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

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Abstract: The relationship between cardiovascular diseases (CVD) and osteoporosis two common diseases 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), interleukons, 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 phytoestrogens 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.

Keywords: Osteoporosis, cytokines, 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) initiate early in the life asymptptomatically 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 (Boukhis 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; Montalvo et al., 2004; Pennisi et al., 2004; Tanko et al., 2003; Uyama et al., 1997). However, some studies showed diverse results.
(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 (Hasan-Ranjbar et al., 2010; Rahami 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 (Imanishi et al., 2004; Murakata et al., 2003; Yamasina et al., 2003) associated with low bone mineral density (BMD) in postmenopausal women (Frost et al., 2008; Hirase 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 bisphosphonates 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 (Croozo, 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 unidentified 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; Witzum 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 Druke, 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 Witzum, 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
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 (Sugahara 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), interferon-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

<table>
<thead>
<tr>
<th>Marker/cell type</th>
<th>Cardiovascular system</th>
<th>Bone</th>
</tr>
</thead>
<tbody>
<tr>
<td>M-CSF</td>
<td>Foam cell formation</td>
<td>Osteoclastogenesis</td>
</tr>
<tr>
<td>RANKL</td>
<td>Vascular calcification</td>
<td>Osteoclastogenesis</td>
</tr>
<tr>
<td>T-cells</td>
<td>Inflammation</td>
<td>Osteoclastogenesis</td>
</tr>
<tr>
<td>TNF-α</td>
<td>Atherosclerosis</td>
<td>Osteoclastogenesis</td>
</tr>
<tr>
<td>Macrophages</td>
<td>Vascular inflammation</td>
<td>Inflammation</td>
</tr>
<tr>
<td>IL-1</td>
<td>Regulates CRP production</td>
<td>Resorption</td>
</tr>
<tr>
<td>IL-6</td>
<td>CRP, Lipids</td>
<td>Osteoclast differentiation, remodeling, IL-1, TNF-α, CTX</td>
</tr>
<tr>
<td>RANKL</td>
<td>Vascular calcification</td>
<td>Osteoporosis</td>
</tr>
<tr>
<td>Lipids</td>
<td>Atherosclerosis</td>
<td>Osteolysis</td>
</tr>
<tr>
<td>isoprostane</td>
<td>Present in atheroma</td>
<td>Osteoporosis</td>
</tr>
</tbody>
</table>

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 (Lacatova 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 (Kanja 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 pemenopausal 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) (Bennmeur 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 (Marhofer et al., 1998) 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 (Pascoc 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, Nabiopoulos 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). Pascoc 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 (Braunsgard et al., 2000; Cesari et al., 2003) as well as recurrent myocardial infarction (Ridker et al., 2000).

TNF-α mediates atherosclerosis 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, proliferation and apoptosis of cells (Wajant et al., 2003). The most function of TNF-α is mediated by p55 TNF and p75 TNF receptors (TNFR) (Vanderhebee 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 (Xanthoula 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 factor-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 (Gnivotta 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). Kadoğlu 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 (Giacchelli 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 (Olmori 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 Kadoglu 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; Tirtut 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 osteoclasts 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 (Jormajo 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). Samekhn 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 remodelling and atherosclerosis including BMP-2 and transcription factor for osteoclasts 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 (Mikhailova 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 release 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). Abidaar 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 phytoestrogens 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 (Hasami-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.

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