International Journal of Pharmacology

ISSN 1811-7775

science alert

ansinet
Asian Network for Scientific Information

International Journal of Pharmacology 7 (5): 552-567, 2011
ISSN 1811-7775 / DOI: 10.3923/ijp.2011.552.567

A Comprehensive Review of the Shared Roles of Inflammatory Cytokines in Osteoporosis and Cardiovascular Diseases as Two Common Old People Problem; Actions Toward Development of New Drugs

[1]Pooneh Salari and [2]Mohammad Abdollahi
[1]Medical Ethics and History of Medicine Research Center,
Tehran University of Medical Sciences, Tehran, Iran
[2]Faculty of Pharmacy and Pharmaceutical Sciences Research Center,
Endocrinology and Metabolism Research Institute, Tehran University of Medical Sciences, Tehran, Iran

Abstract: The relationship between cardiovascular diseases (CVD) and osteoporosis two common disease in aged people has been theorized since several years ago but many controversies exist yet. In this study, the role of inflammatory cytokines in both diseases has been studied in depth. In the pathophysiology of diseases, estrogen deficiency (in women), oxidative stress, vitamin K deficiency, vitamin D overload, secondary hyperparathyroidism, hyperhomocysteinemia and inflammation play substantial role. Meanwhile, drug therapy of each disease may affect the other one, a spectacle potentiating the common inflammatory link theory. Results of this review indicate that cytokines or proteins such as interleukin (IL)-1, IL-6, IL-11, IL-12, IL-15, IL-17, tumor necrosis factor-α (TNF-α), interferons, macrophage colony stimulating factor (M-CSF), granulocyte M-CSF (GM-CSF), receptor activator of nuclear factor κB ligand (RANKL), osteoprotegerin (OPG), osteopontin (OPN), osteonectin, bone morphogenic proteins (BMPs), bone morphogenic protein-2 (BMP-2), transcription factor for osteoblasts differentiation (Runx2), C-reactive protein (CRP), cyclooxygenase (COX), oxidized LDL, paraoxonase, lysosomal cysteine protease cathepsin K and platelets are shared in the pathophysiology of both diseases. Accordingly, drugs such as bisphosphonates, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors known as statins, non-steroidal anti-inflammatory drugs (NSAIDs), anti-platelet drugs such as clopidogrel or ticlopidine and phytoesteroges affect conditions of both diseases. The inflammatory elements sharing in pathogenesis of both CVD and osteoporosis lead us to revise developments of new drugs in this specific area of science that is much relevant to the health of elderly people who are increasing in developed world.

Key words: Osteoporosis, cytokine, cardiovascular disease, oxidative stress, systematic review

INTRODUCTION

Osteoporosis and cardiovascular diseases are considered as two common chronic debilitating diseases which have serious effects on health especially in elderly. In both diseases, aging and menopause are two common characteristics. Cardiovascular diseases (CVD) initiates early in the life asymptomatically and its advancement creates serious complications such as obvious coronary artery disease (CAD). Osteoporosis mostly begins in elderly however peak bone mass at young age and several environmental and genetic factors change disease incidence. Overtime, the association of CVD and osteoporosis has become more evident especially as part of the aging process.

Previously, the relationship between osteoporosis and CVD was considered as an artifact of aging, however after adjusting for age, the relationship still persists (Boukhris and Becker, 1972; Jie *et al*., 1996).

Evidences about the link: Several previous and recent studies confirmed the significant relationship between osteoporosis and CAD (Seo *et al*., 2009) osteoporosis and peripheral artery diseases (PAD) (Mangiafico *et al*., 2006; Pennisi *et al*., 2004; Vogt *et al*., 1997a; Van der Klift *et al*., 2002), osteoporosis and atherosclerosis (Barengolts *et al*., 1998; Jorgensen *et al*., 2004; Kiel *et al*., 2001; Montalcini *et al*., 2004; Pennisi *et al*., 2004; Tanko *et al*., 2003; Uyama *et al*., 1997). However, some studies showed diverse results

Corresponding Author: Mohammad Abdollahi, Faculty of Pharmacy and Pharmaceutical Sciences Research Center, Endocrinology and Metabolism Research Institute, Tehran University of Medical Sciences, Tehran, Iran

(Aoyagi *et al*., 2001; Reid *et al*., 1991; Vogt *et al*., 1997b). A large prospective study indicated the positive relationship between the increased risk of CVD and severity of osteoporosis (Tanko *et al*., 2005). Osteoporosis was shown to be associated with CAD mortality in postmenopausal women (Hak *et al*., 2000). Furthermore, higher prevalence of osteoporosis was associated with risk factors of CAD such as hypertension, diabetes mellitus (DM) and hyperlipidemia (Hasani-Ranjbar *et al*., 2010; Rahimi *et al*., 2005; Sharif and Abdollahi, 2011).

In a longitudinal study it was determined that reduction of one standard deviation (SD) in distal forearm bone mineral content is associated with 2.3 fold increase in the risk of cardiovascular mortality within the next 17 years (Von der Recke *et al*., 1999). Also it was reported that in osteoporotic women, the prevalence of coronary atherosclerosis is higher than osteopenic and healthy women (Seo *et al*., 2009). Brachial artery pulse wave velocity (baPWV) is a useful indicator of future CVD events as well as their mortality (Imamishi *et al*., 2004; Munakata *et al*., 2003; Yamashina *et al*., 2003) associated with low bone mineral density (BMD) in postmenopausal women (Frost *et al*., 2008; Hirose *et al*., 2003; Sumino *et al*., 2006). In addition, treatment of hypertension and hyperlipidemia with special drug classes increase BMD (Edwards *et al*., 2000; Lynn *et al*., 2006) likewise biphosphonates reduce the risk of CAD (Luckman *et al*., 1998; Price *et al*., 2001). Other than oxidative stress which contributes in osteoporosis (Abdollahi *et al*., 2005; Yousefzadeh *et al*., 2006) and atherosclerosis (Orozco, 2004), several bone proteins and signaling pathways such as receptor activator of nuclear factor κB ligand (RANKL), osteoprotegerin (OPG), osteopontin (OPN), osteonectin and bone morphogenic proteins (BMPs) as well as common genes are indentified in atherosclerosis which intensifies the link between these two chronic diseases (Hofbauer *et al*., 2007). In asymptomatic osteoporotic postmenopausal women, higher coronary calcium scores were indicated (Barengolts *et al*., 1998). Vascular calcification may histologically be identical to bone, supposing the similarity between vascular calcification and osteogenesis (Jayalath *et al*., 2005; McFarlane *et al*., 2004; Vattikuti and Towler, 2004). Instead, some studies have demonstrated the negative association between BMD and abdominal aortic calcification (AAC) independent of age and other confounders (Hyder *et al*., 2007; Schulz *et al*., 2004; Sumino *et al*., 2006).

Several etiologic mechanisms may explain the relationship between osteoporosis and atherosclerosis. Estrogen deficiency is contributing in the pathogenesis of both diseases by increasing bone loss and low density lipoprotein (LDL) oxidative derivatives which inhibits differentiation of osteoblasts and promotes differentiation of osteoblast-like cells of the artery wall (Gaspard *et al*., 1995; Parhami *et al*., 1997; Raisz, 1999).

In the pathogenesis of both conditions, common pathway in the metabolism of cholesterol and bone (Bergstrom *et al*., 2000; Orozco, 2004; Parhami *et al*., 1997; Witztum and Steinberg, 1991), vitamin K deficiency (Vermeer and Braam, 2001), vitamin D overload (Moon *et al*., 1992), secondary hyperparathyroidism (McKane *et al*., 1997; Rostand and Drueke, 1999) and hyperhomocysteinemia (Salari *et al*., 2008a) play substantial role. However the most justified mechanism seems to be inflammation which obviously contributes in the pathology of both diseases. Therefore, we aimed at reviewing the role of inflammation and pro-inflammatory cytokines in the pathophysiology of both diseases.

Pathogenesis of CVD: Damage to the vascular endothelium by several risk factors including hyperlipidemia, genetic predisposition, hypertension, free radicals, diabetes mellitus, hyperhomocysteinemia, infections and smoking lead to develop progressive chronic inflammatory process and finally atherosclerosis (Bui *et al*., 2009; Glass and Witztum, 2001; Lusis *et al*., 2004; Weber *et al*., 2008). Leukocytes activation (mainly monocytes) and platelets induce inflammation which is followed by production of cytokines, growth factors, chemokines and vasoactive molecules. Migration of T cells and vascular smooth muscle cells (VSMCs) into the artery lead to progression of the lesion. Foam cells are forming the early atherosclerotic lesions.

Advanced atherosclerotic lesions consist of dead macrophages. Antibody mediated immunological defense in response to an inflammatory trigger begins with cytokine release including interleukin-6 (IL-6), interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α) and interferons which is followed by systemic inflammatory reactions (Omoigui, 2005; Ross, 1999; Von der Thusen *et al*., 2003; Yudkin *et al*., 2000). The schematic view of atherosclerosis process and the influence of bone cells and biomarkers on atherosclerosis was shown in Fig. 1.

Pathogenesis of osteoporosis: Osteoporosis is the result of an imbalance between bone formation and bone resorption. Its pathophysiology is fairly complex and not completely known. Various cells, cytokines, mediators and numerous signaling pathways as well as genetic and environmental factors are controlling bone remodeling process. Osteoclasts and osteoblasts are responsible for bone resorption and bone formation respectively. Every effector can enhance bone resorption or bone formation

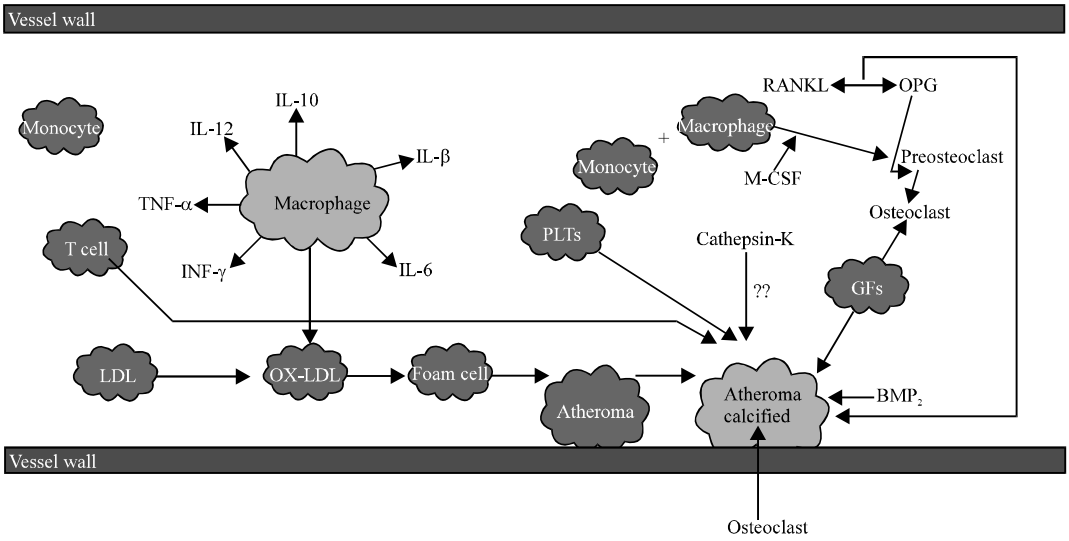

Fig. 1: A schematic view of the relationship between atherosclerosis and osteoporosis. IL-6: Interleukin 6; IL-1β: Interleukin 1β; IL-10: Interleukin 10; IL-12: Interleukin 12; IFNγ: Interferon γ; LDL: Low density lipoprotein; oxLDL: Oxidized lipoprotein; TNFα: Tumor necrosis factor α; BMPs: Bone morphogenic proteins; M-CSF: Macrophage colony stimulating factor; OPG: Osteoprotegerin; PLTs: Platelets; RANKL: Receptor activator of nuclear factor κB ligand; GFs: Growth factors

by inducing osteoclastogenesis or osteoblastogenesis. Stimulation of osteoclastogenesis results in expression of RANKL and its receptor on progenitor cells which acts in counteraction with OPG in bone metabolism.

The link: Histologic studies have shown that in atherosclerotic plaques, there are resorptive and remodeling sites similar to bone (Abedin *et al*., 2004). These plaques have abundant numbers of monocytes and macrophages as preosteoclasts (Gerrity and Naito, 1980). These preosteoclasts for osteoclastogenesis need two cytokines including M-CSF and RANKL (Matsuzaki *et al*., 1998) which are present in vascular cells. A brief process of vascular calcification is shown in Fig. 1.

Apart from several common proteins and pathways in the development of osteoporosis and atherosclerosis, inflammation play substantial role which was known from years ago. In fact, osteoporosis is considered as a low chronic inflammatory disease. Many cytokines and mediators adversely affect bone remodeling (Manolagas and Jilka, 1995). Animal studies have proposed a crucial role for T cells in bone metabolism after ovariectomy which produce TNF-α and RANKL resulting in upregulation of osteoclastogenesis (Roggia *et al*., 2001; Cenci *et al*., 2003).

Macrophages are one of the cell types contributing in the chronic inflammation of bone and vascular tissues (Suganami *et al*., 2005). In support of the former findings, a recent study indicated direct in vivo evidence about correlation between macrophage burden in arteries and aortic valves and calcification and inverse association of inflammation with bone mineralization. They suggested strong systemic and local inflammatory drive for the link between both diseases (Hjortnaes *et al*., 2010).

Activated T cells, macrophages and stromal bone cells produce a variety of inflammatory cytokines including IL-1 and TNF-α (Kong *et al*., 1999), IL-6 (Manolagas, 2000), interferone-γ (IFN-γ) (Gao *et al*., 2007), M-CSF and GM-CSF (Miyaura *et al*., 1995), IL-12 (De Martinis *et al*., 2006), IL-11, IL-15 and IL-17 (Lacativa and Farias, 2010). TNF-α and IL-1 are considered as two potent stimulators of bone resorption (Bertolini *et al*., 1986; Gowen and Mundy, 1986). Surprisingly there are similarities between alterations in cytokine profile in osteoporosis and atherosclerosis. These proinflammatory cytokines affect bone resorption via RANKL (Walsh and Choi, 2003). The essential role of M-CSF and RANKL for osteoclastogenesis is well known (Boyle *et al*., 2003), however, M-CSF is a substantial growth factor for survival of osteoclasts. In addition M-CSF has crucial role in foam cell formation (Faccio *et al*., 2003).

IL-6 and c-reactive protein (CRP) are two well-known inflammatory mediators in both diseases. A summary of special cells and biomarkers are shown in the Table 1.

Table 1: A summary of special cells and markers in both diseases

Marker /cell type	Cardiovascular system	Bone
M-CSF	Foam cell formation	Osteoclastogenesis
RANKL	Vascular calcification	Osteoclastogenesis
T-cells	Inflammation	Osteoclastogenesis
TNF-α	Atherogenesis	Osteoclastogenesis
Macrophages	Vascular inflammation	Inflammation
IL-1	Regulates CRP production	Resorption
IL-6	↑ CRP, ↓ Lipids	Osteoclast differentiation, remodeling, ↑ IL-1, TNF-α, CTX
OPG-RANKL	Vascular calcification	Osteoporosis
Lipids	Atherosclerosis	Osteolysis
isoprostane	Present in atheroma	osteoporosis

IL-6: Interleukin 6; IL-1: Interleukin 1; TNFα: Tumor necrosis factor α; OPG: Osteoprotegerin; RANKL: Receptor activator of nuclear factor κB ligand; CTX: C-terminal cross-liuking of type I collagen; M-CSF: Macrophage colony stimulating factor; CRP: C-reactive protein

IL-6: IL-6 is produced by osteoblasts, monocytes, adipocytes, endothelial cells, fibroblasts and T cells and acts as a promoter and activator of osteoclast differentiation; also accelerates bone remodeling (Chapman *et al*., 2003; Manolagas and Jilka, 1995; Manolagas, 2000) and can be considered as a predictor of bone loss in postmenopausal women (Scheidt-Nave *et al*., 2001). It controls production of monocytes chemotactic proteins and adhesion molecules and finally affects release of inflammatory cytokines such as TNF-α and IL-1β (Barton 1996).

In bone, both IL-6 and IL-11 are under influence of systemic bone metabolism regulating hormones such as estrogen, parathyroid hormone (PTH), vitamin D and thyroxine (Lacativa and Farias, 2010). Estrogen inhibits IL-6 synthesis by osteoblasts and antagonizes the IL-6 receptors (Tabibzadeh *et al*., 1989).

The results of the investigations on the role of IL-6 in osteoporosis are controversial. Although, a negative association was found between BMD at radius ultradistal and IL-6 levels in postmenopausal women (Papadopoulos *et al*., 1997), the other cross-sectional studies could not support that (Kania *et al*., 1995; Khosla *et al*., 1994; McKane *et al*., 1994). In a German longitudinal study, IL-6 was indicated as a significant predictor of femoral bone loss in early postmenopausal women (Scheidt-Nave *et al*., 2001) while in a Danish study, its levels was correlated to the increase in lumbar spine BMD in premenopausal women (Abrahamsen *et al*., 2000). Cohen-Solal *et al*. (1993) observed that the serum levels of IL-1, IL-6 and TNF-α are directly correlated to bone resorption mediated by monocytes in healthy pre- (Salamone *et al*., 1998) and post-menopausal women, the action neutralized by antibodies of IL-1 and TNF-α (Cohen-Solal *et al*., 1993). The role of IL-6 and its deregulation in the link between osteoporosis and CVD has been indicated formerly. A previous study showed that gene polymorphisms regulating IL-6 gene expression is associated with higher serum level of CRP stimulated by IL-6 and C-terminal cross-linking of type I collagen (CTX) (a marker of bone resorption) in healthy postmenopausal women (Ferrari *et al*., 2003). Therefore, it can be suggested that inappropriate expression of IL-6 gene may have a role in the link between osteoporosis and atherosclerosis. It was observed that production of IL-6 is stimulated by coronary artery bypass graft (CABG) (Bennermo *et al*., 2004).

In contrast to the association between IL-6 levels and risk of CVD and its mortality, IL-6 reduces serum levels of lipids. In a study, 24 h after administration of IL-6 to healthy subjects, total cholesterol, apolipoprotein B and triglyceride were decreased (Papanicolaou *et al*., 1998). The exact mechanism is not fully known but some mechanisms were suggested including stimulating hepatic fatty acid synthesis, adipose tissue lipolysis, increasing cholesterol synthesis as well as decreasing cholesterol secretion (Dayer and Choy, 2010; Khovidhunkit *et al*., 2004).

Considering the influence of age in the link between CVD and osteoporosis, in previous studies it was indicated that in elderly people serum concentrations of some cytokines such as IL-6 and TNF-α are increased (Krabbe *et al*., 2004). In addition to the influence of these cytokines in increasing bone resorption (Troen, 2003), IL-6 is known as a marker of subclinical CVD and its mortality in elderly population (Harris *et al*., 1999; Jenny *et al*., 2002). Although, in Health ABC cohort, the significant association between IL-6 and TNF-α and clinical disease was found, however these two mediators did not affect the relationship between BMD and CVD (Farhat *et al*., 2006).

CRP: CRP a member of pentraxin family of innate immune recognition proteins is a crucial marker of systemic inflammation which its production in liver is regulated by IL-1, IL-6 and TNF-α (Weinhold and Ruther, 1997; Yoshida *et al*., 2002). The association between higher CRP levels and lower BMD and higher bone turnover was demonstrated in patients with rheumatoid arthritis (Devlin *et al*., 1996; Oelzner *et al*., 1999), ankylosing spondylitis (Marhoffer *et al*., 1995) and seronegative spondyloarthropathy (MacDonald *et al*., 1997). Furthermore, it was observed that highly sensitive serum c-reactive protein (hsCRP) positively correlates with serum concentrations of IL-6 and TNF-α in healthy (Yudkin *et al*., 1999) as well as subjects with myocardial infarction (Ridker *et al*., 2000). IL-6 and IL-1 stimulate production of CRP in liver (Moshage, 1997). It was reported that higher levels of hsCRP are associated with

lower BMD (Koh *et al*., 2005), higher risk of fracture (Pasco *et al*., 2006; Schett *et al*., 2006) and higher serum levels of bone biomarkers (Kim *et al*., 2007).

Ding *et al*. (2008) reported a significant correlation between hsCRP and alteration in serum levels of IL-6. In contrast to these findings, Nabipour *et al*. (2009) reported no association between chronic low grade inflammation and variance in BMD at all sites as well as RANKL/OPG, BMD and hsCRP. In accordance with their results, two out of three studies did not observe the association between CRP and BMD in healthy postmenopausal women (Bhupathiraju *et al*., 2007; Ganesan *et al*., 2005). Pasco *et al*. (2006) indicated hsCRP as an independent predictor of fracture risk in older women with no significant correlation between hsCRP and BMD. From the other point of view and by measuring bone biomarkers as key indicators of bone metabolism, a link between urinary N-terminal telopeptide of type I collagen (NTX) and hsCRP levels in postmenopausal women was reported (Kim *et al*., 2007). Also, in a longitudinal study, a positive association between urinary pyridinoline and hsCRP was reported (Ding *et al*., 2008).

In the National Health and Nutrition Examination Survey (NHANES), after adjusting for demographic, anthropometric and lifestyle variations, the relationship between CRP and BMD was not significant (Ganesan *et al*., 2005). In contrast, Shaffer *et al*. (2007) identified weak association between BMD, lipids, paraoxonase 1(PON1) and CRP.

TNF: There are clear evidences of TNF-α synthesis in plaque microenvironments by macrophages and smooth muscle cells (Niemann-Jonsson *et al*., 2000; Schreyer *et al*., 2002). Furthermore there is a positive relationship between TNF-α serum levels and the incidence of CVD (Bruunsgaard *et al*., 2000; Cesari *et al*., 2003) as well as recurrent myocardial infarction (Ridker *et al*., 2000).

TNF-α mediates atherogenesis by affecting several cell types including macrophages, endothelial cells and smooth muscle cells via inducing expression of adhesion molecules, production of cytokines and chemokines and migration, proliferaltion and apoptosis of cells (Wajant *et al*., 2003). The most function of TNF-α is mediated by p55 TNF and p75 TNF receptors (TNFR) (Vandenabeele *et al*., 1995) existing on nearly all nucleated cells, however their exact role in atherosclerosis is not fully understood. In terms of p55 TNFR, it was observed that p55 TNFR expression in bone marrow-derived cells enhances formation of foam cell and promotes expression of pro-atherosclerotic chemokines (Xanthoulea *et al*., 2008).

The negative association between TNF-α and lumbar spine BMD in postmenopausal women or men was observed in some studies (Ding *et al*., 2008; Zheng *et al*., 1997), whereas Salamone *et al*. (1998) did not confirm the same results in premenopausal women. IL-1 has synergistic effect with TNF-α in bone loss.

Another mechanism of action of TNF-α in stimulating bone resorption is activation of transforming growth foctor-B (TGF-β) (Lacativa and Farias, 2010). Yousefzadeh *et al*. (2006) also reported changes of TGF-β in blood and saliva of osteoporotic patients. In addition, it may induce M-CSF and intercellular adhesion molecules (ICAM-1) in endothelial cells which more augment TNF-α production and increase survival of osteoclasts (Lacativa and Farias, 2010).

Cyclooxygenase (COX): COX-1 and COX-2 are expressing on endothelial progenitor cells (EPCs). COX inhibition in cultured EPCs suppresses their proliferation in a dose dependent manner (Colleselli *et al*., 2006). Other studies have reported the preventive effect of high concentration of aspirin on EPCs migration, adhesion and proliferation (Chen *et al*., 2006; Hu *et al*., 2008); however COX selectivity should be concerned.

COX-derived prostaglandins and isoprostanes potentially contribute to different biological activities including platelets aggregation (Liu *et al*., 1998), endothelin-1 release in endothelial cells (Yura *et al*., 1999) and vascular smooth muscle cells activities (Fukunaga *et al*., 1993) but the net effect is system specific. Isoprostanes can be found in atheroma (Gniwotta *et al*., 1997; Pratico *et al*., 1997) as well as in body fluids after oxidative stress (Lawson *et al*., 1999) also they may contribute in osteoporosis (Parhami *et al*., 1997; Parhami *et al*., 2000; Tintut *et al*., 2002). Parhami *et al*. (2000) reported the regulatory effect of iso-prostaglandin E2 (isoPGE2) on osteoblastic differentiation of osteoprogenitor cells in the artery wall and bone.

In osteoporosis due to estrogen deficiency, the level of osteoclastogenic cytokines such as IL-1, IL-6 and TNF-α are increased which induce COX-II expression and is followed by production of PGE2. TNF-α in cooperation with PGE2 increases RANKL expression which is in favor of bone loss (Salari *et al*., 2008b; Sharif *et al*., 2010a, b, 2011; Sun *et al*., 2003).

Instead PGE2 controls local bone metabolism by inducing osteoblast formation and inhibiting bone resorption (Kaji *et al*., 1996) as well as inducing cyclic adenosine monophosphate (cAMP) pathway in osteoblasts which leads to cytokine release such as IL-1 and IL-6 (Amano *et al*., 1996).

OPG: One protein which is obviously involved in the pathogenesis of both diseases is OPG which works in counteraction with RANKL (Sharif *et al*., 2010a, b, 2011). OPG is found in vascular smooth cells and normal arteries (Dhore *et al*., 2001; Hofbauer *et al*., 2001).

Lack of OPG was associated with osteoporosis as well as arterial calcification in animal studies (Bucay *et al*., 1998; Schoppet *et al*., 2002) which consists the regulatory effect of OPG and RANKL on bone metabolism and vascular diseases.

In some pathological conditions including bone metabolism, inflammation and arterial calcification, OPG is involved. The elevated levels of OPG have been observed in patients with CAD and carotid atherosclerosis and its levels positively associated with severity of CAD (Jono *et al*., 2002). OPG is produced in endothelial and vascular smooth muscle cells and acts as an anti-apoptotic factor by binding to the TNF-related apoptosis-inducing ligand (TRAIL) and controls vascular inflammation (Schoppet *et al*., 2003).

In non-atherosclerotic arteries, OPG exerts angioprotective function by inhibiting vascular calcification (Parhami *et al*., 1997). Recent evidences present OPG as a counter-regulatory mediator in atherosclerosis. One hypothesis explaining the contradiction is the compensatory vasculoprotective effect of OPG to excessive inflammation (Kiechl *et al*., 2004). Until now, several investigations evaluated the relationship between OPG and inflammatory mediators, however the results are conflicting (Anand *et al*., 2006; Kim *et al*., 2005). Kadoglou *et al*. (2008) reported significant positive correlation between OPG and hsCRP in atherosclerosis.

Osteopontin (OPN) a matrix protein inhibits calcification by binding to α-v, β-3 integrin, also contributes in atherosclerosis (Giachelli *et al*., 1993). The OPN is produced by several cell types including osteoblasts, macrophages, etc., inhibits mineral deposition and regulates bone remodeling (Parhami *et al*., 1997). Its significant higher plasma levels were found in CAD which shows the severity of the disease (Ohmori *et al*., 2003).

Expression of OPN and OPG are both under the control of glucose (Bidder *et al*., 2002) and higher serum levels of these two bone regulators were observed in patients with diabetes (Takemoto *et al*., 2000; Vik *et al*., 2007) but Kadoglou *et al*. (2008) could not confirm it.

Lipids: Upon activation of an immune response, lipids accumulate in vascular and bone tissues which result in atherosclerosis and osteolysis (Demer, 2002). PON1 which presents antioxidant activity to high-density lipoprotein (HDL) is potentially involved in atherosclerosis in association with BMD in Japanese women (Yamada *et al*., 2003), however some other investigators observed inverse results (Verit *et al*., 2006). Farhat *et al*. (2007) confirmed the inverse link between BMD and CVD while oxidized LDL (oxLDL), IL-6 and TNF-α levels could not explain the association of BMD with CVD and they indicated the possible involvement of other cytokines.

The contribution of minimally oxidized LDL (MM-LDL) in inhibiting differentiation of osteoblasts, inducing differentiation of osteoclasts and inducing T cell apoptosis was demonstrated in *in vitro* studies (Bustamante *et al*., 2007; Parhami *et al*., 1997; Tintut *et al*., 2002). Mildly oxidized LDL reduces production of IL-2 by T cells (Caspar-Bauguil *et al*., 1999). Graham *et al*. (2009) observed that production of RANKL is significantly increased by *ex vivo* unmanipulated human T cells and *in vitro* activated T cells exposed to MM-LDL, lipoprotein oxidation products or iso-PGE2. Additionally these T cells showed higher RANKL/OPG ratios which further affects bone metabolism. In accordance with these observations former studies showed that splenic T cells in hyperlipidemic mice express more RANKL mRNA (Parhami *et al*., 1999). Taken together T cells may light on a novel common inflammatory link between osteoporosis and CVD (Von der Recke *et al*., 1999; Parhami, 2003; Banks *et al*., 1994; Towler, 2008). LOX-1- the specific receptor of oxidized lipids acts as a receptor of various ligands such as platelets (Chen *et al*., 2007). CRP binds to LOX-1 (Blake *et al*., 2003).

Cathepsin K: A lysosomal cysteine protease cathepsin K is predominantly produced by osteoclatsts and its inhibitors are under development for treatment of osteoporosis (Sharif *et al*., 2011), however its participation in atherosclerosis is a new hypothesis in atherosclerosis (Jormsjo *et al*., 2002; Liu *et al*., 2004) which is under investigation. In addition, cathepsin K is expressed in macrophages, smooth muscle and human endothelial atheroma cells (Sukhova *et al*., 1998; Platt *et al*., 2007). Samokhin *et al*. (2008) reported decreased rate of apoptosis in atherosclerotic plaques in arteries of cathepsin K deficient mice by contribution of lower level of inflammation.

Bone morphogenic protein-2 (BMP-2): Other than two key proteins RANKL and OPG, several other proteins contribute in both bone remodeling and atherosclerosis including BMP-2 and transcription factor for osteoblasts differentiation (Runx2). In addition, the binding of wingless and Int-1 (Wnt) to LDL-receptor related protein-5 (LRP-5) and 6 and their inhibition by sclerostin

and dickkopf-related protein-1 (DKK1) is another common pathway in both diseases needing more investigations (Mikhaylova *et al*., 2007).

BMP-2 is regulated by matrix gamma-carboxylated glutamate protein (MGP) a vitamin K dependent protein that may contribute in arterial calcification (Sweatt *et al*., 2003). In atherosclerotic plaque, development of bone formation mediators including BMP-2, BMP-4, osteopontin and osteonectin are upregulated (Tobin and Celeste, 2006).

Platelets (PLT): Platelets contribute in bone remodeling as well as atherosclerosis. Their interaction with activated T cells and degranulation leads to release of a wide variety of growth factors and inflammatory mediators. The releasate can influence bone remodeling by affecting several bone markers including RANKL, OPG and COX enzyme. Newly, the hypothesis of platelet involvement in the pathogenesis of osteoporosis is considered in the relationship between osteoporosis and CVD (Sharif and Abdollahi, 2010). Their regulatory effects in chronic inflammation in the artery wall and endothelial cells were demonstrated formerly (Gasparyan *et al*., 2010).

The therapeutic pathways and interactions: Other than the mentioned pathophysiological pathways and mediators which intensify the probability of the association between osteoporosis and CVD, drug classes which are used in treatment of each disease may affect the other. Biphosphonates, the main drug class for prevention and treatment of osteoporosis affect the proinflammatory process. In paget's disease, biphosphonate therapy was associated with significant reduction of IL-6 receptor (Rendina *et al*., 2002). It was shown that biphosphonates are suppressing production of IL-6 in tumor cell lines of human osteoblastic phenotype and peripheral blood mononuclear cells (Olmos *et al*., 1999). In addition, biphosphonates inhibit TNF-α and IL-1 production induced by IL-6 in human osteoblastic osteosarcoma cells (Giuliani *et al*., 1998). Abidgaard *et al*. (1998) reported significant reduction in the serum level of IL-6 after biphosphonate treatment in multiple myeloma.

The effect of HMG-CoA reductase inhibitors as the therapeutic cornerstone of CVD in reduction of CRP levels brings the anti-inflammatory properties of this class of drugs into attention. It was shown that atorvastatin can reduce IL-6 levels significantly (Nawawi *et al*., 2003). In addition to their anti-inflammatory effects, their osteoprotective properties are under investigation; however several studies support their protective effect on bone (Sharif and Abdollahi, 2011).

Aspirin a non steroidal anti-inflammatory drug is another main drug used in CVD. Its antiplatelet activity as well as anti-inflammatory property and bone effects potentiate its consideration in inflammatory diseases. It downregulates CRP, IL-6, TGF-β and TNF-α production (Gasparyan *et al*., 2008), however the net effect of NSAIDs on bone is not completely elucidated (Salari and Abdollahi, 2009).

The direct and indirect effects of antiplatelet drugs supports the anti-inflammatory properties of this class of drugs on bone. Other than aspirin, the other anti-platelet drugs such as clopidogrel and ticlopidine not only recover endothelial dysfunction but also may affect bone metabolism which are under investigation. Clopidogrel inhibits TNF-α, IL-6 and TGF-β mostly by preventing platelets T cells interactions (Sharif and Abdollahi, 2010). Interestingly a recent meta-analysis indicated benefit of phytoesteroges in postmenopausal women osteoporosis that also affects blood lipids and rate of CVD (Sharif *et al*., 2010b).

CONCLUSION

Considering all relevant studies in the term of the common inflammatory pathogenesis for CVD and osteoporosis, the hypothesis of treating both diseases in one direction (suppressing or preventing the inflammation) provides more areas for further investigations. Although most of studies support the hypothesis but there are still some inverse results which should be explained or ruled out. In this regard, a few points must be considered and taken into account for future surveys. One of these concerns is to consider several confounders such as various diseases or drug therapies which may affect blood level of inflammatory mediators. For instance there are many senile diseases in which inflammatory cytokines are elevated such as inflammatory bowel disease (Rezaie *et al*., 2007), diabetes (Kajbaf *et al*., 2007), multiple sclerosis (Nikfar *et al*., 2010a, b), or chronic toxicity due to inevitable exposure to environmental toxins (Abdollahi *et al*., 2004). On the other hand, although, some medications have anti-inflammatory properties but their frequent usage as an over the counter drug may significantly change the final results. For instance, a new report indicated that there are many medicinal herbs that have phosphodiesterase inhibition activity and are used traditionally (Hasani-Ranjbar *et al*., 2009; Rahimi *et al*., 2010) where they are also subject of development of new anti-inflammatory drugs.

In addition, as mentioned in most studies, BMD was the major indicator of bone health status; however the

substantial role of bone biomarkers in evaluating bone metabolism should not be ignored. Setting up new and easy methods of measuring bone biomarkers is one of concerns. Therefore, we highly recommend further investigations on inflammatory cytokines that shared among CVD and osteoporosis to develop successful new drugs.

ACKNOWLEDGMENT

This paper is the outcome of an in-house non-financially supported study upon invitation of International Journal of Pharmacology. Authors have no conflict of interest to disclose.

REFERENCES

Abdollahi, M., A. Ranjbar, S. Shadnia, S. Nikfar and A. Rezaie, 2004. Pesticides and oxidative stress: A review. Med. Sci. Monit., 10: 141-147.

Abdollahi, M., B. Larijani, R. Rahimi and P. Salari, 2005. Role of oxidative stress in osteoporosis. Therapy, 2: 787-796.

Abedin, M., Y. Tintut and L.L. Demer, 2004. Vascular calcification: Mechanisms and clinical ramifications. Arterioscler. Thromb. Vasc. Biol., 24: 1161-1170.

Abidgaard, N., J. Rungby, H. Glerup, K. Brixen and M. Kassem *et al*., 1998. Long-term oral pamidronate treatment inhibits osteoclastic bone resorption and bone turnover without affecting osteoblastic function in multiple myeloma. Eur. J. Haematol., 61: 128-134.

Abrahamsen, B., V. Bonnevie-Nielsen, E.N. Ebbesen, J. Gram and H. Beck-Nielsen, 2000. Cytokines and bone loss in a 5-year longitudinal study-hormone replacement therapy suppresses serum soluble interleukin-6 receptor and increases interleukin-1 receptor antagonist: The Danish Osteoporosis Prevention Study. J. Bone. Miner. Res., 15: 1545-1554.

Amano, S., K. Naganuma, Y. Kawata, K. Kawakami, S. Kitano and S. Hanazawa, 1996. Prostaglandin E2 stimulates osteoclast formation via endogenous IL-1 β expressed through protein kinase A. J. Immunol., 156: 1931-1936.

Anand, D.V., A. Lahiri, E. Lim, D. Hopkins and R. Corder, 2006. The relationship between plasma osteoprotegerin levels and coronary artery calcification in uncomplicated type 2 diabetic subjects. J. Am. Coll. Cardiol., 47: 1850-1857.

Aoyagi, K., P.D. Ross, J. Orloff, J.W. Davis, H. Katagiri and R.D. Wasnich, 2001. Low bone density is not associated with aortic calcification. Calcif. Tissue. Int., 69: 20-24.

Banks, L.M., B. Lees, J.E. MacSweeney and J.C. Stevenson, 1994. Effect of degenerative spinal and aortic calcification on bone density measurements in post-menopausal women: Links between osteoporosis and cardiovascular disease. Eur. J. Clin. Invest., 24: 813-817.

Barengolts, E.I., M. Berman, S.C. Kukreja, T. Kouznetsova, C. Lin and E.V. Chomka, 1998. Osteoporosis and coronary atherosclerosis in asymptomatic postmenopausal women. Calcif. Tissue Int., 62: 209-213.

Barton, B.E., 1996. The biological effects of interleukin 6. Med. Res. Rev., 1: 87-109.

Bennermo, M., C. Held, S. Stemme, C.G. Ericsson, A. Silveira, F. Green and P. Tornvall, 2004. Genetic predisposition of the interleukin-6 response to inflammation: Implications for a variety of major diseases. Clin. Chem., 50: 2136-2140.

Bergstrom, J.D., R.G. Bostedor, P.J. Masarachia, A.A. Reszka and G. Rodan, 2000. Alendronate is a specific, nanomolar inhibitor of farnesyl diphosphate synthase. Arch. Biochem. Biophys., 373: 231-241.

Bertolini, D.R., G.E. Nedwin, T.S. Bringman, D.D. Smith and G.R. Mundy, 1986. Stimulation of bone resorption and inhibition of bone formation *in vitro* by human tumour necrosis factors. Nature, 319: 516-518.

Bhupathiraju, S.N., D.L. Alekel, J.W. Stewart, L.N. Hanson and K.M. Shedd *et al*., 2007. Relatioship of circulating total homocysteien and C-reactive protein to trabecular bone in postmenopausal women. J. Clin. Densitom., 10: 395-403.

Bidder, M., J.S. Shao, N. Charlton-Kachigian, A.P. Loewy, C.F. Semenkovich and D.A. Towler, 2002. Osteopontin transcription in aortic vascular smooth muscle cells is controlled by glucose-regulated upstream stimulatory factor and activator protein-1 activities. J. Biol. Chem., 277: 44485-44496.

Blake, G.J., N. Rifai, J.E. Buring and P.M. Ridker, 2003. Blood pressure, C-reactive protein and risk of future cardiovascular events. Circulation, 108: 2993-2999.

Boukhris, R. and K.L. Becker, 1972. Calcification of the aorta and osteoporosis. A roentgenographic study. J. Am. Med. Assco., 219: 1307-13011.

Boyle, W.J., W.S. Simonet and D.L. Lacey, 2003. Osteoclast differentiation and activation. Nature, 423: 337-342.

Bruunsgaard, H., P. Skinhoj, A.N. Pedersen, M. Schroll and B.K. Pedersen, 2000. Aging, tumor necrosis factor-alpha (TNF-α) and atherosclerosis. Clin. Exp. Immunol., 121: 255-260.

Bucay, N., I. Sarosi, C.R. Dunstan, S. Morony and J. Tarpley *et al*., 1998. Osteoprotegerin-deficient mice develop early onset osteoporosis and arterial calcification. Genes. Dev., 12: 1260-1268.

Bui, Q., M. Prempeh and R. Wilensky, 2009. Atherosclerotic plaque development. Int. J. Biochem. Cell. Biol., 41: 2109-2113.

Bustamante, M., F. Diaz, M. Munoz, H.J. Gross and C.I. Rivas *et al*., 2007. Oxidized low density lipoproteins induce apoptosis in human lymphocytes: Involvement of mitogen-activated protein kinases. Cell. Mol. Biol., 53: OL954-OL964.

Caspar-Bauguil, S., J. Tkaczuk, M.J. Haure, M. Durand and J. Alcouffe *et al*., 1999. Mildly oxidized low-density lipoproteins decrease early production of interleukin 2 and nuclear factor κ binding to DNA in activated T-lymphocytes. Biochem. J., 337: 269-274.

Cenci, S., G. Toraldo, M.N. Weitzmann, C. Roggia and Y. Gao *et al*., 2003. Estrogen deficiency induces bone loss by increasing T cell proliferation and lifespan through IFN-gamma-induced class II transactivator. Proc. Natl. Acad. Sci. USA., 100: 10405-10410.

Cesari, M., B.W. Penninx, A.B. Newman, S.B. Kritchevsky and B.J. Nicklas *et al*., 2003. Inflammatory markers and onset of cardiovascular events: Results from the health ABC study. Circulation, 108: 2317-2322.

Chapman, C.M., J.P. Beilby, S.E. Humphries, L.J. Palmer, P.L. Thompson and J. Hung, 2003. Association of an allelic variant of interleukin-6 with subclinical carotid atherosclerosis in an Australian community population. Eur. Heart. J., 24: 1494-1499.

Chen, T.G., J.Z. Chen and X.D. Xie, 2006. Effect of aspirin on number, activity and inducible nitric oxide synthase of endothelial progenitor cells from peripheral blood. Acta. Pharmacol. Sin., 27: 430-436.

Chen, X.P., T.T. Zhang and G.H. Du, 2007. Lectin-like oxidized low-density lipoprotein receptor-1: A new promising target for the therapy of atherosclerosis. Cardiovasc. Drug. Rev., 25: 146-161.

Cohen-Solal, M.E., A.M. Graulet, M.A. Denne, J. Gueris, D. Baylink and M.C. de Vernejoul, 1993. Peripheral monocyte culture supernatants of menopausal women can induce bone resorption: Involvement of cytokines. J. Clin. Endocrinol. Metab., 77: 1648-1653.

Colleselli, D., K. Bijuklic, B.A. Mosheimer and C.M. Kahler, 2006. Inhibition of cyclooxygenase (cox)-2 affects endothelial progenitor cell proliferation. Exp. Cell. Res., 312: 2933-2941.

Dayer, J.M. and E. Choy, 2010. Therapeutic targets in rheumatoid arthritis: The interleukin-6 receptor. Rheumatology, 49: 15-24.

De Martinis, M., M.C. Di Benedetto, L.P. Mengoli and L. Ginaldi, 2006. Senile osteoporosis: Is it an immune-mediated disease?. Inflamm. Res., 55: 399-404.

Demer, L.L., 2002. Vascular calcification and osteoporosis: Inflammatory responses to oxidized lipids. Int. J. Epidemiol., 31: 737-741.

Devlin, J., J. Lilley, A. Gough, A. Huissoon and R. Holder *et al*., 1996. Clinical associations of dual-energy X-ray absorptimetry measurement of hand bone mass in rheumatoid arthritis. Br. J. Rheumatol., 35: 1256-1262.

Dhore, C.R., J.P. Cleutijens, E. Lutgens, K.B. Cleutjens and P.P. Geusens *et al*., 2001. Differential expression of bone matrix regulatory proteins in human atherosclerotic plaques. Arterioscler. Thromb. Vasc. Biol., 221: 1998-2003.

Ding, C., V. Parameswaran, R. Udayan, J. Burgess and G. Jones, 2008. Circulating levels of inflammatory markers predict change in bone mineral density and resorption in older adults: A longitudinal study. J. Clin. Endocrinol. Metab., 93: 1952-1958.

Edwards, C.J., D.J. Hart and T.D. Spector, 2000. Oral statins and increased bone mineral density in postmenopausal women. Lancet, 355: 2218-2219.

Faccio, R., S. Takeshita, A. Zallone, F.P. Ross and S.L. Teitelbaum, 2003. c-FMS and the v 3 integrin collaborate during osteoclast differentiation. J. Clin. Invest., 111: 749-758.

Farhat, G.N., E.S. Strotmeyer, A.B. Newman, K. Sutton-Tyrrell and D.C. Bauer *et al*., 2006. Volumetric and areal bone mineral density measures are associated with cardiovascular disease in older men and women: the health, aging and body composition study. Calcif. Tissue. Int., 79: 102-111.

Farhat, G.N., A.B. Newman, K.S. Sutton-Tyrrell, K.A. Matthews and R. Boudreau *et al*., 2007. The association of bone mineral density measures with incident cardiovascular disease in older adults. Osteoporos. Int., 18: 999-1008.

Ferrari, S.L., L. Ahn-Luong, P. Garnero, S.E. Humphries and S.L. Greenspan, 2003. Two promoter polymorphisms regulating interleukin-6 gene expression are associated with circulating levels of C-reactive protein and markers of bone resorption in postmenopausal women. J. Clin. Endocrinol. Metab., 88: 255-259.

Frost, M.L., R. Grella, S.C. Millasseau, B.Y. Jiang, G. Hampson, I. Fogelman, P.J. Chowienczyk, 2008. Relationship of calcification of atherosclerosis plaque and arterial stiffness to bone mineral density and osteoprotegerin in postmenopausal women referred for osteoporosis screening. Calcif. Tissue. Int., 83: 112-120.

Fukunaga, M., N. Makita, L.J. Roberts, J.D. Morrow, K. Takahashi and K.F. Badr, 1993. Evidence for the existence of F2-isoprostane receptors on rat vascular smooth muscle cells. Am. J. Physiol., 264: C1619-C1624.

Ganesan, K., S. Teklehaimanot, T.H. Tran, M. Asuncion and K. Norris, 2005. Relationship of C-reactive protein and bone mineral density in community-dwelling elderly females. J. Nat. Med. Assoc., 97: 329-333.

Gao, Y., F. Grassi, M. Robbie, M. Terauchi and K. Page *et al*., 2007. IFN-γ stimulates osteoclast formation and bone loss *in vivo* via antigen-driven T cell activation. J. Clin. Invest., 117: 122-132.

Gaspard, U.J., J.M. Gottal and F.A. van den Brule, 1995. Postmenopausal changes of lipid and glucose metabolism: A review of their main aspects. Maturiras, 21: 171-178.

Gasparyan, A.Y., T. Watson and G.Y. Lip, 2008. The role of aspirin in cardiovascular prevention: Implications of aspirin resistance. J. Am. Coll. Cardiol., 51: 1829-1843.

Gasparyan, A.Y., A. Stavropoulos-Kalinoglou, D.P. Mikhailidis and K.M. Douglas, 2010. Platelet function in rheumatoid arthritis: arthritic and cardiovascular implications. Rheumatol. Int., 31: 153-164.

Gerrity, R.G. and H.K. Naito, 1980. Ultrastructural identification of monocyte-derived foam cells in fatty streak lesions. Artery., 8: 208-214.

Giachelli, C.M., N. Bae, M. Almeida, D.T. Denhardt, C.E. Alpers and S.M. Schwartz, 1993. Osteopontin is elevated during neointima formation in rat arteries and is a novel component of human atherosclerotic plaques. J. Clin. Invest., 92: 1686-1696.

Giuliani, N., M. Pedrazzoni, G. Passeri and G. Girasole, 1998. Biphosphonates inhibits IL-6 production by human osteoblast-like cells. Scand. J. Rheumatol., 27: 38-41.

Glass, C.K. and J.L. Witztum, 2001. Atherosclerosis: The road ahead. Cell, 104: 503-516.

Gniwotta, C., J.D. Morrow, L.J. Roberts and H. II, Kuhn, 1997. Prostaglandin F2-like compounds, F2-Isoprostanes are present in increased amounts in human atherosclerotic lesions. Arterioscler Thromb Vasc. Biol., 17: 3236-3241.

Gowen, M. and G.R. Mundy, 1986. Actions of recombinant interleukin 1, interleukin 2 and interferon-gamma on bone resorption *in vitro*. J. Immunol., 136: 2478-2482.

Graham, L.S., F. Parhami, Y. Tintut, C.M.R. Kitchen, L.L. Demer L and R.B. Effros, 2009. Oxidized lipids enhance RANKL production by T lymphocytes: Implications for lipid-induced bone loss. Clin. Immunol., 133: 265-275.

Hak, A.E., H.A. Pols, A.M. van Hemert, A. Hofman and J.C. Witteman, 2000. Progression of aortic calcification is associated with metacarpal bone loss during menopause: A population-based longitudinal study. Arterioscler. Thromb. Vasc. Biol., 20: 1926-1931.

Harris, T.B., L. Ferrucci, R.P. Tracy, M.C. Corti and S. Wacholder *et al*., 1999. Associations of elevated interleukin-6 and C-reactive protein levels with mortality in the elderly. Am. J. Med., 106: 506-512.

Hasani-Ranjbar, S., B. Larijani and M. Abdollahi, 2009. A systematic review of the potential herbal sources of future drugs effective in oxidant-related diseases. Inflamm. Allergy Drug Targets, 8: 2-10.

Hasani-Ranjbar, S., N. Nayebi, L. Moradi, A. Mehri, B. Larijani and M. Abdollahi, 2010. The efficacy and safety of herbal medicines used in the treatment of hyperlipidemia: A systematic review. Curr. Pharm. Des., 16: 2935-2947.

Hirose, K.I., H. Tomiyama, R. Okazaki, T. Arai and Y. Koji *et al*., 2003. Increased pulse wave velocity associated with reduced calcaneal quantitative osteo-sono index: Possible relationship between atherosclerosis and osteopenia. J. Clin. Endocrinol. Metab., 88: 2573-2578.

Hjortnaes, J., J. Butcher, J.L. Figueiredo, M. Riccio and R.H. Kohler *et al*., 2010. Arterial and aortic valve calcification inversely correlates with osteoporotic bone remodeling: A role for inflammation. Eur. Heart. J., 31: 1975-1984.

Hofbauer, L.C., C. Shui, B.L. Riggs, C.R. Dunstan, T.C. Spelsberg, T. O'Brien and S. Khosla, 2001. Effects of immunosuppressants on receptor activator of NF-kappaB ligand and osteoprotegerin production by human osteoblastic and coronary artery smooth muscle cells. Biochem. Biophys. Res. Common., 280: 334-339.

Hofbauer, L.C., C.C. Brueck, C.M. Shanahan, M. Schoppet and H. Dobnig, 2007. Vascular calcification and osteoporosis-from clinical observation towards molecular understanding. Osteoporosis. Int., 18: 251-259.

Hu, Z., F. Zhang, Z. Yang, J. Zhang and D. Zhang, 2008. Low-dose aspirin promotes endothelial progenitor cell migration and adhesion and prevents sensecnce. Cell. Biol. Int., 32: 761-768.

Hyder, J.A., M.A. Allison, M.H. Criqui and C.M. Wright, 2007. Association between systemic calcified atherosclerosis and bone density. Calcif. Tissue. Int., 80: 301-306.

Imanishi, R., S. Seto, G. Toda, M. Yoshida and A. Ohtsuru *et al*., 2004. High brachial-ankle pulse wave velocity in an independent predictor of the presence of coronary artery disease in men. Hypertens. Res., 27: 71-78.

Jayalath, R.W., S.H. Mangan and J. Golledge, 2005. Aortic calcification. Eur. J. Vasc. Endovasc. Surg., 30: 476-488.

Jenny, N.S., R.P. Tracy, M.S. Ogg, le A. Luong and L.H. Kuller *et al*., 2002. In the elderly, interleukin-6 plasma levels and the -174G>C polymorphism are associated with the development of cardiovascular disease. Arterioscler. Thromb. Vasc. Biol., 22: 2066-2071.

Jie, K.S.G., M.L. Bots, C. Vermeer, J.C.M. Witteman and D.E. Grobbee, 1996. Vitamin K status and bone mass in women with and without aortic atherosclerosis: A population-based study. Calcif. Tissue. Int., 59: 352-356.

Jono, S., Y. Ikari, A. Shioi, K. Mori, T. Miki, K. Hara and Y. Nishizawa, 2002. Serum osteoprotegerin levels are associated with the presence and severity of coronary artery disease. Circulation, 106: 1192-1194.

Jorgensen, L., O. Joakimsen, G.K. Rosvold Berntsen, I. Heuch and B.K. Jacobsen, 2004. Low bone mineral density is related to echogenic carotid artery plaques: A population-based study. Am. J. Epidemiol., 160: 549-556.

Jormsjo, S., D.M. Wuttge, A. Sirsjo, C. Whatling, A. Hamsten, S. Stemme and P. Eriksson, 2002. Differential expression of cysteine and aspartic proteases during progression of atherosclerosis in apolipoprotein E-deficient mice. Am. J. Pathol., 161: 939-945.

Kadoglou, N.P.E., T. Gerasimidis, S. Golemati, A. Kapelouzou, P.E. Karayannacos and C.D. Liapis, 2008. The relationship between serum levels of vascular calcification inhibitors and carotid plaque vulnerability. J. Vasc. Surg., 47: 55-62.

Kajbaf, F., M. Mojtahedzadeh and M. Abdollahi, 2007. Mechanisms underlying stress-induced hyperglycemia in critically ill patients. Therapy, 4: 97-106.

Kaji, H., T. Sugimoto, M. Kanatani, M. Fukase, M. Kumegawa and K. Chihara, 1996. Prostaglandin E_2 stimulates osteoclast-like cell formation and bone-resorbing activity via osteoblasts: Role of cAMP-dependent protein kinase. J. Bone. Miner. Res., 11: 62-71.

Kania, D.M., N. Binkley, M. Checovich, T. Havighurst, M. Schilling and W.B. Ershler, 1995. Elevated plasma levels of in postmenopausal women do not correlate with bone density. J. Am. Geriatr. Soc., 43: 236-239.

Khosla, S., J.M. Peterson, K. Egan, J.D. Jones and B.L. Riggs, 1994. Circulation cytokine levels in osteoporotic and normal women. J. Clin. Endocrinol. Metab., 79: 707-711.

Khovidhunkit, W., M.S. Kim, R.A. Memon, J.K. Shigenaga, A.H. Moser, K.R. Feingold and C. Grunfeld, 2004. Effects of infection and inflammation on lipid and lipoprotein metabolism: mechanisms and consequences to the host. J. Lipid Res., 45: 1169-1196.

Kiechl, S., G. Schett, G. Wenning, K. Redlich and M. Oberhollenzer *et al*., 2004. Osteoprotegerin is a risk factor for progressive atherosclerosis and cardiovascular disease. Circulation, 109: 2175-2180.

Kiel, D.P., L.I. Kauppila, L.A. Cupples, M.T. Hannan, C.J. O'Donnell and P.W. Wilson, 2001. Bone loss and the progression of abdominal aortic calcification over a 25-year period: The Framingham heart study. Calcif. Tissue. Int., 68: 271-276.

Kim, S.M., J. Lee, O.H. Ryu, K.W. Lee and H.Y. Kim *et al*., 2005. Serum osteoprotegerin levels are associated with inflammation and pulse wave velocity. Clin. Endocrinol., 63: 594-598.

Kim, B.J., Y.M. Yu, E.N. Kim, Y.E. Chung, J.M. Koh and G.S. Kim, 2007. Relationship between serum hsCRP concentration and biochemical bone turnover markers in healthy pre-and postmenopausal women. Clin. Endocrinol., 67: 152-158.

Koh, J.M., Y.H. Khang, C.H. Jung, S. Bae, D.J. Kim, Y.E. Chung and G.S. Kim, 2005. Higher circulating hsCRP levels are associated with lower bone mineral density in healthy pre-and postmenopausal women: Evidence for a link between systemic inflammation and osteoporosis. Osteoporosis Int., 16: 1263-1271.

Kong, Y.Y., U. Feige, I. Sarosi, B. Bolon and A. Tafuri *et al*., 1999. Activated T cells regulate bone loss and joint destruction in adjuant arthritis through osteoprotegerin ligand. Nature, 402: 304-309.

Krabbe, K.S., M. Pedersen and H. Bruunsgaard, 2004. Inflammatory mediators in the elderly. Exp. Gerontol., 39: 687-699.

Lacativa, P.G. and M.L. Farias, 2010. Osteoporosis and inflammation. Arq. Bras. Endocrinol. Metab., 54: 123-132.

Lawson, J.A., J. Rokach and G.A. FitzGerald, 1999. Isoprostanes: Formation, analysis and use as indices of lipid peroxidation *in vivo*. J. Biol. Chem., 274: 24441-24444.

Liu, J., G.K. Sukhova, J.S. Sun, W.H. Xu, P. Libby and G.P. Shi, 2004. Lysosomal cysteine proteases in atherosclerosis. Arterioscler. Thromb. Vasc. Biol., 24: 1359-1366.

Liu, T.Z., A. Stern and J.D. Morrow, 1998. The isoprostanes: unique bioactive products of lipid peroxidation. An overview. J. Biomed. Sci., 5: 415-420.

Luckman, S.P., D.E. Hughes, F.P. Coxon, R.G.G. Russell and M.J. Rogers, 1998. Nitrogen-containing biphosphonates inhibit the mevalonate pathway and prevent post-translational prenylation of GTP-binding proteins, including ras. J. Bone Mineral Res., 13: 581-589.

Lusis, A.J., R. Mar and P. Pajukanta, 2004. Genetics of atherosclerosis. Annu. Rev. Genomics. Hum. Genet., 5: 189-218.

Lynn, H., T. Kwok, S.Y.S. Wong, J. Woo and P.C. Leung, 2006. Angiotensin converting enzyme inhibitor use is associated with higher bone mineral density in elderly Chinese. Bone, 38: 584-588.

MacDonald, A.G., G. Birkinshaw, B. Durham, R.C. Bucknall and W.D. Fraser, 1997. Biochemical markers of bone turnover in seronegative spondylarthropathy: relationship to disease activity. Br. J. Rheumatol., 36: 50-53.

Mangiafico, R.A., E. Russo, S. Riccobene, P. Pennisi, M. Mangiafico, F. D'Amico and C.E. Fiore, 2006. Increased prevalence of peripheral arterial disease in osteoporotic postmenopausal women. J. Bone Miner. Metab., 24: 125-131.

Manolagas, S.C., 2000. Birth and death of bone cells: Basic regulatory mechanism and implications for the pathogenesis and treatment of osteoporosis. Endocrinol. Rev., 21: 115-137.

Manolagas, S.G. and R.L. Jilka, 1995. Mechanisms of disease: Bone marrow, cytokines and bone remodeling-emerging insights into the pathophysiology of osteoporosis. N. Engl. J. Med., 332: 305-311.

Marhoffer, W., H. Stracke, I. Masoud, M. Scheja, V. Graef, W. Bolten and K. Federlin, 1995. Evidence of impaired cartilage/bone turnover in patients with active ankylosing spondylitis. Ann. Rheum. Dis., 54: 556-559.

Matsuzaki, K., N. Udagawa, N. Takahashi, K. Yamaguchi and H. Yasuda *et al*., 1998. Osteoclast differentiation factor (ODF) induces osteoclast-like cell formation in human peripheral blood mononuclear cell cultures. Biochem. Biophys. Res. Commun., 246: 199-204.

McFarlane, S.I., R. Muniyappa, J.J. Shin, G. Bahtiyar and J.R. Sowers, 2004. Osteoporosis and cardiovascular disease: Brittle bones and boned arteries, is there a link. Endocrine, 23: 1-10.

McKane, W.R., S. Khosla, J. Risteli, S.P. Robins, J.M. Muhs and B.L. Riggs, 1997. Role of estrogen deficiency in pathogenesis of secondary hyperparathyroidism and increased bone resorption in elderly women. Proc. Assoc. Am. Phys., 109: 174-180.

McKane, W.R., S. Khosla, J.M. Peterson, K. Egan and B.L. Riggs, 1994. Circulating levels of cytokines that modulate bone resorption: Effects of age and menopause in women. J. Bone. Miner. Res., 9: 1313-1318.

Mikhaylova, L., J. Malmquist and M. Nurminskaya, 2007. Regulation of *in vitro* vascular calcification by BMP4, VEGF and Wnt3a. Calcif. Tissue. Int., 81: 372-381.

Miyaura, C., K. Kusano, T. Masuzawa, O. Chaki and Y. Onoe *et al*., 1995. Endogenous bone-resorbing factors in estrogen deficiency: Cooperative effects of IL-1 and IL-6. J. Bone. Miner. Res., 10: 1365-1373.

Montalcini, T., V. Emanuele, R. Ceravolo, G. Gorgone, G. Sesti, F. Perticone and A. Pujia, 2004. Relation of low bone mineral density and carotid atherosclerosis in postmenopausal women. Am. J. Cardiol., 94: 266-269.

Moon, J., B. Bandy and A.J. Davison, 1992. Hypothesis: Etiology of atherosclerosis and osteoporosis: are imbalances in the calciferol endocrine system implicated? J. Am. Coll. Nutr., 11: 567-583.

Moshage, H., 1997. Cytokines and the hepatic acute phase response. J. Pathol., 181: 257-266.

Munakata, M., N. Ito, T. Nunokawa and K. Yoshinaga, 2003. Utility of automated brachial ankle pulse wave velocity measurements in hypertensive patients. Am. J. Hypertens., 16: 653-657.

Nabipour, I., B. Larijani, K. Vahdat, M. Assadi and S.M. Jafari *et al*., 2009. Relationships among serum receptor of nuclear factor-kB ligand, osteoprotegerin, high-sensitivity C-reactive protein and bone mineral density in postmenopausal women: Osteoimmunity versus osteoinflammatory. Menopause, 16: 950-955.

Nawawi, H., N.S. Osman, R. Annuar, B.A. Khalid and K. Yusoff, 2003. Soluble intercellular adhesion molecule-1 and interleukin-6 levels reflect endothelial dysfunction in patients with primary hypercholesterolaemia treated with atorvastatin. Atherosclerosis, 169: 283-291.

Niemann-Jonsson, A., P. Dimayuga, S. Jovinge, F. Calara, M.P. Ares, G.N. Fredrikson and J. Nilsson, 2000. Accumulation of LDL in rat arteries is associated with activation of tumor necrosis factor-α expression. Arterioscler. Thromb. Vasc. Biol., 20: 2205-2211.

Nikfar, S., R. Rahimi and M. Abdollahi, 2010a. A meta-analysis of the efficacy and tolerability of interferon-β in multiple sclerosis, overall and by drug and disease type. Clin. Ther., 32: 1871-1888.

Nikfar, S., R. Rahimi and M. Abdollahi, 2010b. A systematic review on the efficacy of interferon β in relapsing remitting multiple sclerosis: Comparison of different formulations. Int. J. Pharmacol., 6: 638-644.

Oelzner, P., S. Franke, A. Muller, G. Hein and G. Stein, 1999. Relationship between soluble markers of immune activation and bone turnover in post-menopausal women with rheumatoid arthritis. Rheumatology (Oxford), 38: 841-847.

Ohmori, R., Y. Momiyama, H. Taniguchi, R. Takahashi, M. Kusuhara, H. Nakamura and F. Ohsuzu, 2003. Plasma osteopontin levels are associated with the presence and extent of coronary artery disease. Atherosclerosis, 170: 333-337.

Olmos, J.M., T. De Vega, L. Perera, J.A. Riancho, J.A. Amado and J. Gonzalez-Macias, 1999. Etidronate inhibits the production of IL-6 by osteoblast-like cells. Meth. Find. Exp. Clin. Pharmacol., 21: 519-522.

Omoigui, S., 2005. Cholesterol synthesis is the trigger and isoprenoid dependent interleukin-6 mediated inflammation is the common causative factor and therapeutic target for atherosclerotic vascular disease and age-related disorders including osteoporosis and type 2 diabetes. Med. Hypotheses, 65: 559-569.

Orozco, P., 2004. Atherogenic lipid profile and elevated lipoprotein (a) are associated with lower bone mineral density in early postmenopausal overweight women. Eur. J. Epidemiol., 19: 1105-1112.

Papadopoulos, N.G., K. Georganas, V. Skoutellas, E. Konstantellos and G.P. Lyritis, 1997. Correlation of interleukin-6 serum levels with bone density in postmenopausal women. Clin. Rheumatol., 16: 162-165.

Papanicolaou, D.A., R.L. Wilder, S.C. Manolagas and G.P. Chrousos, 1998. The pathophysiologic roles of interleukin-6 in human disease. Ann. Intern. Med., 128: 127-137.

Parhami, F., A.D. Marrow, J. Balucan, N. Leitinger and A.D. Watson *et al*., 1997. Lipid oxidation products have opposite effects on calcifying vascular cell and bone cell differentiation. A possible explanation for the paradox of arterial calcification in osteoporotic patients. Aterioscler. Thromb. Vasc. Biol., 17: 680-687.

Parhami, F., S. Jackson, Y. Tintut, V. Le, J.P. Balucan, M. Territo and L.L. Demer, 1999. Atherogenic diet and minimally oxidized low density lipoprotein inhibit osteogenic and promote adipogenic differentiation of marrow stromal cells. J. Bone Miner. Res., 14: 2067-2078.

Parhami, F., A. Garfinkel and L.L. Demer, 2000. Role of lipids in osteoporosis. Aterioscler. Thromb. Vasc. Biol., 20: 2346-2348.

Parhami, F., 2003. Possible role of oxidized lipids in osteoporosis: Could hyperlipidemia be a risk factor: Prostaglandins Leukot Essent. Fatty Acids, 68: 373-378.

Pasco, J.A., M.A. Kotowicz, M.J. Henry, G.C. Nicholson, H.J. Spilsbury, J.D. Box and H.G. Schneider, 2006. High-sensitivity C-reactive protein and fracture risk in elderly women. JAMA., 296: 1353-1355.

Pennisi, P., S.S. Signorelli, S. Riccobene, G. Celotta, L. Di Pino, T. La Malfa and C.E. Fiore, 2004. Low bone density and abnormal bone turnover in patients with atherosclerosis of peripheral vessels. Osteoporos. Int., 15: 389-395.

Platt, M.O., R.F. Ankeny, G.P. Shi, D. Weiss, J.D. Vega, W.R. Taylor and H. Jo, 2007. Expression of cathepsin K is regulated by shear stress in cultured endothelial cells and is increased in endothelium in humanatherosclerosis. Am. J. Physiol. Heart Circ. Physiol., 292: 1479-1486.

Pratico, D., J. luliano, A. Mauriello, L. Spagnoli and J.A. Lawson *et al*., 1997. Localization of distinct F2-isoprostanes in human atherosclerosis lesions. J. Clin. Invest., 100: 2028-2034.

Price, P.A., S.A. Faus and M.K. Williamson, 2001. Biphosphonates alendronate and ibandronate inhibit artery calcification at doses comparable to those that inhibit bone resorption. Arterioscler. Thromb. Vasc. Biol., 21: 817-824.

Rahimi, R., S. Nikfar, B. Larijani and M. Abdollahi, 2005. A review on the role of antioxidants in the management of diabetes and its complications. Biomed. Pharmacother., 59: 365-373.

Rahimi, R., S. Ghiasi, H. Azimi, S. Fakhari and M. Abdollahi, 2010. A review of the herbal phosphodiesterase inhibitors: future perspective of new drugs. Cytokine, 49: 123-129.

Raisz, L.G., 1999. Osteoporosis: Current approaches and future prospects in diagnosis, pathogenesis and management. J. Bone Miner. Metab., 17: 79-89.

Reid, I.R., M.C. Evans, R. Ames and D.J. Wattie, 1991. The influence of osteophytes and aortic calcification on spinal mineral density in postmenopausal women. J. Clin. Endocrinol. Metab., 72: 1372-1374.

Rendina, D., L. Postiglione, P. Vuotto, F.G. Numis and G. Di Domenico *et al*., 2002. Clodronate treatment reduces serum levels of interleukin-6 soluble receptor in Paget's disease of bone. Clin. Exp. Rheumatol., 20: 359-364.

Rezaie, A., R.D. Parker and M. Abdollahi, 2007. Oxidative stress and pathogenesis of inflammatory bowel disease: An epiphenomenon or the cause. Dig. Dis. Sci., 52: 2015-2021.

Ridker, P.M., N. Rifai, M. Pfeffer, F. Sacks, S. Lepage and E. Braunwald, 2000. Elevation of tumor necrosis factor-alpha and increased risk of recurrent coronary events after myocardial infarction. Circulation, 101: 2149-2153.

Roggia, C., Y. Gao, S. Cenci, M.N. Weitzmann, G. Toraldo, G. Isaia and R. Pacifici, 2001. Up-regulation of TNF producing T cells in the bone marrow: A key mechanism by which estrogen deficiency induces bone loss *in vivo*. Proc. Natl. Acad. Sci. USA., 98: 13960-13965.

Ross, R., 1999. Atherosclerosis: An inflammatory disease. N. Eng. J. Med., 340: 115-126.

Rostand, S.G. and T.B. Drueke, 1999. Parathyroid hormone, Vitamin D and cardiovascular disease in chronic renal failure. Kidney Int., 56: 383-392.

Salamone, L.M., T. Whiteside, D. Friberg, R.S. Epstein, L.H. Kuller and J.A. Cauley, 1998. Cytokine production and bone mineral density at the lumbar spine and femoral neck in premenopausal women. Clacif. Tissue Int., 63: 466-470.

Salari, P. and M. Abdollahi, 2009. Controversial effects of non-steroidal anti-inflammatory drugs on bone: A review. Inflamm. Allergy Drug Targets, 8: 169-175.

Salari, P., A. Rezaie, B. Larijani and M. Abdollahi, 2008a. A systematic review of the impact of n-3 fatty acids in bone health and osteoporosis. Med. Sci. Monitor, 14: RA37-44.

Salari, P., B. Larijani and M. Abdollahi, 2008b. Association of hyperhomocysteinemia with osteoporosis: A systematic review. Therapy, 5: 215-222.

Samokhin, A.O., A. Wong, P. Saftig and D. Bromme, 2008. Role of cathepsin K in structural changes in brachiocephalic artery during progression of atherosclerosis in apoE-deficient mice. Atherosclerosis, 200: 58-68.

Scheidt-Nave, C., H. Bismar, G. Leidig-Bruckner, H. Woitge, M.J. Seibel, R. Ziegler and J. Pfeilschifter, 2001. Serum interleukin 6 is a major predictor of bone loss in women specific to the first decade past menopause. J. Clin. Endocrinol. Metab., 86: 2032-2042.

Schett, G., S. Kiechl, S. Weger, A. Pederiva and A. Mayr *et al*., 2006. High-sensitivity C-reactive protein and risk of nontraumatic fractures in the Bruneck study. Arch. Intern. Med., 166: 2495-2501.

Schoppet, M., K.T. Preissner and L.C. Hofbauer, 2002. RANK ligand and osteoprotegerin: Paracrine regulators of b one metabolism and vascular function. Arterioscler. Thromb. Vasc. Biol., 22: 549-553.

Schoppet, M., A.M. Sattler, J.R. Schaefer, M. Herzum, B. Maisch and L.C. Hofbauer, 2003. Increased osteoprotegerin serum levels in men with coronary artery disease. J. Clin. Endocrinol. Metab., 88: 1024-1028.

Schreyer, S.A., C.M. Vick and R.C. LeBoeuf, 2002. Loss of lymphotoxin-α but not tumor necrosis factor-α reduces atherosclerosis in mice. J. Biol. Chem., 277: 12364-12368.

Schulz, E., K. Arfai, X. Liu, J. Sayre and V. Gilsanz, 2004. Aortic calcification and the risk of osteoporosis and fractures. J. Clin. Endocrinol. Metab., 89: 4246-4253.

Seo, S.K., S. Cho, H.Y. Kim, Y.S. Choi, K.H. Park, D.J. Cho and B.S. Lee, 2009. Bone mineral density, arterial stiffness and coronary atherosclerosis in healthy postmenopausal women. Menopause, 16: 937-943.

Shaffer, J.R., C.M. Kammerer, D.L. Rainwater, D.H. O'Leary, J.M. Bruder, R.L. Bauer and B.D. Mitchell, 2007. Decreased bone mineral density is correlated with increased subclinical atherosclerosis in older but not younger, Mexican American women and men: The san antonio family osteoporosis study. Calcif. Tissue Int., 81: 430-441.

Sharif, P.S. and M. Abdollahi, 2010. The role of platelets in bone remodelling. Inflamm. Allerg. Drug. Targets, 9: 393-399.

Sharif, P.S., M. Asalforoush, F. Ameri, B. Larijani and M. Abdollahi, 2010a. The effect of n-3 fatty acids on bone biomarkers in Iranian postmenopausal osteoporotic women: A randomized clinical trial. Age, 32: 179-186.

Sharif, P.S., S. Nikfar and M. Abdollahi, 2010b. Prevention of bone resorption by intake of phytoestrogens in postmenopausal women: A meta-analysis. Age,

Sharif, P.S. and M. Abdollahi, 2011. A systematic review on the relation between use of statins and osteoporosis. Int. J. Pharmacol., 7: 180-188.

Sharif, P.S., M. Abdollahi and B. Larijani, 2011. Current, new and future treatments of osteoporosis. Rheumatol. Int., 31: 289-300.

Suganami, T., J. Nishida and Y. Ogawa, 2005. A paracrine loop between adipocytes and macrophages aggravates inflammatory changes: Role of free fatty acids and tumor necrosis factor α. Arterioscler. Thromb. Vasc. Biol., 25: 2062-2068.

Sukhova, G.K., G.P. Shi, D.I. Simon, H.A. Chapman and P. Libby, 1998. Expression of the elastolytic cathepsins S and K in human atheroma and regulation of their production in smoth muscle cells. J. Clin. Invest., 102: 576-583.

Sumino, H., S. Ichikawa, S. Kasama, T. Takahashi and H. Kumakura *et al*., 2006. Elevated arterial stiffness in postmenopausal women with osteoporosis. Maturitas, 55: 212-218.

Sun, D., A. Krishnan, K. Zaman, R. Lawrence, A. Bhattacharya and G. Fernandes, 2003. Dietary n-3 fatty acids decrease osteoclastogenesis and loss of bone mass in ovariectomized mice. J. Bone. Mine. Res., 18: 1206-1216.

Sweatt, A., D.C. Sane, S.M. Hutson and R. Wallin, 2003. Matrix Gla protein (MGP) and bone morphogenetic protein-2 in aortic calcified lesions of aging rats. J. Thromb. Haemost., 1: 178-185.

Tabibzadeh, S.S., U. Santhanam, P.B. Sehgal and L.T. May, 1989. Cytokine induced production of IFN-β 2/IL-6 by freshly explanted human endometrial stromal cells. Modulation by estradiol 17β. J. Immunol., 142: 3134-3139.

Takemoto, M., K. Yokote, M. Nishimura, T. Shigematsu and T. Hasegawa *et al*., 2000. Enhanced expression of osteopontin in human diabetic artery and analysis of its functional role in accelerated atherogenesis. Arterioscler. Thromb. Vasc. Biol., 20: 624-628.

Tanko, L.B., Y.Z. Bagger and C. Christiansen, 2003. Low bone mineral density in the hip as a marker of advanced atherosclerosis in elderly women. Calcif. Tissue Int., 73: 15-20.

Tanko, L.B., C. Christiansen, D.A. Cox, M.J. Geiger, M.A. McNabb and S.R. Cummings, 2005. Relationship between osteoporosis and cardiovascular disease in postmenopausal women. J. Bone Miner Res., 20: 1912-1920.

Tintut, Y., F. Parhami, A. Tsingotjidou, S. Tetradis, M. Territo and L.L. Demer, 2002. 8-Isoprostaglandin E2 enhances receptor-activated NF κB ligand (RANKL)-dependent osteoclastic potential of marrow hematopietic precursors via the cAMP pathway. J. Biol. Chem., 277: 14221-14226.

Tobin, J.F. and A.J. Celeste, 2006. Bone morphogenetic proteins and growth differentiation factors as drug targets in cardiovascular and metabolic disease. Drug Discov. Today., 11: 405-411.

Towler, D.A., 2008. The osteogenic-angiogenic interface: Novel insights into the biology of bone formation and fracture repair. Curr. Osteoporos. Rep., 6: 67-71.

Troen, B.R., 2003. Molecular mechanisms underlying osteoclast formation and activation. Exp. Gerontol., 38: 605-614.

Uyama, O., Y. Yoshimoto, Y. Yamamoto and A. Kawai, 1997. Bone changes and carotid atherosclerosis in postmenopausal women. Stroke, 28: 1730-1732.

Van der Klift, M., H.A.P. Pols, A.E. Hak, J.C.M. Witteman, A. Hofman and C.E.D.H. de Laet, 2002. Bone mineral density and the risk of peripheral arterial disease: The rotterdam study. Calcif. Tissue Int., 70: 443-449.

Vandenabeele, P., W. Declercq, R. Beyaert and W. Fiers, 1995. Two tumor necrosis factor receptors: Strudcture and function. Trends Cell. Biol., 5: 392-399.

Vattikuti, R. and D.A. Towler, 2004. Osteogenic regulation of vascular calcification: An early perspective. Am. J. Physiol. Endocrinol. Metab., 286: E686-E696.

Verit, F.F., H. Celik, P. Yazgan, O. Erel and I. Geyikli, 2006. Paraoxonase-1 activity as a marker of atherosclerosis is not associated with low bone mineral density in healthy postmenopausal women. Arch. Gynecol. Obstet., 275: 353-359.

Vermeer, C. and L. Braam, 2001. Role of K vitamins in the regulation of tissue calcification. J. Bone. Miner. Metab., 19: 201-206.

Vik, A., E.B. Mathiesen, A.T.W. Noto, B. Sveinbjornsson, J. Brox and J.B. Hansen, 2007. Serum osteoprotegerin is inversely associated with carotid plaque echogenicity in humans. Atherosclerosis, 191: 128-134.

Vogt, M.T., J.A. Cauley, L.H. Kuller and M.C. Nevitt, 1997a. Bone mineral density and blood flow to the lower extremities: The study of osteoporotic fractures. J. Bone. Miner. Res., 12: 283-289.

Vogt, M.T., R. San Valentin, K.Y. Forrest, M.C. Nevitt and J.A. Cauley, 1997b. Bone mineral density and aortic calcification: the study of osteoporotic fractures. J. Am. Geriatr. Soc., 45: 140-145.

Von der Recke, P., M.A. Hansen and C. Hassager, 1999. The association between low bone mass at the menopause and cardiovascular mortality. Am. J. Med., 106: 273-278.

Von der Thusen, J.H., J. Kuiper, T.J.C. van Berkel and E.A.L. Biessen, 2003. Interleukins in atherosclerosis: Molecular pathways and therapeutic potential. Pharmacol. Rev., 55: 133-166.

Wajant, H., K. Pfizenmaier and P. Scheurich, 2003. Tumor necrosis factor signaling. Cell Death Differ., 10: 45-65.

Walsh, M.C. and Y. Choi, 2003. Biology of the TRANCE axis. Cytokine Growth Factor Rev., 14: 251-263.

Weber, C., A. Zernecke and P. Libby, 2008. The multifaceted contributions of leukocyte subsets to atherosclerosis: Lessons from mouse models. Nat. Rev. Immunol., 8: 802-815.

Weinhold, B. and U. Ruther, 1997. Interleukin-6-dependent and-independent regulation of the human c_reactive protein gene. Biochem. J., 327: 425-429.

Witztum, J.L. and D. Steinberg, 1991. Role of oxidized low density lipoprotein in atherogenesis. J. Clin. Invest., 88: 1785-1792.

Xanthoulea, S., M.J.J. Gijbels, I. van der Made, H. Mujcic and M. Thelen *et al*., 2008. P55 Tumor necrosis factor receptor in bone marrow-derived cells promotes atherosclerosis development in low-density lipoprotein receptor knock-out mice. Cardiovasc. Res., 80: 309-318.

Yamada, Y., F. Ando, N. Niino, T. Miki and H. Shimokata, 2003. Association of polymorphisms of paraoxonase 1 and 2 genes, alone or in combination, with bone mineral density in community-dwelling Japanese. J. Hum. Genet., 48: 469-475.

Yamashina, A., H. Tomiyama, T. Arai, K. Hirose and Y. Koji *et al*., 2003. Brachial-ankle pulse wave velocity as a marker of atherosclerotic vascular damage and cardiovascular risk. Hypertens. Res., 26: 615-622.

Yoshida, N., S. Ikemoto, K. Narita, K. Sugimura and S. Wada *et al*., 2002. Interleukin-6, tumor necrosis factor alpha and interleukin-1beta in patients with renal cell carcinoma. Br. J. Cancer, 86: 1396-1400.

Yousefzadeh, G., B. Larijani, B. Mohammadirad R. Heshmat, G. Dehghan, R. Rahimi and M. Abdollahi, 2006. Determination of oxidative stress status and concentration of TGF-β1 in the blood and saliva of osteoporotic subjects. Ann. N. Y. Acad. Sci., 1091: 142-150.

Yudkin, J.S., C.D. Stehouwer, J.J. Emeis and S.W. Coppack, 1999. C-reactive protein in healthy subjects: Associations with obesity, insulin resistance and endothelial dysfunction: A potential role for cytokines originating from adipose tissue? Arterioscler. Thromb. Vasc. Biol., 19: 972-978.

Yudkin, J.S., M. Kumari, S.E. Humphries and V. Mohamed-Ali, 2000. Inflammation, obesity, stress and coronary heart disease: Is interleukin-6 the link? Atherosclerosis, 148: 209-214.

Yura, T., M. Fukunaga, R. Khan, G.N. Nassar, K.F. Badr and A. Montero, 1999. Free-radical-generated F2-isoprostane stimulate cell proliferation and endothelin-1 expression on endothelial cells. Kidney. Int., 56: 471-478.

Zheng, S.X., Y. Vrindts, M. Lopez, D. De Groote and P.F. Zangerle *et al*., 1997. Increase in cytokine production (IL-1 β, IL-6, TNF-α but not IFN-γ, GM-CSF or LIF) by stimulated whole blood cells in postmenopausal osteoporosis. Maturitas, 26: 63-71.