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Chapter

Osteoporosis and Dietary Inflammatory Index

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Abstract

Healthy bones are constantly being renewed and proper nutrition is an important factor in this process. Anti-inflammatory diet is designed to improve health and prevent the occurrence and development of chronic diseases associated with inadequate diet. Proper nutrition is based on the anti-inflammatory pyramid and changes in poor eating habits are the long-term strategy for preventing inflammation and chronic diseases. Inflammatory factors from food may play a role in the development of osteoporosis and an anti-inflammatory diet may be a way to control and reduce long-term inflammation and prevent bone loss. Pro-inflammatory cytokines from the fat tissue, through activation of the RANKL/RANK/OPG system could intervene with bone metabolism in a way of increased bone loss. Therefore the special attention need to be given to obese patients due to twofold risk, one related to pro-inflammatory cytokines release and the other related to the deprivation of the vitamin D in the fat tissue.

Keywords: chronic diseases, cytokines, dietary inflammatory index, obesity, osteoporosis

1. Introduction

Along with water and oxygen, food is the basis of life. The food contains essential compounds, and their lack leads to imbalance, affects the metabolism and functioning of organic systems, creating a prerequisite for diseases [1]. Adequate nutrition is one of the crucial factors in maintaining good health in adulthood. It also forms the basis of proper growth and development of children and adolescents [2].

The main guidelines for improving nutrition are listed in the National Food Policies. Similarly to existing policies, the Croatian Food Policy, states that proper nutrition is one that:

- establishes a balance between energy ingested by food and energy consumed;
- allows proper distribution between carbohydrates, fats and proteins;

- ensures a sufficient amount of minerals;
- ensures sufficient intake of vitamins;
- provides the body's needs for water [3].

According to data available from the World Health Organization, it is important to recognize the dangers arising from excessive food consumption and the danger of insufficient energy intake of some nutrients. Hundreds of millions of people suffer from diseases that are the result of an unbalanced diet or consuming excessive amounts of food. There is increasing data that diet rich in lipids, rather saturated fatty acids than unsaturated, high intake of sugar and sodium, but lower intake of micronutrients and complex carbohydrates leads to an increase in cardiovascular diseases, obesity, diabetes, osteoporosis, and cancer [4].

Available data that refers to the science of nutrition, suggest two major directions in history. Firstly, energy intake and nutritional needs were investigated, while nowadays, research is focused on nutrients that have a positive impact on human health and the impact of diet on gene expression [5].

Many nutrients have been linked to bone health, including some like dairy, fish, vegetables and soy which can improve it, while unbalanced and salty diet can influence it negatively. Calcium is the most abundant mineral in the body, 1.5-2% of total body weight is mostly found in bones and teeth, about 99% and 1% is found in extracellular fluid and soft tissues. Calcium plays a role in regulating normal muscle and nerve irritability, regulates cell membrane permeability to sodium and participates in blood coagulation. Calcium ingested with food is absorbed by 10-30%. There is an increased need for calcium in pregnancy and lactation [6]. Milk and dairy products are the best sources of calcium, but it can also be found in some types of green leafy vegetables, fish, meat, and grains [7]. The recommended daily intake of calcium in Croatia is 800 mg [8].

Phosphorus is also linked to bone health. Phosphorous and calcium are major constituents of the hydroxyapatite [9]. Recommended daily intake of phosphorus is 700 mg/day [9]. Foods rich in phosphorus are fish, meat, cereals and carbonated beverages [10].

Vitamin D plays a leading role in bone health. It is a fat-soluble vitamin and needs bile salts for its absorption [6]. The metabolism of phosphorus and calcium affects the physiological role of vitamin D, as it conditions their resorption and deposition in bone tissue. Vitamin D deficiency in the body causes rickets in children, and osteomyelitis in adults [6]. Vitamin D is found in eggs, liver, fish oil and butter. Food is poor in vitamin D, so it is necessary to expose the skin to UV radiation.

Proteins of animal or vegetable origin are important part of the diet of children and adults. The recommended daily protein intake is 0.8 g/kg per day and is not sufficient for the elderly [11, 12]. Proteins are needed for the collagen synthesis in bone and have a positive effect on bone health especially in the elderly when protein-energy malnutrition leads to an increased risk of fractures [11].

In addition to macronutrient proteins, fats additionally affect bone. Fats area unit outlined as organic compounds found in foods of animal and plant origin. The role of fats within the body is multiple: additionally to carbohydrates, they are the most supply of energy, change the perform of nerve impulses, regulate temperature, and area unit carriers of fat-soluble vitamins. The counseled daily fat intake ought to be a minimum of 15% of the overall daily energy intake (WHO) [6]. Diet wealthy in saturated fatty acids and lack of physical activity will result in blubber. Fat tissue produces adipokines, which are pleiotropic molecules that not solely

regulate food intake and energy metabolism however are concerned within the complicated interactions between fat tissue and bone [13, 14]. Some investigations imply that cytokines of fat tissue intervene with bone metabolism. General inflammation, a key element within the pathological process of metabolic syndrome, could negatively influence bone health [15].

The anti-inflammatory diet is similar to the Mediterranean diet, designed to improve health and to prevent the occurrence and development of chronic diseases associated with an inadequate diet. Excessive consumption of certain foods, especially industrially processed, stress, insufficient physical activity and too much adipose tissue cause low-grade chronic inflammation, which can precipitate cardiovascular disease, insulin resistance, type II diabetes, arthritis, neurological diseases, thyroid disease, carcinomas and some mental diseases. An anti-inflammatory diet does not necessarily mean a major change to the usual diet, it may contain local, common foods, but it is of utmost importance to avoid food with a high risk for diseases. On the other hand, an anti-inflammatory diet provides a certain ratio of nutrients that regulate energy consumption in a better way, acts on satiety and consumes less energy.

It is important to note that this diet is rich in many nutrients that balance health and prevent the onset and development of various chronic diseases.

In addition to the usual foods that make up the Mediterranean diet, the basis of the anti-inflammatory diet is vegetables that grow above ground - cabbage, broccoli, cauliflower, kale, Brussels sprouts, spinach, chicory, chard, kale, eggplant, olives, beans, artichokes, asparagus, zucchini, lettuce, endive, dill, chicory, rocket, cucumbers, tomatoes, peppers, fennel, celery, pumpkin, onions, spring onions, shallots, garlic, leeks.

Of the fruits, these are avocado, lemon, and spices such as ginger, turmeric with pure herbs that have a special role - parsley leaf, thyme, oregano, basil, rosemary, sage, cinnamon, cumin, clove, mint, lavender, anise, and fennel. Of the oils, cold-pressed oils are recommended - olive, pumpkin, flaxseed, and less often hemp and coconut [16].

2. Osteoporosis and dietary inflammatory index

Postmenopausal osteoporosis is characterized by rapid bone loss, especially in during the first 5 years of the menopause. Clinical symptoms of osteoporosis are usually not present, which is why it is called silent disease. Decrease in estrogen levels trigger numerous changes in bone metabolism which result in bone mass loss and bone quality disorders. They firstly alter trabecular bone and subsequently cortical frame, all together leading to fracture of single bones. Fractures can occur in any bone, but mostly affect hip, vertebrae of the spine, and wrist [17].

In clinical practice, there are several approaches in diagnosing osteoporosis, and they can all fall into two categories:

- Clinical assessment of risk factors for osteoporosis
- Determination of bone mineral density (BMD)

The technique most commonly used by physicians to make a quantitative diagnosis of osteoporosis is to measure bone mineral density by dual-energy X-ray absorptiometry - DEXA. The advantage of this technique is simple and quick application, which enables BMD values to be available to the physician in a short period of time. Usually, BMD is measured in the places that are most susceptible

to fractures (hip, spine and forearm). Based on bone mineral density values, the World Health Organization has defined indicators for the diagnosis of osteoporosis in menopausal women. Thus, osteoporosis can be diagnosed in women whose BMD values are 2.5 and more standard deviations (SD) lower than the average peak bone mass values that apply to young, healthy, white women (standard). By comparing the measured values of BMD and standards (peak bone mass), the T coefficient is obtained. The Z coefficient represents the deviation of the measured value of BMD from the average bone mass of persons of the same age, expressed in standard deviations. Values of T coefficient of -2.5 and less, and Z coefficient of -1 and less, speak in favor of osteoporosis. Values of T > 1 indicate increased bone mass; values of T coefficient between -1 and -2 indicate osteopenia and those values of T coefficient between -1 and -2.5 indicate normal bone mass [17]. Numerous prospective studies have given bone mineral density results that have shown a good association with the occurrence of fractures in subjects (R2 = 0.4 - 0.9). In a study conducted by Marshall et al. on 90,000 women, more than 2,000 of whom had fractures, it was shown, that decrease in BMD of 1 SD for a given age, is associated with the risk of one to one and a half bone fractures [17]. Referring to the results of Marshall et al., BMD values have increasingly been used in clinical practice to assess the risk of bone fractures. However, there are a number of limiting circumstances that do not allow the notion of BMD as a surrogate in the assessment of bone strength and bone biomechanical abilities. Interpretation of BMD values is sometimes illogical and cannot be used in fracture risk assessment. This is supported by the finding of 50% of women who had a fracture, and whose BMD values measured on the spine and hip were above the -2.5 SD threshold to be able to diagnose osteoporosis at all. Another limitation relates to faults that occur during scanning, so that poor patient position or changes in patient orientation in serial images give inaccurate BMD values or values that are often difficult to interpret [18]. Risk factors for bone fractures include excessive alcohol consumption, female gender, positive fracture in medical history, female hip fracture, oral glucocorticoid use, lack of physical activity and nutritional factors [18, 19]. Lifestyle factors which are the most investigated in relation to bone health are nutrition and physical activity. Recent Meta-Analyses showed that exercises can significantly improve trabecular volumetric BMD values measured on tibia and can increase lumbar spine and femoral neck BMD, in postmenopausal women [19]. Mechanical strain activates osteocytes, which initiate bone remodeling resulting in repair of bone tissue damaged by microcracks. On the opposite, bone damage or long-term immobilization results in osteocyte apoptosis and increased osteoclastogenesis.

Low values of body mass index are also associated with the risk of bone fractures as well as low values of bone mineral density [18]. When for some reason it is not possible to determine bone mineral density values, then the body mass index provides useful data to assess fracture risk. It can be said that the above risk factors are not in themselves sufficient in the assessment of fracture risk or in the assessment of bone mineral density values. However, risk factors are useful as a complement to the densitometry finding in the clinical interpretation of fracture risk. The intensity of bone remodeling can be assessed by determining the values of biochemical markers in serum and urine [20].

Under physiological conditions, bone remodeling maintains the bone mass that the body needs not only for metabolic needs, but also to perform important biomechanical functions.

Higher intensity of bone resorption leads to a negative balance of bone remodeling which affects the change of structural and material properties of bone.

Bone resorption markers include tartrate-resistant acid phosphatase (TRAP) and type I collagen cleavage products such as C-terminal telopeptide (CTx),

N-terminal telopeptide (NTx), and deoxypyridinoline. Bone-forming markers include bone-specific alkaline phosphatase (bALP), osteocalcin and residuals that are released by the action of lysine on the procollagen molecule [20]. A large number of investigations which have taken inflammatory etiology of osteoporosis into consideration, have measured experimentally and also in patients the levels of the receptor activator of nuclear factor κB (RANK), its functional ligand (sRANKL) and decoy receptor to RANKL, osteoprotegerin (OPG). sRANKL is a member of the TNF-α family of the cytokines and induces maturation, differentiation and activity of osteoclasts in direct manner or indirectly, as result of macrophage-colony stimulating factor stimulation. Estrogen related bone loss, which is pronounced in the first 5 years of the menopause can be also related to RANKL activation. Care should be taken in determining the value of bone markers so that the results obtained are not misinterpreted [21, 22] .

To relate research with dietary inflammatory potential and its effect on human health, scientists have developed and validated the "Dietary Inflammatory Index - DII" [23]. DII has been shown to be statistically significantly associated with inflammatory biomarkers, particularly IL-6, TNF-α, hs-CRP, and with the combined score of inflammatory biomarkers [24]. DII is an index for assessment of an individual's dietary inflammatory ability, designed on 1943 scientific papers, and is composed of 45 nutritional parameters, which are rated according to pro-inflammatory or anti-inflammatory effect [23] (**Table 1**). It is based on results published in the scientific literature and then standardized with global intake values for all dietary parameters included in the DII index. (Parameter that has a pro-inflammatory effect is scored with +1, while parameter with anti-inflammatory effect with -1 and with 0 parameters without effect. The DII index is increasingly used to assess the association of the inflammatory potential of the diet with various inflammatory chronic diseases [25], cardiovascular disease [25], carcinomas [26–33], premature death as a result of chronic non-communicable diseases [25], asthma [34] and depression and anxiety [35, 36] (**Table 2**). The biggest potential of the DII index is in the selection of anti-inflammatory food, and control over inflammatory diseases.

Nutrient	Inflammation effective score*	World average daily intake	Nutrient	Inflammation effective score*	World average daily intake
Curcuma	-0,785	533 mg	Saturated fats	0,373	28,6 g
Isoflavonoids	-0,593	1,20 mg	Total fats	0,298	71,4 g
Beta carotene	-0,584	3718 mcg	Trans fats	0,229	3,15 g
Green/black tea	-0,536	1,69 g	Energy	0,180	2056 kcal
Mg	-0,484	310 mg	Cholesterol	0,110	279 mg
Ginger	-0,453	59 g			
Vitamin D	-0,446	6,26 mcg			
Omega-3 FA	-0,436	1,06 g			
Vitamin C	-0,424	118 mg			
Garlic	-0,412	4,35 g			

**Positive inflammation effective score = proinflammatory; negative inflammation effective score = antiinflammatory.*

Table 1.
10 most effective antiinflammatory nutrients based on their activity level (inflammation effective score).

Authors/design of the study	Ethnicity/ participants	DII	Objectives	Main results
Shivappa N et al. 2014/prospective cohort	United States (lowa)/34,703 postmenopausal women of the IWHS	DII based on 37 nutrient parameters	To examine association between DII (quintile) and CRC	Significantly higher risk for CRC in the 5th quintile (high DII)
Shivappa N et al. 2015/case-control study	Italy/326 patients with pancreatic carcinoma and 652 controls (median age 63 years)	DII based on 45 nutrient parameters	To analyze the association between the DII and the risk of pancreatic cancer	Subjects in the 2nd, 3rd, 4th and 5th quintiles had increased risk for pancreatic cancer
Mohseni R et al. 2018/ meta-analysis	Italy, Jamaica, France, Mexico, Iran, Canada/age span 40-94/*depending on publication	DII dependent on each publication/ DII is ranged between 18 and 36 nutrient parameters	To investigate relationship between DII and risk of developing prostate cancer	Men who had followed a pro-inflammatory diet were more at risk at developing prostate cancer
Zamora-Ros R et al. 2014/ case-control study	Spain/424 male participants and 401 control/age span 39-60	DII based on 37 nutrient parameters	To investigate association between DII and CRC and its interaction with polymorphisms of inflammatory genes	High DII diets are associated with increased risk of CRC association differed on the genotype of the cytokines
Tabung FK et al. 2014/prospective study	United States/161808 postmenopausal women	DII based on 45 nutrient parameters	To examine the association of DII with increased risk for CRC in WHI	Consumption of more DII diet was associated with increased risk of CRC, especially proximal colon
Schivappa N et al. 2016/case control study	Italy/454 women/age span 18-79	DII based on 45 nutrient parameters	To examine the association of DII with increased risk of endometrial cancer	Consumption of more DII diet was associated with increased risk of endometrial cancer
Schivappa N et al. 2015/case control study	Italy/258 participants/age span 43-84 years	DII based on 45 nutrient parameters	To examine the association of DII with increased risk for hepatocellular cancer	Consumption of more DII diet was associated with increased risk for hepatocellular cancer
Ghazizadeh H et al. 2020/cross sectional study	Iran/7083 adults of the MASHAD cohort study (age span 35-65 years)	DII based on 65 nutrient parameters	To quantify the possible inflammatory effect of diet on the occurrence of depression and anxiety	Significant association between 3rd and 4th quartiles of DII score with severe depression level

Authors/design of the study	Ethnicity/ participants	DII	Objectives	Main results
Salari-Moghaddam A et al. 2018/cross sectional study	Iran/3363 adult participants (age span 35-45 years)	DII based on 45 nutrient parameters	To examine the association between DII score and psychological disorders	Higher DII score was associated with anxiety and psychological distress
Ruiz-Canela M. et al. 2015/cross sectional study	Spain/7447 PREDIMED participants (men aged 55-80; women aged 60-80)	DII food parameter-specific for an individual	To examine the relationship between DII and indices of general and abdominal obesity	Pro-inflammatory diet is associated with central and abdominal obesity

DII and its correlation with carcinomas and other diseases.
IWHS - Iowa Women's Health Study; CRC – colorectal carcinoma; WHI - Women's Health Initiative; MASHAD - Mashhad Stroke and Heart Atherosclerotic Disorder; PREDIMED - Prevención con Dieta Mediterránea.

Table 2.
Association between dietary inflammatory indeks with chronic diseases and cancers.

Authors/design of the study	Ethnicity/participants	DII	Objectives	Main results
Veronese N et al. 2017/longitudinal cohort study	North America/3648 participants (mean age 60.6 years)	DII based on 24 nutrient parameters	To investigate whether the DII scores are associated with increased risks of fractures	Higher DII scores are associated with higher incidence of fractures in women
Orchard T et al. 2016/ cross sectional study	United States/160191 postmenopausal women	DII based on 32 nutrient parameters	To examine DII in relation to risk of fracture and BMD	Lower risk of fractures in women with highest DII
Correa-Rodríguez M et al. 2018/cross sectional study	Spain/599 participants (age span 18-25)	DII based on 25 nutrient parameters	To investigate association between DII with bone health and obesity in young adults	DII is associated with obesity parameters but not to osteoporosis in adulthood
Shivappa N et al. 2015/ cross sectional study	Iran/160 postmenopausal women	DII based on 25 nutrient parameters	To examine the relationship between the DII and BMD in lumbar spine and femoral neck	No significant association between DII and femoral neck BMD

DII - Dietary Inflammatory Index; BMD - Bone Mineral Density.

Table 3.
Association between dietary inflammatory index (DII) with bone mineral density and fracture risk.

Proper nutrition based on the anti-inflammatory pyramid and changes in poor eating habits is a long-term strategy for preventing inflammation and developing osteoporosis. The level of inflammation can be measured and monitored using several biomarkers, including pro-and anti-inflammatory cytokines. The main pro-inflammatory cytokines are tumor necrosis factor (TNF), interleukin (IL) -1, L-6 and interferon (IFN). Anti-inflammatory cytokines are IL-4 and IL-10. C-reactive protein (CRP), and the more recently highly sensitive C-reactive protein (hs-CRP), are clinical markers of inflammation that were used in the study that investigated the association between different conditions and levels of inflammation [37].

Proinflammatory cytokines such as TNF-α, NF-κB, IL-1, and IL-6 are key mediators of the osteoclast differentiation and bone resorption. Bone resorption and bone loss due to chronic inflammation and increased proinflammatory cytokines is found in patients with periodontitis [38], pancreatitis [39] and rheumatoid arthritis [40]. It is also been established that upregulated proinflammatory cytokines are primary mediators of osteopenia or osteoporosis. These proinflammatory cytokines stimulate osteoclast activity through the regulation of the RANKL/RANK/OPG pathway [41]. The assorted increase within the event of osteoarthritis in obese human subjects is another evidence that chronic inflammation influences bone metabolism.

Since the introduction of the inflammatory diet index, numerous studies have related this method to bone health (**Table 3**). All the investigations represented in **Table 3** have analyzed relationship between DII and BMD or fracture risk and results are inconclusive. In a study of Rodrigez et al., association between DII and obesity in young adults was found, with no implication for bone health. Even though, there are rising evidences that in elderly women fat tissue can compromise bone structure and quality. Accordingly, some clinical data showed that obesity is not always protective against osteoporosis. This is supported by the fact that in obesity BMD values are usually falsely increased due to fat deposition and incorrect positioning during bone densitometry scanning [42, 43]. More adequate interpretation of the bone mass has been given by NMR imaging, which revealed decreased values of the trabecular bone volume in elderly women, due to bone marrow infiltration with fat. Given the fact that postmenopausal women have more bone marrow fat in the forearm bones, their trabecular bone volume is deteriorated, which could lead to bone fracture [42]. Replacement of the osteoblasts with adipocytes due to aging or hormones deprivation can also occur as a result of immobilization or physical inactivity. The results of the experimental studies suggest that obesity is epigenetic factor, which can compromise new bone formation in a male offspring of fat mothers. The possible mechanism that prevents bone formation includes systemic inflammation and activation of the RANK/RANKL/OPG system [21, 22]. Pro-inflammatory cytokines, such as TNF-α, activate NF-κB from fat cells in obesity, which could affect bone metabolism in a manner of enhanced bone resorption mediated by osteoclasts and sRANKL [21, 22].

3. Conclusion

Considering everything, it is clear that further clinical randomized studies are needed to better understand the influence of DII on bone mineral density. Of utmost importance are prospective studies that will follow up dietary habits (DII) along with concentrations of the bone remodeling markers as dynamic indicators of the bone metabolism.

Special attention should be given to obese patients who are at one hand prone to osteoporosis due to increased production of the proinflammatory cytokines from

the fat tissue and, on the other hand, lower concentrations of the vitamin D in serum [38]. DII and bone remodeling markers should be followed in patients who lose and gain weight to better understand the influence of the inflammatory diet on bone metabolism and to answer the question, whether an anti-inflammatory diet has a positive impact on bone health.

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Conflict of interest

"The authors declare no conflict of interest."

Appendix and nomenclature

sRANKL	solubile receptor activator of nuclear factor κ-B ligand
RANK	receptor activator of nuclear factor κB
OPG	osteoprotegerin
WHO	World Health Organization
DEXA	dual- energy X-ray absorptiometry
BMD	bone mineral density
SD	standard deviations
TRAP	tartrate-resistant acid phosphatase
CTx	C-terminal telopeptide
NTx	N-terminal telopeptide
bALP	bone-specific alkaline phosphatase
TNF-α	tumor necrosis factor alpha
DII	Dietary Inflammatory Index
IL-6	interleukin 6
IL-4	interleukin 4
IL-10	interleukin 10
CRP	C-reactive protein
IFN	interferon
NFκB	nuclear factor-kappa B
NMR	nuclear magnetic resonance

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