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The role of hormonal therapy in osteoporosis

Terapia hormonalna w osteoporozie

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Abstract

In developed societies, the post-menopausal period covers approximately one third of a woman's life. The deficit of oestrogens observed during the post-menopausal period significantly affects the course of many metabolic processes, causing a number of diseases and in consequence diminishing quality of life. Among others, bones belong to oestrogen-dependent tissues. The deficit of the protective influence of oestrogens compromises the dynamic balance of the bone transformation process towards resorption, thus reducing bone mass and quality, while increasing the risk of low-energy fractures. In recent years, differing views on the application of oestrogen/gestagen therapy have reached the level of controversy. The results of numerous clinical studies are far from unequivocal, with the whole subject one of heated debate. It has been confirmed that hormonal therapy prevents bone quality deterioration, while opening a protective umbrella around the bone, reducing the risk of osteoporotic fractures. A rational approach to weighing possible advantages against possible risks and a thorough evaluation of a patient's health condition allows for optimal therapy selection.
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Key words: *osteoporosis, hormone replacement therapy, benefits, risk factors*

Streszczenie

W społeczeństwach rozwiniętych na okres po menopauzie przypada 1/3 długości życia kobiety. Występujący w tym czasie deficyt estrogenów istotnie wpływa na przebieg wielu procesów metabolicznych przyczyniając się do rozwoju chorób, a w konsekwencji pogorszenia jakości życia. Do tkanek estrogenozależnych należą między innymi kości. Brak ochronnego wpływu estrogenów prowadzi do przesunięcia dynamicznej równowagi przemian kostnych w kierunku resorpcji, przez co zmniejszeniu ulega masa kostna, pogorsza się jej jakość i zwiększa ryzyko niskoenergetycznych złamań. W ostatnich latach poglądy na temat stosowania estrogenowo-gestagennej terapii hormonalnej stały się bardzo kontrowersyjne. Wyniki licznych badań klinicznych nie są jednoznaczne, a argumenty zarówno za, jak i przeciw często podyktowane emocjami. Potwierdzono, że terapia hormonalna zapobiega pogarszaniu jakości kości oraz wpływa ochronnie na kość zmniejszając ryzyko złamań osteoporotycznych. Racjonalna analiza korzyści w stosunku do ryzyka oraz wnikliwa ocena stanu zdrowia pacjentek umożliwia optymalny wybór terapii. Indywidualizacja w doborze leków zmniejszających ryzyko złamań pozwala na skorzystanie z dostępnych dobrodziejstw terapii hormonalnej z równoczesnym zachowaniem jej bezpieczeństwa.
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Słowa kluczowe: *osteoporoza, terapia hormonalna, korzyści, zagrożenia*

Introduction

Climacterium is the time period between the end of the reproductive period and the onset of ageing. Menopause, when women cease to menstruate, is, in general, observed around the age of 50 (in Poland, 51.2) [1]. Afterwards, certain changes occur in a woman's body associated with the extinction of ovarian functions, which terminates the secretion of sex hormones. In consequence, the concentration of oestrogens falls very quickly, especially of 17 beta estradiol and estriol. The main oestrogen is oestrone, which is further produced by means of the presence of aromatase enzyme in adipose tissue. Hormonal changes are at the base of many adverse symptoms, such as vasomotor symptoms (hot flushes and sudden facial flashes), arterial blood pressure variations, depression and insomnia. Metabolic changes concern, among others, the metabolism of carbohydrates and lipids. Hyperinsulinism is more often observed with abnormal glucose tolerance, revealed in the mechanism of insulin resistance. Lipid disorders consist of an increased cholesterol level, especially its LDL fraction, increased synthesis of lipoprotein fraction (Lp-a) and triglycerides with a parallel reduction of HDL fraction, A1 apolipoprotein and the synthesis of LDL receptors. Skin and mucosa quality deterioration is observed (vaginal atrophy) along with a clear libido drop. Bone metabolism becomes disturbed, some-

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thing manifested by an increased pool of cell lines, which mature towards osteoclasts, with a parallel increase in their activity. These processes, when juxtaposed with reduced intensity of maturation and survival of osteoblasts, shift the metabolic balance towards increased bone resorption. These changes in bone metabolism rate, with a consequent loss of bone mass (reduced bone mineral density) and its compromised quality, often lead to the development of osteoporosis.

The number of women of peri- and post-menopausal age exceeds 700 million in the world. The continuous growth of ageing, observed in developed societies, and the greater mortality of men, unequivocally demonstrate that the health problems of women will only grow, with all their economic and social consequences. In Poland, there are approximately 6 million women of post-menopausal age, most of whom are professionally active. It should be noted that, taking into account the average lifespan of women, the post-menopausal period occupies one third of their life.

The delay of ageing and lifespan extension have for many years been the subject of intensive research. Hormonal replacement (HR) for women who have experienced the menopause seemed for a long time to be something of a panacea for all the ailments characteristic of that period of life, with the initial results of HR very promising. After HR administration, menopausal symptoms regressed, the comfort of life improved and clinical observations were very optimistic. The delayed (by one decade) occurrence of ischaemic heart disease and hypertension in women as against men was explained by the effects of the hormonal environment. Knowledge of the protective effects of oestrogens on circulation, observed during the reproductive period, raised hopes for a similar effect of hormonal replacement after menopause. The protective effects of oestrogens were observed on vascular walls, endothelial functions, lipid profile, the metabolism of carbohydrates, and on the system of blood clotting and fibrinolysis. Following the theories as to the role of oestrogens in metabolism control, it was expected that HR administration could stimulate the synthesis of diastolic factors in the vascular wall (an increased release of NO and prostacyclin), suppression of hyperplasia of the smooth muscular coat in coronary arteries and calcium channel blocking. In many studies of that time, the favourable effects of HR were observed, regarding diseases of the cardiovascular system, including prevention of atherosclerosis and vasospasms, reduction of free radicals, inhibition of inflammatory processes, RR normalisation and the effectiveness of primary atherosclerosis prophylactics after the administration of oestrogens alone [2–4].

It was only the HERS (Heart and Estrogen/progestin Replacement Study), of 2,763 women at various ages after the menopause, which provided data on HR-associated risks. It should be emphasised that the group of examined women was fairly differentiated, including overweight women and those with benign breast changes in their history, and some participants were active smokers. Women as much as ten years after the menopause were also included. The HERS demonstrated an increased risk of HR-related thromboembolic complications. According to the obtained results, this risk is higher during the first year of hormonal replacement therapy (HRT), when higher oestrogen doses and combined oestrogen/gestagen therapy are applied.

Those observations triggered a certain amount of caution and HRT-related threats were more frequently identified. HR-related fears increased much more after the publication of the results of the Women's Health Initiative Study (WHI), where the oestrogen/gestagen arm had to be terminated before the scheduled end of the study because of an increased incidence of cardiological episodes. Additional arguments against HR have emerged from the studies, in which an increased risk of carcinoma of the breast, ovaries or gall bladder was observed in women on chronic (> 5 years) oestrogen-gestagen replacement therapy. Data from the years 2002––2008 demonstrated increased risks among HR-using women for the following diseases and in the following order: ischaemic heart disease, thromboembolic disease, Alzheimer's disease and cerebral strokes. Subsequent studies into HR's effects on diseases of the cardiovascular system (WAVE, CARS, PHASE, ERA, ESPRIT) have not confirmed the positive results of earlier observations.

The results of the above-mentioned analyses did, in fact, strongly question the usefulness and sense of HRT at all. Taking into consideration all the obtained data, subsequent teams of experts withdrew their recommendations for the use of HRT, and the FDA has added oestrogens to its list of carcinogens. Only the recommendation to administer HR to alleviate early menopausal symptoms was maintained, albeit with the caveats that the therapy duration should be "the shortest" and the hormonal doses "the smallest" possible [5].

However, new doubts have appeared. HERS did demonstrate an increased incidence of coronary episodes during the first year of HR therapy, but that result could have also been associated with the characteristic features of the studied group. Hormonal therapy was administered in women with earlier diagnosed ischaemic heart disease (HR as a secondary prophylactic attempt), with inflammations of deep veins in their history and, in general, very late (as much as 10 years) after menopause.

On the other hand, it has been proven that HR, as a primary therapy, especially when subcutaneously administered, exerts a positive effect and does not increase

the risk of ischaemic heart disease. An important point in the discussion on HR values was when the chief researcher of the WHI published the meaningful title: "NIH and WHI time for a *mea culpa*….", indicating that the results of the study should be approached with caution, as their earlier interpretation seemed too simplified. Certain objections may be raised to the selection of patients in the study group, such as large age differences, but also to the time of HR introduction, the oestrogen doses, higher than those recommended today, and to the combined use of the medroxyprogesterone derivative which is at present contraindicated [6, 7].

Among 26,000 examined women, in whom an increased risk of myocardial infarction was diagnosed, neither was any necessity for cardiological intervention demonstrated (aortic-coronary bridging, coronary angioplasty) nor an increased death threat. Nevertheless, the WHI study was completed in time (still before the scheduled deadline). Simultaneously, regarding the continued and finished study, no increased incidence of either myocardial infarction or breast cancer was found in the group of women treated with oestrogens alone (patients after hysterectomy).

A review of the studies into an increased risk of cerebral stroke in women on HRT indicates that the effect is not observed in women < 60 [8]. In turn, another study, the report from which has recently been published, has demonstrated that women using an oral HRT gained an advantage in terms of reduced total risk of colon carcinoma [9].

The use of hormonal therapy (HR) raises many emotions. The arguments of both proponents and opponents often lack substance, being dictated mainly by those emotions. The negative effects of HR can be ascribed to several factors. The doses of oestrogen used in the past were high, the added gestagens were derived from the medroxyprogesterone group, the time point of therapy onset was too distant from menopause, and the participating patients had many other conditions which should have excluded them from therapy, e.g. a positive history of thrombotic phlebitis or breast pathology.

A rational consideration of all the pros and cons and an individual approach to each patient allows for an optimal selection of therapy, providing the available advantages of HR with simultaneous safety in its application. New perspectives are opening for studies in the field of basic sciences. Already, molecular analysis allows the identification of the women likely to obtain more advantages from HR and, conversely, those put at higher risk by its use [10].

Building on actual knowledge, the greatest therapeutic benefits may be observed in those women in whom hormonal therapy is initiated early in the perimenopausal period, taking into account the higher sensitivity of oestrogen receptors. That period coincides with the time when early menopausal symptoms occur. The favourable effect on the lipid profile prevails in that time over the increased thromboembolic risk. In younger age groups (50–59 years), hormonal therapy decreases the risk of ischaemic heart disease and reduces general mortality. In systemic hormonal therapy, prescribed in patients after hysterectomy, it is recommended to use only 17β-estradiol-containing preparations. In women with a preserved uterus, the addition of a well-selected progestagen, derived from the nortestosterone group, is advised.

An oestrogen/progestagen low-dose therapy is recommended, while oestrogen therapy alone should be administered to women after hysterectomy.

At present, the primary indications for the introduction of hormonal therapy include the need for life quality improvement after menopause. Hormonal therapy is recommended in cases of moderate and enhanced early menopausal symptoms and related sleep disorders. Hormonal therapy is not recommended in women aged over 65. Nonetheless, hormonal therapy, even if introduced at a later stage, exerts anti-fracture effects [11].

The conclusions, based on an evaluation of 30 meta-analyses, involving 26,708 women in total, and the data collected from 19 randomised studies between 1996 and 2008 involving 16,000 women, may confirm such a strategy of management. HR reduces mortality in the group of younger women (< 60) and provides positive effects, not only in terms of lifespan but also quality of life at particular age levels. [12–16].

Absolute contraindications for the use of oestrogen/ /gestagen therapy include breast cancer and endometrial cancer, hepatic insufficiency and active thromboembolic disease. Relative contraindications include endometrial and breast cancer in family history, unexplained bleeding episodes from the genital tract and thromboembolic episodes in history.

The most serious adverse effects of hormonal therapy include the increased risk of thromboembolic complications. This risk is lowered with transcutaneous administration and low-dose therapy. It should also be remembered that thromboembolic complications are not only associated with HR but are also observed in oral contraception and with the use of drugs from the specific oestrogen receptor modulators (SERM). Both the hormonal therapy and SERM agents improve bone mass volume and decrease the risk of low-energy fractures in the course of perimenopausal osteoporosis [17].

Oestrogen deficit increases bone metabolism and leads to an increased number of osteoclasts and greater bone mass loss. Oestrogens inhibit the process of bone resorption, thus counteracting its loss. The mechanism

of oestrogen activity consists in suppression of the particular stages of osteoclastogenesis (recruitment, differentiation, fusion and activation). Oestrogens decrease also the production of proresorption cytokines. They shift the metabolic balance between bone synthesis and resorption in the anabolic direction, affecting the apoptosis of osteoclasts and, in mature osteoblasts, they inhibit the production of lisosomal enzymes. The protective effect on bone is also mediated by OPG, through an oestrogen-induced increased expression of the gene for osteoprotegerin.

Bone protection against osteoporotic fractures reduces the risk of physical disability and premature death, thus it has a positive impact both in the medical and the economic sense. Among women on HR therapy, cost savings have been observed regarding sick-leave periods at work, treatment, rehabilitation and care of others [18].

Notwithstanding all these facts, hormonal therapy is not the therapy of choice in the management of postmenopausal osteoporosis. It mainly results from the availability of other groups of medications with anti-fracture efficacy and a good safety profile. However, a new discussion should, at least, be initiated as to whether, in the light of new data, the earlier accepted approach to oestrogen therapy should be re-evaluated. Perhaps posing the question as to which women will achieve real benefit from HR would be more appropriate and rational than asking why we do not propose the therapy.

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