THE POTENTIAL OF PHYTOCHEMICALS LYCOPENE IN PREVENTION OF BONE LOSS DUE TO DECREASED ESTROGEN HORMONE IN HUMANS AND EXPERIMENTAL ANIMALS

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ABSTRACT

Osteoporosis is a condition of decreased bone mass and disruption of bone microarchitecture that often occurs in the elderly. One of the causes of osteoporosis is menopause as reduced estrogen secretion increases bone resorption by osteoclasts activity, and the body's oxidative stress. Currently, osteoporosis is still a major cause of morbidity and mortality in the elderly. Prevention is vital in reducing this disease. Recent studies have shown a reduction in bone loss with lycopene consumption. High serum lycopene is also reported to be associated with decreased protein oxidation and bone resorption in postmenopausal women. This literature aimed to examine and analyze the research results related to the potential of lycopene on bone loss based on molecular and clinical research evidence in preventing osteoporosis in elderly women. Literature review on published papers in English in the last 10 years (2011 – 2021) was conducted using electronic database. Reviewed experimental and cohort studies on elderly women and experimental animals showed influence and effect of lycopene on bone loss. Lycopene may contribute in reduction of oxidative stress caused by reduced secretion of estrogen.

Keywords: estrogen, lycopene, osteoporosis, bone loss, antioxidant

INTRODUCTION

Osteoporosis is one of the major health problems among the elderly. It is a condition of decreased bone mass and changes in bone microstructure that make bones to be brittle and weak and increases risk of factures (Sözen et al., 2017). The 2005-2006 NHANES study stated that at the age of ≥50 years, 10% of women and 2% of men are at risk to get osteoporosis (Looker et al., 2010). In Indonesia, in 2013, osteoporosis in women in 2013 was 23% for 50-70 years old and 53% for those over 70 years (Kemenkes, 2020). These data showed that women aged ≥50 years are four times more likely to have osteoporosis and at fracture risk for 5-10 years earlier than men (Alswat, 2017).

Risk factors for osteoporosis that cannot be controlled include a fall history, old age, gender, race or ethnicity, family osteoporosis history (Pouresmaeili et al., 2018), and menopause (Thulkar et al., 2016). Menopause is the permanent cessation of menstruation due to the loss of activity and the last sign of ovarian follicles in female reproduction (Messier et al., 2011). Menopause usually occurs in the mid-40s, begin with periods of irregular menstrual cycles known as the menopausal transition or perimenopause. The menopausal transition period begins with hormonal changes due to a decrease in the number of ovarian follicles (Burger et al., 2007). In this period the hypothalamus-pituitary insensitivity decreases estrogen secretion (Weiss et al., 2004). It is triggers an increase in luteinizing hormone (LH) levels in perimenopausal women (Weiss et al., 2004), and a significant increase in follicle stimulating hormone (FSH) (Burger et al., 2007). High levels of LH and FSH due to the absence of negative feedback from the ovaries make the menstrual cycle irregular in menopausal women.

A low level of estrogen is one of the main causes of post-menopausal osteoporosis (Shihab et al., 2018). Low level of estrogen interferes stimulation of osteoblast activity (Callaway & Jiang, 2015) and also management of oxidative stress (Geng et al., 2019). Oxidative stress can stimulate differentiation and bone resorption by osteoclasts (Domazetovic et al., 2017) and may increase risk of osteoporosis (Emmanuelle et al., 2021). Most of the osteoporosis complications are fractures of the hip, spine, and distal forearm,

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which are currently still one of the main risks of death among elderly (Rao & Rao, 2015). In general, one of three women aged ≥50 years is likely to have an osteoporosis fracture (Kemenkes, 2020). So, it shows that osteoporosis is a significant cause of morbidity and mortality in the elderly. Osteoporosis and related health consequences increases medical costs and economic burden of the society, especially those with high life expectancy (Mithal et al., 2014).

While menopause cannot be controlled, a risk of developing osteoporosis can be reduced through management of oxidative stress, alcohol consumption, smoking, physical activity level, and diet (Nawrat-Szołtysik et al., 2020). Antioxidants have been reported to be capable of decreasing the risk of osteoporosis and several studies reported that regular consumption of carotenoids from vegetables and fruits is effective in helping bone mineralization (Domazetovic et al., 2017; Sugiura et al., 2011).

Lycopene is a plant carotenoid pigment that produces a yellow or orange color in fruits and vegetables (Imran et al., 2020). Lycopene is fat-soluble with all-trans and cis isomers in nature, often found in tomatoes and processed products (Mohamed & Iikay, 2019). It has some characteristics such as not easily crystallize, easily soluble in oil, easily absorbed by the intestine, and easily transported in cells, so that it makes the cis-isomer concentration high in plasma and tissues (Cooperstone et al., 2016). The process of cooking and processing food with the oil addition can increase the release of carotenoids from the food matrix, so the absorption will be increased (Bhowmik et al., 2012). While tomatoes are known to have the highest lycopene content, processed tomatoes such as tomato paste, tomato sauce, soup, and juice have a higher content than raw tomatoes (Burton-Freeman & Reimers, 2011).

Lycopene has the highest ability to quench singlet oxygen (Islamian & Mehrali, 2015). Recent in-vivo and in-vitro studies have shown a reduction in bone loss with tomato/lycopene consumption. High serum lycopene is also reported to be associated with decreased protein oxidation and bone resorption in postmenopausal women (Rao et al., 2007). Since lycopene is suggested to stimulate the growth and differentiation of osteoblasts and inhibit the formation and resorption activity of osteoclasts (Rao et al., 2003), it has a potential to reduce the risk of osteoporosis (Walallawita et al., 2020).

However, studies discussing beneficial effects of lycopene on bone loss in post-menopausal women are still limited. This paper is therefore aimed to review relevant literatures to summarize the effect of lycopene on bone loss based on molecular and clinical research evidence.

METHODS

This study used a literature review design by searching scientific articles published in the last ten years (2011-2021). Figure 1 shows a protocol of literature search. Literature search was conducted through electronic databases (i.e. PubMed, Science Direct, and SpringerLink). Published papers in English were searched using keywords “osteoporosis” or “bone loss” and “lycopene”.

Identified scientific articles were then selected according to inclusion criteria that show the roles and effects of lycopene on bone loss (decreased protein oxidation and bone resorption, differentiation of osteoblasts) both in humans and experimental animals. Research subjects with comorbidities such as diabetes mellitus and cancer were excluded from this study. In addition, scientific articles with a literature review design, systematic review, meta-analysis, and research with cross-sectional studies were excluded from this study. Selected articles were obtained and studied in-depth and analyzed. From a total of 1307 studies found from several database, 1280 are go through the screening process, but only 128 study included in further process based on exclusion criteria. After reviewing the full text and deep analysis of method, only 9 studies match with the review criteria.

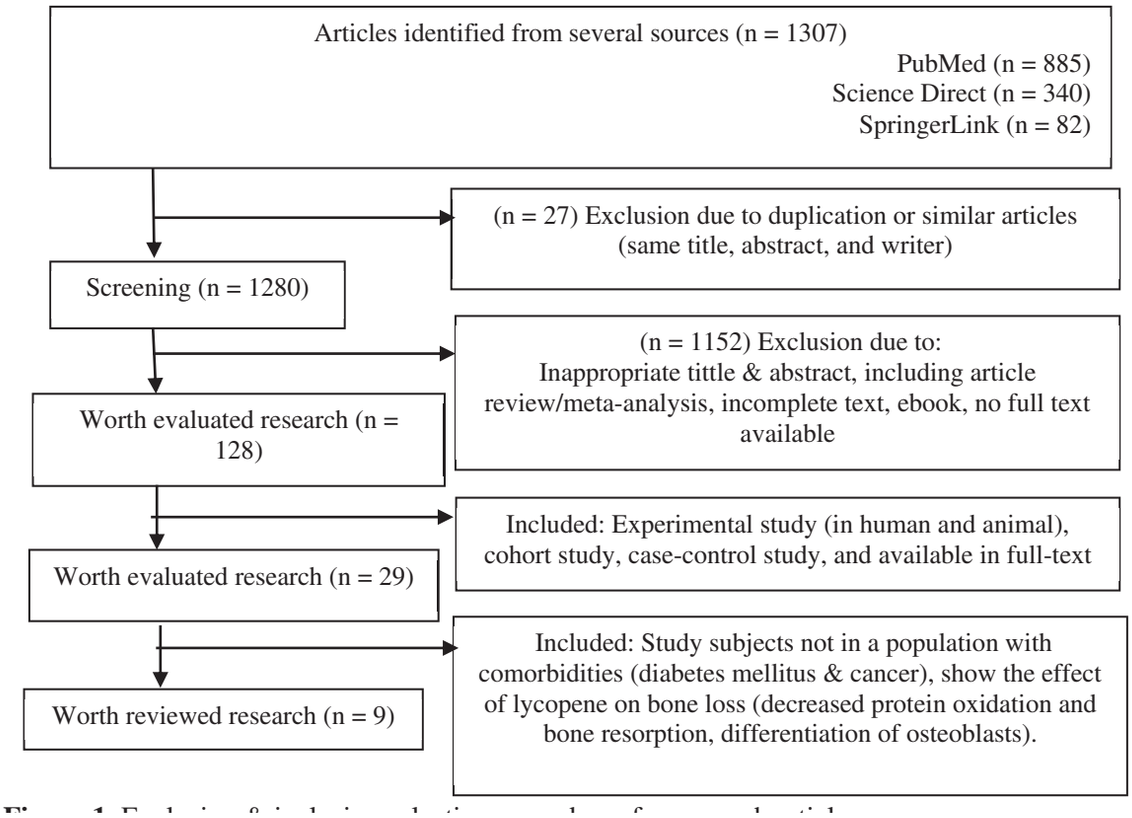

Figure 1. Exclusion & inclusion selection procedures for research articles**.**

Table 1. Effects of Lycopene on Osteoporosis in Post-Menopausal Women

Study Design	Methods	Dosage	Duration	Results	Reference
Cohort Study Subjects: (n = 60) 50-60 years old women who have been postmenopausal for at least 1 year.	Postmenopausal women were divided into 4 groups: (1) regular tomato juice, (2) lycopene-rich tomato juice, (3) tomato Lyc-O-Mato lycopene capsules, or (4) placebo capsules, twice daily for total lycopene intakes	Lycopene supplementation 30 mg/day (regular tomato juice), 70 mg/ day (lycopene-fortified tomato juice), 30 mg/ day (Lyc-O Mato capsules)	4 months	Lycopene supplementation at least for 4 months significantly increased serum lycopene compared to placebo ($p<0.001$) Giving lycopene in of juice or supplements in postmenopausal women of at least 30 mg/day significantly ($p<0.001$) reduced bone resorption and oxidative stress. Oxidative stress parameters such as lipid peroxidation, protein oxidation, and N-telopeptide (NTx) were significantly different from the corresponding changes resulting from placebo supplementation ($p<0.05$, $p<0.005$, and $p<0.02$, respectively)	MacKinnon et al., (2011a)

Continued Table 1. Effects of Lycopene on Osteoporosis in Post-Menopausal Women

Study Design	Methods	Dosage	Duration	Results	Reference
Cohort Study Subjects: (n = 23) Healthy postmenopausal women, 50-60 years old.	Participants were instructed to reduce consumption of food sources containing lycopene (according to the list of foods provided) and supplements. Measuring food intake with 7-day dietary records. Blood samples were measured. Provided blood samples at baseline and following a one-month lycopene-depletion period.	Limitation of lycopene intake to 3.5 mg/day initially and 0.13 mg/day after 1 month	1 month	Dietary lycopene restriction resulted in significant decrease of serum lycopene ($p<0.0001$) and glutathione peroxidase (GPx) ($p<0.01$) There was a significant increase ($p<0.05$) in bone resorption (NTx increased) The level of lipid and protein were not significantly increased. Significant increase in GPx ($p<0.01$) significant decrease in antioxidant levels of superoxide dismutase (SOD) ($p<0.005$) and catalase (CAT) ($p<0.005$) were observed.	Mackinnon et al., (2011b)
A pilot prospective clinical study Subjects: (n = 39) Post-menopausal women aged 63 or ± 70 years	There are 2 groups consisting of a treatment group and a control group. The treatment group was treated by consuming 150 ml/day of tomato sauce.	Tomato sauce 150 ml/day or lycopene content was 3,9 mg/day as tomato sauce	3 months	No significant difference (p = 0.97) bone mineral density (BMD) in postmenopausal women who consumed tomato sauce with the control group. There was a significant decrease in bone alkaline phosphatase (BAP) in women who consumed tomato sauce compared to the control group.	Russo et al., (2020)

Table 2. Effects of Lycopene on Osteoporosis in Experimental Animals

Study	Method	Dosage	Duration	Results	Reference
An experimental study Subjects: (n = 264) 6 months old female Wistar rats with ovariectomized (OVX) and SHAM surgery	Wistar rats were divided into 6 groups: (1) The SHAM group received oral vehicle only, (2) lycopene serum to OVX rats 0 mg/kg BW/day (control), (3) lycopene serum to OVX rats 15 mg/kg BW/day, (4) lycopene serum to OVX rats 30 mg/kg BW/day, (5) lycopene serum to OVX rats 45 mg/kg BW/day, (6) one group receiving alendronate (ALN) (2 µg/kg body weight per day)	Lycopene serum 15, 30, 45 mg/kg BW per day	12 weeks.	Lycopene in ovariectomized (OVX) rats reduced the risk of increased bone turnover (increased bone mineral density (BMD) & bone mineral content (BMC)) and decreased bone reabsorption compared to control OVX rats. Lycopene (30 or 45 mg/kg BW/day) in OVX rats significantly ($p<0.001$) increased bone formation and decreased bone reabsorption. The OVX control group had significantly lower ($p<0.05$) plasma GPx activity as compared with the sham surgery (SHAM) group but lycopene treatment significantly increased GPx activity (30.6–57.2%) compared to the OVX control ($p<0.001$ in each case). Lycopene treatment significantly prevented OVX induced bone loss with marked increases in both BMC and BMD in the lumbar spine ($p<0.001$) and humerus ($p<0.05$) compared with the OVX control group.	Ardawi et al., (2016)

Continued Table 2. Effects of Lycopene on Osteoporosis in Experimental Animals

Study	Method	Dosage	Duration	Results	Reference
An experimental study Subjects: Wistar rats were ovariectomized (n = 18) and paired with sham animals (n = 18)	Wistar rats were ovariectomized and paired with sham animals. In vitro evaluations were performed after 60 days of surgery, when cells were cultured in osteogenic medium and divided in control (C), ovariectomized (OVX) and ovariectomized+1 µmol/L lycopene (OVXL) groups	Lycopene 10 mg/kg BW/ day	10 mg/ kg BW/ day for 4 weeks for pre-OVX and 8 weeks for post-OVX.	Lycopene intake reduced bone loss in the epiphyseal femur in OVX Lycopene rats compared to control OVX. Cell proliferation had a significant increase after 10 days for OVX and OVXL experimental groups ($p<0.0001$), with a subsequent decrease at 14 days culture for all groups ($p<0.0001$)	Ribeiro et al. (2019)
An experimental study Subjects: Female Sprague–Dawley 6-week-old rats with OVX	Ovariectomized rats were grouped into 4 groups according to the lycopene content of their diet: 0, 50, 100, and 200 ppm. Lycopene was incorporated into the diet as a tomato extract containing 6 % lycopene (Lyc-O-Mato 6 %, LycoRed Ltd., Israel)	Lycopene to OVX rats 0, 50, 100, and 200 mg lycopene/kg diet	9 weeks.	Lycopene (100 mg/kg BW) in OVX can increase the BDM of the lumbar spine and decrease bone resorption compared to the control OVX. No significant difference in the levels of oxidative stress in all OVX groups.	Iimura et al., (2015)
An experimental study Subjects: (n = 24) 6 week old Sprangue-Dawley	24 rats were grouped into 3 groups according to the lycopene content in their diet: 0, 50, 100 mg/kg dose lycopene. Lycopene was incorporated into the diet as a tomato extract containing 6 % lycopene (Lyc-O-Mato 6 %, LycoRed Ltd., Israel)	Giving lycopene to OVX rats 0, 50, 100 mg lycopene/kg diet	9 weeks.	Giving lycopene (100 mg/kg) can increase the BMD of the lumbar spine and proximal tibial metaphysis compared to the control OVX. The tibial proximal metaphyseal BMD in the 100 ppm groups was also significantly higher than in 50 ppm group ($p<0.05$) No significant differences or trends in BMD of tibial diaphysis were observed in among the groups. No significant difference in the serum oxidative stress level among the 3 groups.	Iimura et al., (2014)
An experimental study Subjects: (n = 50) 2 month female Wistar rats with OVX and sham	Fifty female Wistar rats were grouped into 5 groups: (1) Sham, (2) OVX, (3) OVX + 20 mg/ kg bw, (4) OVX + 30 mg/ kg body weight, (5) OVX + 40 mg/kg body weight. This study investigated the beneficial effect of lycopene on bone biomarkers in ovariectomized (OVX) rats	Lycopene 20, 30, 40 mg/kg BW	8 weeks.	Giving lycopene at 30 and 40 mg/ kg BW can increase BMD ($p<0.05$) and BMC ($p<0.01$) in OVX rats compared to the control OVX group. Serum estrogen level was markedly ($p<0.01$) decreased compared with sham control. Interleukin 6 (IL-6), Bone Gla Protein (BGP), and Collagen Type 1-C-Tellopeptide (CTx) levels were significantly decreased in OVX + lycopene. IL6 plays a role in stimulating bone resorption.	Liang et al., (2012)

Table 3. The Effect of Lycopene on the Osteoclasts and Osteoblasts Development

Study	Method	Dosage	Duration	Results	Reference
An experimental study using osteoblastic culture (human mesenchymal stem cells bone marrow) and osteoclastic culture (human peripheral blood mononuclear cells) in humans aged 25-35 years old.	Osteoblastic and osteoclastic culture were maintained for 21 days in the absence (base medium, BM). Cell cultures were incubated in a 5% CO2 humidified atmosphere at 37°C, and culture medium was replaced once a week. Culture cell will treated with lycopene. Then observed apoptosis, expression of several culture cell and involvement of several intracellular pathways in cell response. Cultures were assessed at days 14 and 21 as described below.	Lycopene concentrations of 5 nM to 50 µM in cell culture	21 days.	Giving lycopene (≥500 nM) helped the proliferation and differentiation of osteoblast (osteoblastogenesis) and inhibit the differentiation of osteoclast (osteoclastogenesis) so it does not affect bone density. Giving lycopene (≥500 nM) can promote a significantly decreased Tartrate-Resistant Acid Phospatase (TRAP) (~20%-46%) on osteoclastic culture. TRAP concentration in serum is utilized as a biochemical marker of osteoclast function and degree of bone resorption. Cell density in osteoblasts was seen based on the total protein value that could be seen with the dexamethasone (-dex or +dex) content. The results showed that lycopene supplementation (≥500 nM) can significantly increase the content of dexamethasone (~18%–22% and ~19%–25% in −dex and +dex conditions, respectively).	Costa-Rodrigues et al., (2021)
An in vitro investigation using Human osteoblast cells (Saos-2) in the American Type Culture Collection (ATCC)	Cell cultures were incubated at 37 °C in 5% CO2. The cell cultures were incubated with dexamethasone 10 nM to obtain a more differentiated cell line. For the evaluation of cell proliferation, Saos-2 cells were seeded at a density of 200,000 cells/ well in 6-well dishes. Cells were incubated with lycopene (≥98%), from tomato (Sigma Aldrich, St. Louis MO, USA), 5 and 10µM or vehicle Tetrahydrofuran, THF (Sigma Aldrich, St. Louis MO, USA) in serum free medium for 24 hours.	Lycopene to cells with a concentration of 5 and 10 µM	24 hours	Lycopene incubation at the dose of 10µM resulted in higher phERK1/2 protein expression levels than the respective vehicle ($p = 0.006$). Lycopene in tomatoes can suppress bone resorption as indicated by decreased Receptor activator of NF-κB ligand (RANKL) expression. Lycopene helps suppress Alkaline Phospatase (ALP) stimulation thereby indicating the occurrence of bone mineralization. The ALP activity was significantly increased with lycopene 5 and 10µ ($p<0.001$) in comparison to their vehicles ($p = 0.02$)	Russo et al., (2020)

Continued Table 3. The Effect of Lycopene on the Osteoclasts and Osteoblasts Development

Study	Method	Dosage	Duration	Results	Reference
An experimental study using osteoblast cells from the medullary femur of OVX female Wistar rats	The cultured cells are grouped into 3 parts: Control (C), ovariectomized (OVX) and ovariectomized with lycopene (OVXL). The lycopene (Sigma-Aldrich®, St. Louis, Missouri, USA) was presented in powder form and mixed in the above-mentioned culture medium to reach a concentration of 1 μmol/L. Cell proliferation was assessed by MTT assay at 7, 10, and 14 days	1μmol/L lycopene in cell culture	14 days	Lycopene can increase the metabolism of osteoblastic cells for 3-10 days for OVX and OVXL ($p<0.0001$). On day 10 ALP activity was still slow in the OVXL group ($p = 0.755$), but on day 14 ALP activity increased in the OVX group compared to the control group ($p = 0.0024$).	Ribeiro et al., (2019)

RESULTS AND DISCUSSIONS

One of the main causes of post-menopausal osteoporosis is low level of estrogen secretion which functions to regulate bone turnover with osteocytes, osteoclasts, and osteoblast formation (Brennan et al., 2014). Under condition of a low estrogen secretion, greater osteoclast activity compared with osteoblast activity that will affect bone formation and increases risk of post-menopausal osteoporosis. Based on epidemiological studies, low estrogen secretion also triggers a decrease in antioxidants and therefore increases oxidative stress, one of the risk factors of osteoporosis (Geng et al., 2019).

Oxidative stress, such as lipid peroxidation, is formed due to an imbalance between of Reactive Oxygen Species (ROS) production and the intravital antioxidant capacity. ROS are formed due to cellular respiration, mitochondrial enzymatic activities, and cellular responses to cytokines due to external stimuli (Birben et al., 2012). ROS are associated with aging and the pathogenesis of various inflammatory and degenerative diseases (Cervellati & Bergamini, 2016), including osteoporosis (Bonaccorsi et al., 2018). The reactive oxygen and free radical contents in ROS oxidize lipids and proteins. As ROS damage cells and deteriorate its function, ROS in bone suppress osteoblast differentiation and significantly help osteoclast differentiation (Callaway & Jiang, 2015) that accelerates bone resorption and cause bone fragility because it increases proinflammatory cytokines, especially tumor necrosis factor (TNF-α) (Domazetovic et al., 2017). Until today the correlation between proinflammatory cytokines with bone fragility and bone deformation and its correlation with estrogen level in menopause women still have no clear explanation.

The results from the present literature review was in line with a study by Azab et al., (2019) that showed antioxidant intake effectively reduced the body's oxidative stress by reducing the production of ROS and proinflammatory cytokines, as well as increasing endogenous antioxidants. Based on the literature search, nine relevant pieces of literature studied benefits of lycopene for bone health based on experimental animal studies, cell culture, and epidemiological/clinical research. The following are the literature review results listed in Table 1-3 with the context of osteoporosis in low estrogen secretion/menopause.

Epidemiological and Clinical Research

An increase in oxidative stress in post-menopausal women is characterized by an increase in serum lipid peroxide and a lower Total Antioxidant Capacity (TAC), as indicated by a decrease in glutathione peroxidase activity compared to reproductive women (Montoya-estrada et al., 2020). In the form of superoxidation, oxidative stress triggers increased osteoclastic in osteoporosis (Zhao et al., 2021).

Postmenopausal women experience a decrease in antioxidants due to increased lipid peroxidation

due to a low estrogen level (Kolesnikova et al., 2015). The results of the Framingham Osteoporosis Study for 4 years showed that the intake of antioxidants in carotenoids had a protective effect on bone by increasing the Bone Mineral Density (BMD) value of the male trochanter and female lumbar spine (Sahni et al., 2009). The results of a 17-year follow-up study showed that a high intake of lycopene could reduce the risk of hip fracture ($p = 0.01$) and nonvertebral bone ($p = 0.002$) (Sahni et al., 2009). This study design demonstrated the positive impact of lycopene on bone health, as mentioned in Table 1.

Experimental Research using Animals

Experiments using female Wistar rats may be considered most appropriate to determine the effect of lycopene on bone health because ovariectomy (OVX) can describe hormonal and postmenopausal conditions similar to humans. In OVX bone turnover was not too fast and similar to the control group of SHAM surgery procedure without the ovaries (Calciolari et al., 2017). Several studies related to the bone density with experimental rats have also been conducted with various interventions such as the provision of certain diets (Fischer et al., 2017), hormones (Yan & Ye, 2015), and immobilization (Horge et al., 2016) which showed major influence on bone loss.

Research on the bone marrow of OVX rats with low estrogen secretionshowed an increase in ROS, activities of enzymes such as glutathione reductase, and increased plasma lipid peroxidation compared to SHAM rats (de Oliveira et al., 2018). These are all associated with bone metabolism and the observed differences suggests OVX rats were more prone to bone loss. Research by Nirmala et al., (2020) also showed that giving green tomato extract to OXV rats can reduce bone loss by increasing the regulation of bone homeostasis. Overall, animal studies using OVX rats have shown positive effects of lycopene administration on bone protection (Table 2).

Research in Bone Cell Culture

High concentrations of ROS can inhibit osteoblast activation through H_2O_2 from ROS that can activate NFκB so that it inhibits osteoblast differentiation and increases bone resorption by osteoclasts (Hubert et al., 2014). It is known that carotenoid group antioxidants play a role in regulating both NFkB and cytokine activities (Linnewiel-Hermoni et al., 2014). Intake of antioxidants is therefore important in reducing ROS production and remodeling of bones by inhibiting osteocyte apoptosis. It also takes part in reducing osteoclast differentiation, increasing osteoblast activity, inducing osteogenesis, and reducing inflammation (Domazetovic et al., 2017). Recent studies have shown that lycopene affect osteoblast and osteoclast (Table 3).

Lycopene is known to have the highest antioxidant potential compared to astaxanthin and it plays an important role in lowering singlet oxygen levels, twice better than β-carotene and ten times better than α-tocopherol (Przybylska, 2020). At the cellular level, lycopene has shown its role in stimulating the growth and differentiation of osteoblasts. It can also inhibit bone formation and resorption by osteoclasts by producing Tartrate-Resistant Acid Phosphatase (TRAP) as well as ROS secretion (Bonaccorsi et al., 2018).

A cohort study on postmenopausal women using various types of carotenoids was carried out by Sugiura et al., (2012). The study showed no significant relationship between lycopene and bone health. It also showed that the carotenoids β-cryptoxanthin and β-carotene played more important roles in increasing BMD. This may be influenced by low lycopene intake in subjects. Meanwhile, Hayhoe et al., (2017) showed that intake of various types of carotenoids, including lycopene, had a positive effect on bone health by increasing bone density and reducing the fracture risk in elderly men and women in Europe. In addition, a review by Walallawita et al., (2020) stated that the intake of lycopene mainly sourced from tomatoes and their processed products has a protective effect on bone loss. However, the role of certain tomato varieties in protecting bone loss is not certainly known. As in lycopene and β-cryptoxanthin which play an important role in preventing bone loss (Quilliot et al., 2010), increased consumption of fruits and vegetables rich in carotenoids and antioxidants contributes improvement of bone health, especially in the elderly.

Currently, there is no recommendation for the amount of lycopene ideal for bone health. Research by MacKinnon et al., (2011a) has shown that a lycopene intake of at least 30 mg/day can significantly reduce bone loss and oxidative stress. As for the lycopene half-life in plasma about 6 days, based on intake of 20 mg of lycopene for 8 consecutive days (Moran et al., 2013). However, it seems that the lycopene dose and half-life in the body vary for various health purposes. Based on the results of several epidemiological studies, a daily intake of lycopene 2-20 mg/day can improve bone? health by reducing oxidative stress (Saini et al., 2020). These recommendations can be met by consuming processed tomato products which increase lycopene intake to about 20 mg/day (Marques et al., 2015). Besides, research by Nishimura et al., (2019) stated that a high intake of lycopene (sources from raw tomatoes) did not cause specific side effects on the body with a safe dose of 200 g/day raw tomatoes. Nine studies from the present study showed that an intervention using lycopene reduces a risk of osteoporosis in women with low estrogen secretion. All studies included in the present study used experimental and cohort designs as these study designs better explained the effectiveness of specific intervention. These studies suggested that lycopene reduces a level of oxidative stress in the body and bone resorption by osteoclasts as well as stimulation of growth and differentiation of osteoblasts.

The present study has some limitations to be acknowledged. This study only consists of nine studies. This is because studies focused on effects of lycopene, especially in relation to bone health is still limited. Since there is a lesser number of studies compared with animal studies, there is a need for further research using human subjects. In addition, it is necessary to consider tomato varieties and doses in assessing the effectiveness of the effect of lycopene on bone loss in humans.

CONCLUSION AND SUGGESTION

Based on the review result on nine studies, lycopene was found to have beneficial effects on bone loss. The results from epidemiological studies suggested that lycopene intake of 2-20 mg/day may contribute as an antioxidant to maintain bone health. Consumption of lycopene such as from tomatoes and their processed products can increase the intake of lycopene for bone protection. The bioavailability of lycopene in tomatoes can be increased through cooking techniques with the oil addition and processing it into tomato sauce and paste. In order to increase lycopene consumption in the Public, delivery of nutritional information as well as cooking skills is recommended.

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