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PHYTOESTROGENS FROM LEGUME SEEDS AND THEIR ROLE IN THE PREVENTION OF OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN®

Fitoestrogeny z nasion roślin strączkowych i ich rola w zapobieganiu osteoporozie u kobiet w wieku postmenopauzalnym®

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Menopause is associated with numerous changes and disturbances in a woman's body that reduce her quality of life. They include, among others, disturbances in bone metabolism and with the consequence developing osteopenia and osteoporosis as a result of estrogen deficiency in the body. Legume seeds and their products are a rich source of phytochemicals which, due to their chemical structure similar to estrogens, are estrogenic indicators. The article presents the current state of knowledge on their impact on bone metabolism. Its knowledge is important in planning the nutrition of perimenopausal women due to the knowledge of the risk of developing osteoporosis in this population group.

Key words: phytoestrogens, legume seeds, soybean, menopause, osteoporosis, isoflavones.

Menopauza wiąże się z licznymi zmianami i zaburzeniami w organizmie kobiety, które obniżają jakość jej życia. Należą do nich m.in. zaburzenia metabolizmu kostnego i w konsekwencji rozwijająca się osteopenia i osteoporoza będące skutkiem niedoboru estrogenów w organizmie. Nasiona roślin strączkowych i produkty z nich otrzymywane są bogatym źródłem fitozwiązków, w tym o budowie chemicznej podobnej do estrogenów, wykazujących właściwości estrogenne. W artykule przedstawiono aktualny stan wiedzy na temat ich wpływu na metabolizm kostny. Jego znajomość jest istotna w planowaniu żywienia kobiet w wieku okołomenopauzalnym ze względu na możliwość zmniejszenia ryzyka rozwoju osteoporozy w tej grupie populacyjnej.

Słowa kluczowe: fitoestrogeny, nasiona roślin strączkowych, soja, menopauza, osteoporoza, izoflawony.

INTRODUCTION

Menopause is the term for the last menstrual bleeding, after which menstruation doesn't occur during the next 12 months and no pathological reasons are found to cause this condition. Menopausal period induces significant changes in female organism which trigger many ailments and disorders, including climacteric symptoms, connective tissue lesions, cardiovascular diseases, postmenopausal osteopenia and osteoporosis. All of them lower women's quality of life. Therefore, women in the perimenopausal period should be given a special care by medical professionals, which aims to provide them with access to education about the physiology of the changes occurring in their bodies, the effects of these changes and ways to prevent them and/or minimize their severity. [31].

Osteoporosis is a skeletal disease characterized by an increased risk of bone fractures as a result of an imbalance in bone metabolism with a predominance of resorption over bone formation. In Poland, the problem of osteoporotic fracture applies to nearly 2 million patients over 50 years

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of age. Osteoporotic fracture is associated with huge pain and suffering, it can lead to disability and even death – this is especially true for proximal femur fractures. In order to increase the effectiveness of the fight against osteoporosis, not only efficient diagnosis and treatment are necessary, but above all – effective prevention. [9].

The risk factors for osteoporosis involve: low bone mineral mass, reduction in estrogens production (menopause, including premature and artificial), other concomitant diseases which impair bone metabolism (for example hyperthyroidism, hypogonadism, primary and secondary hyperparathyroidism, anorexia), and applied drugs (for example corticosteroids, proton pump inhibitors, oral anticoagulants, thyroid hormones in suppressive doses). Among them, the primary risk factor for osteoporosis is low bone mineral mass. It depends on both non-modifiable factors (ethnicity, sex, age, genetic factors and familial predisposition) as well as modifiable – nutritional and related to physical activity. Nutritional factors can be divided into two groups – increasing bone mass: 1. protein, calcium, magnesium, zinc, vitamin D, K and C intake in accordance with the demand for these nutrients; 2. appropriate proportions between calcium and phosphorus and 3. presence of phytoestrogens and omega-3 fatty acids in the diet; and reducing bone mass: 1. high calorie diet, excess of sodium in the diet, caffeine, alcohol; 2. smoking tobacco and 3. underweight (defined as body mass index, BMI <18.5). [9, 13, 19].

Nutritional factors, specifically the significance of phytoestrogens contained in processed legume seed products, as modifiable factors, constitute an essential field of the preventive measures and therefore will be discussed in detail in the following article.

ESTROGEN REGULATION OF BONE FUNCTION

Bones as an active metabolic tissue, undergo two opposing processes of the permanent internal reconstruction: formation of the bone marrow through osteoblasts action and resorption of the bone marrow through osteoclasts action. Osteoclasts remove (resorb) bone by acidification and proteolytic digestion, while osteoblasts secrete osteoid (organic matrix of bone) into the resorption cavity. The amount of resorbed bone should be balanced by equal amount of formed bone. The dynamics of this bone remodelling process subjects to hormones regulation, including parathyroid hormone, growth hormone, estrogens, androgens, thyroid hormones, glucocorticoids, and is aiming to maintain a permanent mass on the adequate level of resistance and quality [22].

Estrogens have an important impact on bone physiology. They promote the acquisition of bone mass during puberty and are required for the growth and maintenance of the adult skeleton by slowing the rate of bone remodelling and maintaining a balance between resorption and formation. They primarily are inhibitors of bone resorption that decreases both osteoclast numbers and activity, rather than the enhancers of bone formation. As in other tissues, the effects of estrogens on bone are exerted upon binding with high affinity to the estrogen receptor (ER) alpha and beta. Both ERs have been detected in bone cells, including osteoblasts and osteoclast progenitors and their descendants, as well as B lymphocytes. Estrogens inhibit osteoclast activity and increase osteoclast apoptosis through three different mechanisms. First – through direct signalling, and second – *via* osteoblast secretion of OPG and RANK ligand. Bone resorption and formation are coupled by local factors, and one of the key regulators is the RANK/RANK-ligand/osteoprotegerin (RANK/RANKL/OPG) system. RANK is a receptor expressed on the cell membrane of osteoclast precursors and mature osteoclasts, and its activation stimulates osteoclast differentiation and activity. RANK ligand is secreted by stromal cells or osteoblasts and is the major paracrine factor in activating the bone remodelling unit. OPG is also secreted by osteoblasts and is a soluble decoy receptor that binds to the RANK-ligand and blocks the RANK-ligand/RANK interaction. Therefore OPG is very potent inhibitor of osteoclastogenesis and bone resorption *in vitro* and *in vivo*. The secretion of RANK ligand and OPG is regulated by hormones, including estrogens. These hormones up-regulate OPG expression in osteoblasts mainly through the ERs [17, 39]. Third – indirect – mechanism includes decreased secretion of proresorptive cytokines such as interleukin-1 (IL-1) and 6 (IL-6) and tumour necrosis factor-alpha (TNF-alpha) by bone marrow cells. These cytokines were found to be extremely potent stimulators of bone resorption. Binding of different cytokines to their receptors in osteoblasts causes release of soluble factors that act directly on osteoclasts to modulate their recruitment or activity. Estrogens can inhibit the release of osteoclast stimulatory factors or enhance the release of osteoclast inhibitory factors. They also increase osteoblast differentiation and bone formation, at least partly through inhibition of sclerostin secretion by osteocytes. Sclerostin binding to its receptors on the cell surface of osteoblasts induce a downstream cascade of intracellular signalling with the ultimate effect of inhibiting osteoblastic bone formation. [2, 17].

In premenopausal women 95% of circulating estrogens is secreted by the ovaries, and the remainder is synthesised by extra-gonadal conversion of other sex steroids. In postmenopausal women hormonal activity of the ovaries is minimal and therefore nearly all the circulating estrogens are derived from extra-gonadal conversion of adrenal steroids (by aromatase in fat and other tissues). A decline of estrogens levels in females at menopause is the primary cause of perimenopausal symptoms which significantly lower women's quality of life, among others loss of bone mass and strength and contributes to the development of osteoporosis, one of the most common metabolic disorders of old age. In postmenopausal women, the rate of bone turnover increases dramatically and remains elevated for up to 40 years after cessation of ovarian function, leading to continuous, progressive bone loss. The basis for the increased bone turnover is thought to be due in part to a shortening of the lifespan of osteoblasts and a prolongation of the lifespan of osteoclasts. Moreover, estrogens deficiency may contribute to the development of osteoporosis by decreasing the sensitivity of bone to mechanical loading [2, 22, 39].

PHYTOESTROGENS

Phytoestrogens are non-steroidal compounds of plant origin, which, due to their similarity in structure to natural and synthetic estrogens have a number of estrogen-like effects.

Phytoestrogens have affinity for ERs, therefore they can act as agonists or antagonists of these receptors, competing with estrogens for a binding sites. Phytoestrogens affinity for ERs, compared to estradiol (endogenous estrogen), indicates their less biological activity. However, their effect may be compensated by their amount provided in the diet [16, 18].

Phytoestrogens are divided into various classes of compounds, including flavonoids and non-flavonoids. Among flavonoids two groups are distinguished: isoflavones and coumestans, whereas among non-flavonoids lignans and resorcinol derivatives are distinguished. The most significant group of phytoestrogens and the best studied in terms of their beneficial effects on the human body, including their modulating effect on the ERs, are isoflavonoids. All of the phytoestrogens occur in plants usually in the form of inactive beta-D-glycosides or in a precursor form. Their active forms with a chemical structure similar to estrogens are formed in the digestive tract as a result of complex enzymatic and metabolic transformations. Hydrolysis of glycosides in the human digestive tract occurs under the influence of gastric hydrochloric, intestinal and bacterial beta-glucosidases and beta-glucosidases contained in food. As a result of this process, bioactive forms aglycones are formed which are absorbed in the small intestine. Their further metabolism leads to the formation of active metabolites which have been found in blood, urine, bile, feces, semen, saliva and milk, suggesting the possibility of their effects on the functioning of many cells and organs. The size and range of phytoestrogens metabolism is individual, variable and depends primarily on the amount of absorption of individual phytoestrogens and their metabolites, the qualitative and quantitative composition of the bacterial flora of the gastrointestinal tract and the type of applied diet [7, 11, 18, 29].

Phytoestrogens are found in many plants and their processing products. The richest source of phytoestrogens are soybeans, its processing products and, to a lesser extent, seeds of other legumes (lentils, beans, broad beans, peas, chickpeas), but also their content was detected in fruits and vegetables, and in nuts. Phytoestrogens contained in food products are compounds that are moderately sensitive to the culinary processing techniques used. Soaking the seeds has been shown to reduce the content of polyphenols, including flavonoids, in legume seeds: lentils are the most sensitive and chickpeas the least. Traditional cooking of lentils causes a significant loss of polyphenols (even by more than 50%) and they are comparable to steaming. However, in the case of other legume steaming, it causes significantly lower (even several times) polyphenol losses. Both soaking and cooking are basic and the most popular techniques for culinary processing of legume seeds, it is worth paying attention to the fact that these processes are carried out correctly. No significant changes were shown in soybeans total daidzein/genistein and their glycosides daidzin/genistin content during soaking, while free daidzein and genistein content increased significantly during this process. This can be due to their release from glucosides and/or ester glucosides. In this study the only procedure resulting in the decrease of total phytoestrogens content was boiling [3, 24, 33].

Legume seeds are valued worldwide as an inexpensive meat alternative and are considered the second most important food source after cereals. In addition to their nutritional superiority, legumes have also been ascribed economical, cultural, physiological and medicinal roles owing to their possession of beneficial bioactive compounds. The consumption of legumes has also been reported to be associated with numerous beneficial health attributes. The nutritional demand of legumes is increasing worldwide because of increased consumer awareness of their nutritional and health benefits. Furthermore, recent years have seen more people substituting animal protein with vegetable protein; thus, further increasing the demand for legumes as they are the major source of plant proteins. To meet this demand, there is a need to educate consumers on the nutritional value of legumes. As it was mentioned, soy phytoestrogens are receiving increasing attention for their health benefits related to their consumption. They are also considered natural estrogens with a high safety profile. Soy phytoestrogens with the strongest estrogenic activity because of structural similarity to 17 beta-estradiol are genistein, daidzein and glycitein, which belong to isoflavones [27].

Over the years, there has been a significant decrease in the consumption of dry legume seeds in Polish households. The likely cause of the limited consumption of legumes is probably the necessity of long-term culinary processing of seeds, lack of skills in preparing dishes with their use and the content of anti-nutritional substances. Anti-nutritional substances include: protease and amylase inhibitors, haemagglutinins, phytates, saponins, phenolic compounds, goitrogens, cyanogenic glycosides, allergens, and others. Moreover, legume seed oligosaccharides of the raffinose family do not undergo hydrolysis in the human digestive tract (due to the lack of the α-galactosidase enzyme). High consumption of these sugars with food often leads to an excess of gas production in the gut causing flatulence, abdominal pain and diarrhea. However, although the oligosaccharides in legumes are viewed negatively, their beneficial attributes outweigh their negative properties. Oligosaccharides are prebiotic in nature and therefore, promote the growth of the probiotics, which play a major role in the maintenance of a healthy colon. Therefore, it is worth knowing and using appropriate culinary techniques to reduce their content and avoid or minimize side effects. The process of soaking in hot water (called as "hot soaking") and traditional cooking cause the greatest changes in the content of these sugars. Most of anti-nutrients mentioned above are heat labile and since legumes are consumed after cooking, they do not pose a health hazard. Legumes can also be 'detoxified' by dehulling, soaking, boiling, steaming, sprouting, roasting and fermentation prior to processing. Research has shown that most of these non-nutrients are phytochemicals with antioxidant properties which play a role in the prevention of some cancers, heart diseases, osteoporosis and other chronic degenerative diseases [12, 14, 27, 40].

EFFECTS OF PHYTOESTROGENS ON MENOPAUSE DISORDERS AND ON BONES

Many of perimenopausal women, as recommended, decide to use hormone replacement therapy (HRT) to minimize symptoms of menopause, such as bleeding disorders, vasomotor symptoms, vaginal atrophy, cardiovascular and osteoporosis prevention. According to the statistical data, a number of women receiving hormone replacement therapy is still relatively small. Moreover, most women discontinue therapy after the first year of application because of irregular vaginal bleeding, mastalgia, nausea, migraine headaches, weight gain, water retention and carcinophobia. All this reasons mean that some women approach HRT with caution and do not use it or look for natural forms of therapy. In addition, there are number of women for whom HRT is relatively or absolutely contraindicated regardless of personal preferences. For this reason, search and development of the alternative forms of therapy that may have benefits as with HRT without side effects, and without contraindications is of wide interest. An alternative treatment route, using plant extracts containing polyphenolic compounds with estrogenic activity – phytoestrogens is becoming more and more popular. Due to its hormone-like properties, however, there is a concern that phytoestrogens will cause undesirable side effects related to their affinity for ERs. Many studies have been carried out to assess the efficacy and safety of compounds, mainly based on an extract of soy-derived phytoestrogens. On their basis, it was found that during the use of phytoestrogens, only the incidence of gastrointestinal side effects, i.e. abdominal pain, as well as subtle muscle pain and slight sleepiness, was higher than in the control group. There was also no relationship between the duration of phytoestrogens treatment and the frequency of side effects. On the contrary, side effects were seen less frequently in women taking phytoestrogens for long periods. These observations indicate that there is no phenomenon of phytoestrogen doses accumulation. The research carried out so far also do not indicate serious undesirable side effects of phytoestrogen treatment, such as in women using HRT (e.g. thrombosis, heart attack, stroke and breast cancer). Therefore phytoestrogens should be proposed to women looking for a safe treatment alternative to the HRT [28, 42].

In recent years, many studies have been conducted on the importance of phytoestrogens in the prevention and treatment of osteoporosis. It was documented, that isoflavones – the main class of the phytoestrogens – have the potential to maintain bone health and delay or prevent osteoporosis but they can provide health benefits only when consumed at sufficient levels, conversely, they have been categorized as endocrine disruptors that cause environmental problems and deleterious effects on reproductive systems. It is important to say that phytoestrogens content in their dietary sources and hence their intake can reach the amount which enables them to achieve effective concentrations in bodily fluids. Isoflavones exert biphasic dose-dependent effects on osteoblasts and osteoprogenitor cells: stimulating osteogenesis at low concentrations and inhibiting osteogenesis at high concentrations [6]. Based on the study of Lousuebsakul-Matthews et al. the frequency of consumption of legumes should be once daily or more to significantly influence bone metabolism (to reduce the risk of hip fracture just in this study) [25].

The greatest interest and the best and widest known phytoestrogens are isoflavones, and among them glycosides: genistin and daidzin and their aglycone forms: genistein and daidzein, respectively. Isoflavones are primarily found in the fabaceae family, and among them the richest source in human diet is soy and its derivatives. Hence most of the animal and human in vitro, in vivo and intervention research are based on the effects of soybeans and their products.

Mechanism of action

Phytoestrogens influence the bone metabolism and functioning but the exact and full mechanism of action is still not completely understood. Phytoestrogens may affect cellular function because of their low molecular weight so they can pass through cell membranes and interact with receptors and enzymes. They are best known for their ability to mimic the activity of estrogens. However, they have a number of other biological effects, independent of those of estrogens. The most widely studied in terms of their mechanism of action are isoflavones, a class of phytoestrogens involving daidzein and its metabolite S-equol, and genistein.

Phytoestrogens bind to estrogen receptors (ERs) and have estrogen-like activity. Whether the induced response will be anti-estrogenic or estrogenic depends, among others on the type of ER (alpha or beta) and its distribution in tissues, as well as the method of phytoestrogens administering, its concentration and to a lesser extent, time of exposure of cells to phytoestrogens. It is important to mention that ER-mediated action has focused on the preferential binding of phytoestrogens to ER beta than ER alpha, which acts as a dominant-negative regulator of estrogens signalling. ER beta expression is increased during bone mineralization and the high affinity of isoflavone genistein towards ER beta could make its action efficient at physiological levels. Phytoestrogens may also stimulate transcription of ER alpha and beta in many different tissues, including bone tissue [6].

It was also shown that phytoestrogens may act *via* mechanisms unrelated to ERs. These non-ERs molecular mechanisms are based on enzyme-inhibiting effects: some phytoestrogens, like genistein, inhibit tyrosine kinase, thus phytoestrogens act as intracellular signal transfer modulators and are able to modulate activity of other substances affecting bone tissue, including hormones insulin, or insulin-like growth factor 1 (IGF-1). Other enzymes inhibited by phytoestrogens are topoisomerases I and II, protein histidine kinase, and mitogen-activated protein kinases (MAPKs), which are crucial for bone cellular signal transduction and functions, especially for bone resorption. It was also shown that peroxisome proliferator-activated receptors (PPARs) are additional molecular targets of phytoestrogens. PPARs are ligand-activated transcription factors, suggesting that PPARs are crucial transcriptional targets of phytoestrogens. PPARs are present in bone tissue - they have been found in bone marrow mesenchymal cells, osteoprogenitor cells and osteoblastic cells, and they are involved in the regulation of bone formation and bone resorption. It was shown that phytoestrogens can dose dependently activate PPARs and induce differential effects on bone. As a result, the balance between concurrently activated transcriptional factors like ERs and PPARs determines the dose-dependent biological effects of phytoestrogens in the target tissues, including bone tissue. It also suggests that phytoestrogens can act as selective nuclear receptor modulators [8, 32].

Phytoestrogens stimulate the synthesis of sex hormone binding globulin and are the inhibitors of several enzymes involved in sex hormones metabolism, including 5 alpha reductase, 17 beta hydroxysteroid dehydrogenase and human P450 aromatase system. In this way phytoestrogens modulate the amount of biologically active hormones circulating in the blood which could affect many tissues, including bone [15, 23].

Phytoestrogens may also influence bone function and structure through indirect mechanisms. Namely, *in vitro* studies showed that isoflavones like genistein and daidzein may modulate intestinal and colonic calcium transport. Moreover, they can increase production of an active form of vitamin D – 1,25(OH)$_2$D – through stimulation of 1 alpha OHase transcription (an enzyme activating vitamin D on the last stage of this activation). In these ways phytoestrogens modulate calcium balance and bone structure and function [30].

A considerable number of studies have been published that have sought to investigate the effect of phytoestrogens on bone metabolism and bone loss in both postmenopausal women and in animal models of postmenopausal bone loss.

Epidemiological studies generally suggest a positive association between soy consumption and bone mineral density (BMD). There is strong epidemiological evidence that Asian women have a much lower incidence of the above diseases compared with western women. Interestingly, emigrant Asian women who adopt a western diet lose their protection. Epidemiological studies have demonstrated that Asian populations with a particularly soy-rich diet have a low incidence of postmenopausal fractures and high BMD. The Study of Women's Health Across the Nation (SWAN) – a multi-site longitudinal, epidemiologic study demonstrated that BMD was positively correlated with genistein intake in premenopausal Japanese women who had a higher intake of genistein compared with African-American, Caucasian and even Chinese women, confirming the importance of the amount ingested in yielding better BMD values at the spinal and femoral neck level. These epidemiological observations have given rise to the theory that phytoestrogen-rich diet could contribute to protect women against postmenopausal osteoporosis [4, 6, 32].

Numerous *in vitro* studies with human and animal osteoblasts or osteoblast-like cell lines, and with osteoclasts, have been carried out, with consistent observations of direct effects of phytoestrogens and related compounds on both cell types. In vitro studies indicate that phytoestrogens could be the ideal candidates for treatment of osteoporosis because they are able to stimulate osteoblastic activity and inhibit osteoclast formation.

Both genistein and daidzein stimulate osteoblast proliferation, differentiation, and activation by an ER-dependent mechanism. In osteoblasts isolated from trabecular bone from young piglets, daidzein increased secretion of both OPG and soluble RANKL and increased concentration of membrane-bound RANKL by an ER-mediated mechanism. Phytoestrogens are able to stimulate osteoblasts to produce protein synthesis and alkaline phosphatase release; in culture, ethanol extracted soy stimulated osteoblast-like cell proliferation, collagen synthesis and alkaline phosphatase activity. In vitro, genistein and daidzein inhibit synthesis of the pro-inflammatory cytokine IL-6 by MC3T3-E1/4 osteoblast-like cells [32, 35, 37, 41].

Genistein and daidzein both suppress osteoclast activity by a number of possible mechanisms. Daidzein has been shown to promote apoptosis of osteoclast progenitors by an ER-mediated mechanism. Low-dose genistein (10^{-8} M) decreased osteoclast numbers in bone marrow culture by decreasing osteoclast viability. Higher concentrations of genistein (10^{-5} M) attenuated osteoclast formation. In a cell line capable of differentiating into osteoclasts (RAW264.7 cells) genistein and daidzein stimulate ER alpha expression and promote proliferation but inhibit multinucleation (and therefore differentiation into the mature osteoclast phenotype). Both genistein and daidzein have been found to inhibit inward rectifier K^+ channels in osteoclasts, leading to membrane depolarization, intracellular influx of Ca^{2+} and inhibition of osteoclast-mediated bone resorption. In postmenopausal women supplemented with genistein for 12 months, the ratio of sRANKL:OPG in serum was significantly lower than in non-supplemented controls. This may indicate that genistein inhibits RANKL-induced osteoclastogenesis in postmenopausal women [32, 35, 37, 41].

These *in vitro* studies are highly important because most of the *in vitro* results have been confirmed in *in vivo* studies where it is possible to evaluate more complex effects on bone such as the variation of bone mineral density. While the mechanism of action for isoflavones remains complex and still elusive, it is evident from the many lines of evidence that there are multiple pathways, genomic and nongenomic, that conserve the integrity and activity of osteoblast and osteoclast cells to maintain stable bone mass in adults. Certainly the presence of estrogen receptors in bone and the wide-ranging biological properties of these nonsteroidal dietary estrogens provide good rationale for thinking that dietary phytoestrogens should play a role in bone remodelling.

Animal and human observational and interventional studies with short or long duration had examined the effects of phytoestrogens, especially soy isoflavones on bone mineral density (BMD) or other indices of bone turnover and they confirm the general findings from the *in vitro* effects of phytoestrogens on bone cells in culture. Markers indicative of osteoblast and osteoclast activity and thus bone turnover that have been measured include among others osteoprotegerin, pyridinoline, C-telopeptides, urinary calcium, magnesium and phosphorous, hydroxyproline, bone-specific alkaline phosphatase, tartarate-resistant acid phosphatase, osteocalcin, insulin-like growth factor 1, and interleukin 6. These studies provided promising but mixed and inconclusive results. This is perhaps not surprising due to the large array of variables known to influence the bioavailability, metabolism and, ultimately, physiological effects of phytoestrogens. Explanations for the inconsistencies included differences in menopausal status, age, inadequate doses of isoflavones and relatively short duration of isoflavone treatment. Moreover, The European Food Safety Authority (EFSA) [10] evaluated the health claims related to the reduction of vasomotor symptoms and the maintenance of bone mineral density by soy isoflavones during menopause. It was concluded that the available evidence was not sufficient to establish a relationship between the maintenance of bone mineral density and the consumption of soy isoflavones. Currently, when the recent data is pooled and scrutinized via meta-analyses, the benefits of isoflavones on bone mass are more clear. For the effects of isoflavones to be seen, long-term use of at least six months and sufficiently high dose seem to be required. Specific skeletal areas seem to be important too. Generally, phytoestrogens isoflavone interventions prevent osteoporosis-related bone loss and thus have beneficial effects on BMD outcomes and are safe in postmenopausal women. They may be considered as a complementary or alternative option in the prevention and treatment of menopause-related osteoporosis.probably independently from weight status, treatment duration or subjects' ethnicity [1, 4, 5, 20, 21, 26, 32, 34].

It is important to notice that very few studies have assessed the bioavailability of isoflavones; however, isoflavone bioavailability may differ considerably among their source and in different study populations. There is considerable inter-individual variation in isoflavone metabolizing ability. For example, in Western societies only approximately 33% of the population is capable of producing equol. The composition of the gut microflora is a major factor governing daidzein metabolism. There is some indication that individuals who consume high amounts of isoflavones develop higher amounts of flavonoid-metabolizing bacteria in the colon and, therefore, may produce relatively more active forms of phytoestrogens than those with a lower isoflavone intake. Age, race, and dietary components such as the carbohydrate content, presence of probiotics, total amount of fat in the diet, and its type also influence phytoestrogen metabolism. Then, differences among study populations in terms of isoflavone-metabolizing ability may also considerably impact trial outcome [15, 32].

It must also be said that both therapies repeatedly tested, the hormone replacement therapy and phytoestrogens, have beneficial effects on the bone metabolism, causing a significant decrease in bone resorption process. Comparative assessment showed no significant differences between the effectiveness of the hormone therapy and the phytoestrogens used in the study, in terms of effects on BMD and bone resorption, when administered to groups of women with the same sociodemographic and clinical characteristics. Therefore when there is a choice or when there are contraindications to use HRT phytoestrogen "therapy" can be safely and successfully used in prevention and/or support postmenopausal osteoporosis [38].

Menopause is not a disease, but a normal phase in the women life; postmenopausal osteoporosis is a process lasting 15–20 years which primarily affects the trabecular bone only of women at risk. Physicians should maybe restrict their pharmacological approach in favour of advising women in the premenopausal period to abandon dangerous habits, such as smoking, and adopt good levels of physical activity and correct dietary habits. There is a strong possibility that dietary phytoestrogens can counteract the effects of the increased bone turnover in perimenopause avoiding perimenopausal bone loss, as recent studies have suggested.

Functional food based on products of plant origin is assigned a supporting role the body in maintaining good physical condition, mental and helping to prevent, and even treatment of certain diseases. Legumes are widely used in functional food production because their seeds contain a group natural anti-nutritional compounds which constitute the so-called synergists (enhancing effectiveness antioxidant activity). They are also an advantage indifferent organoleptic properties, that allow to obtain products devoid of a specific taste and smell. Oligosaccharides of the raffinose family contained in legume seeds considered in the past as anti-nutritional substances, and for many years have been incorporated into health-promoting functional foods [36].

SUMMARY

In conclusion, up to now phytoestrogens have been seen as alternatives to HRT, but phytoestrogens have different potentialities, being first of all powerful active components of human diet. It appears that the optimal diet for postmenopausal women should contain legumes because food phytoestrogens promise to be pivotal non-nutrient for estrogen-lacking diseases such as postmenopausal osteoporosis. Phytoestrogen-rich foods, being able to improve bone density and metabolism, and being for the most part safe from unexpected long term risks, are emerging as the ideal candidates for the role of functional foods able to reduce the risk of osteoporosis.

PODSUMOWANIE

Fitoestrogeny zawarte w nasionach roślin strączkowych są związkami aktywnymi bardzo szeroko badanymi pod względem ich wpływu na zdrowie człowieka, w tym na zapobieganie i/lub minimalizowanie skutków menopauzy u kobiet. Przedstawione w artykule wyniki potwierdzają, że są one zdolne do poprawy gęstości kości i ich metabolizmu w okresie okołomenopauzalnym. Dodatkowo z ich stosowaniem nie wiążą się żadne długoterminowe zagrożenia. Optymalna codzienna dieta dla kobiet w okresie okołomenopauzalnym powinna zawierać rośliny strączkowe, jednocześnie mogą one stanowić idealny składnik żywności funkcjonalnej, która zmniejszy ryzyko osteoporozy w tej grupie populacyjnej.

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