else speech.

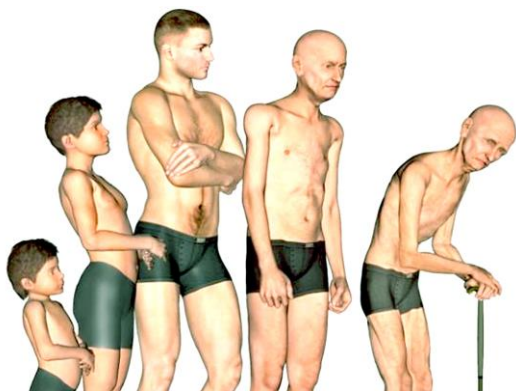


Figure 1. Dynamics of human life and death. World Congress on Osteoporosis 2017, Italy

In addition to cognitive disorders, the following problems were observed in patients:

- 1 Problems with oral health (in 100% of patients), chronic periodontitis and teeth loss;
- 2 Vitamin D deficiency (in 80% of examined patients) commonly caused by insufficient exposure to sunlight;
- 3 Syndrome of falls, hypokinesia (73%);
4. Deficiency of calcium in diet (57%) caused by insufficient consumption of food rich on calcium;
- 5 Gastrointestinal diseases impairing calcium absorption (64%);
- 6 Hormonal status disorders (69%) such as hypothyroidism, decreased androgen or estrogen levels, etc.

Age-related hormonal status disorders in elderly patients with OP were characterized by a whole range of symptoms – emotional, cognitive, sexual, metabolic disorders, and reduced stature and BMD. All these symptoms taken together reflect dynamics of human life. (Figure 1).

Of 510 examined, 68 patients with OP and comorbid CD were selected for the in-depth study of the treatment of OP. Depending on the pharmaceutical composition patients were divided into two comparison groups. Patients of the group I (35 women) received “Osteomed Forte” orally 2 tablets at the morning and before bedtime, three-month courses 3 times a year with a one month pause (1 tablet contained 250 mg of Ca citrate, 50 mg of drone brood, 150 IU of vitamin D3, and 0.5 mg of vitamin B6). Permission of the ethics committee and consent of patients are available.

In the group II (32 women) patients received one antiresorbent from the above cited group (Bonviva, Fosamax, Bivalos, Alendronate, and others) and calcium D3 Nycomed Forte containing per one tablet: 400 IU of vitamin D3 and 1250 mg of Ca carbonate (equivalent to 500 mg of calcium) 2 times a day with the same regimen

as in the group I. In patients of both groups were determined symptoms of cognitive disorders and their dynamics, BMD, sizes of cavity formations (using X-ray absorptiometry) before and after therapy.

Statistical processing of received data was performed using software package “Statistica 10.0” for Windows. There were determined mean values, mode, median, standard deviations (SDs), mean square error (MSE), standard error of the mean (SEM), and pattern of distribution. Reliability of the difference in mean values of indicators was calculated using Student’s t-distribution. Tabular data are in form of arithmetic mean (M) and value of standard error of the mean (m)  $M\pm m$ . Differences were considered statistically significant at  $p<0.05$ .

## RESULTS AND DISCUSSION:

10 months after the end of treatment patients of the group I (“Osteomed Forte”) had improvement in health status. The majority of patients in the group I showed reduction of complaints of neurological disorders. No one had deteriorations in memory and attention during the treatment. Patients had better sleep, lesser irritability compared to what was before treatment. A positive effect of OP treatment was noted in 27 patients ( $77\pm 6\%$ ): 19 patients ( $54\pm 8\%$ ) showed reducing of cavities and 10 patients ( $28\pm 7\%$ ) – closing of cavities.

Patients of the group II that received antiresorbents had much lower rates both in CD and in OP. The complaints were the same as before the treatment. Only 25% of patients showed positive dynamics in CD. In the group II 12 women ( $37\pm 8\%$ ) had improvement in OP compared to the group I ( $M\pm m=77\pm 6\%$ ),  $p<0.05$ .

Higher efficiency in OP treatment with “Osteomed Forte” can be explained by content of drone hormones as substrate for synthesis of endogenous hormones by the body. It can be confirmed by the analysis of hormonal parameters that had shown the following total testosterone levels in women in both groups of patients before treatment: Group I –  $1.1\pm 0.4$  nmol/l; Group II –  $1.2\pm 0.5$  nmol/l ( $p>0.05$ ). After 10 months of the treatment with “Osteomed Forte” the patients of the group I had increase of blood serum testosterone levels from  $1.1\pm 0.4$  to  $2.3\pm 0.6$  nmol/l ( $p<0.05$ ). In the group II (antiresorbents) positive changes in testosterone levels were not observed.

Figure 2 shows an example of closing cavities in a patient (woman, 73 years old) who was administered with “Osteomed Forte”. Before administration of the supplement, osteometry revealed cavity formations (Figure 2a). After 10 months of the treatment cavity formations closed (Figure 2b).



Figure 2. Patient E, female, 73 years old, X-ray densitometry results: a – cavity formations before treatment; b – After 10 months of the treatment: cavities are absent

Based on the above it can be noted that “Osteomed Forte” is more contributive to the normalization of androgen level in women in comparison with antiresorbents. It results in improvement of general health status, reduction of complaints, increase of BMD, reducing or closing cavity formations in trabecular sections of bones [9, 10]. It was also noted positive effect on nervous system function. Mechanism of action of “Osteomed Forte” on central nervous system is not yet investigated. We believe that it is due to the improvement of hormonal levels of all androgens. Commonly, women with senile OP have significant decrease in the levels of all androgens. Therefore, we suggested using drone brood as donor of sex hormones [2, 7, 8]. Drone brood as substrate enhances production of endogenous sex hormones by the body that not only improves BMD but also significantly reduces cognitive disorders. It can be confirmed by the fact that women having OP after the treatment with “Osteomed Forte” have total testosterone serum levels increased from  $1.1 \pm 0.4$  to  $2.3 \pm 0.6$  nmol/l ( $p < 0.05$ ). Patients of the group II receiving antiresorbents had no positive changes in testosterone levels as well as in treatment of CDs.

Deficiency of sex hormones predisposes morphologic changes in bones associated with bone remodeling processes and cavity formations caused by enhanced bone resorption. Clinically it is manifested in systemic disorganization of connective tissue with osteoporosis and the risk of bone fractures, disorders of nervous and endocrine systems that are manifested likewise in form of cognitive disorders. Thus, it is important to diagnose them and to start treatment as soon as possible in order to stop these processes. Otherwise CDs will progress to dementia that is difficult to treat.

Based on the above studies, we believe that osteoporosis – even senile – can be treated. It is possible not only to stop osteoporosis but also to reduce its severity as well as reduce the risks of fractures and cognitive disorders. Unfortunately, broad medical audience has yet insufficient knowledge in this problem. For this reason, patients often fail to obtain an adequate help in due time.

## CONCLUSION:

- 1 In modern therapy of OP it is important to use new pathogenetic approaches aimed at elimination of imbalance in relationship osteoclast – osteoblast using anabolic support of all bone cells. “Osteomed Forte” complies these requirements.
- 2 It is necessary to use supplements of the group “Osteomed” taking into account BMD and severity degree of OP. “Osteomed Forte” is prescribed in severe cases. “Osteovit D3” is more preferable for deposition of calcium salts in soft tissues and blood vessels.
- 3 It is also important early diagnostics of OP with CD. If treatment doesn’t start on time, consequences will negatively change the quality of life of a patient. The use of supplements of the “Osteomed” group allows reduce incidence of CDs or their clinical manifestations. This problem requires further studies.

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