International Journal of Pharmacology

Successes in Understanding Pathophysiology of Osteoporosis

Pooneh Salari

Medical Ethics and History of Medicine Research Center,
Tehran University of Medical Sciences, Tehran, Iran

Osteoporosis-a debilitating chronic disease in elderly population-delineates a major health and economic problem which influences quality of life and life expectancy (Nevitt, 1994; Larijani et al., 2006). Imbalance in bone remodeling-bone formation and bone resorption-predisposes the patient to several bone fractures (McGarry and Kiel, 2000). Different classes of drugs are considered as the mainstay of its treatment but their efficacy and safety profile are still the major concerns. One of the most common drug classes are bisphosphonates which are used as the first line medications in prevention and treatment of osteoporosis in most of the affected patients. After more than a century bisphosphonates prescription and administration, the concerns about their safety are growing. Recently a case control analysis within a primary care cohort of about 6 million people in UK was conducted that demonstrated an increase in the risk of esophageal cancer in bisphosphonates users (Green et al., 2010). Although, reduction of fracture risk is one of the major desired outcomes in treatment with bisphosphonates but there are controversies on the ability of bisphosphonates in reducing the risk of fracture. Fraser et al. (2011) derived meta-analyzed data from 1443 subjects participated in clinical trials and found no significant difference in fracture risk after 5 years administration of bisphosphonates in postmenopausal osteoporotic women. Other than bisphosphonates there are several new and future drugs for prevention and treatment of osteoporosis which were discussed in a newly published paper by Sharif et al. (2011).

Considering the limitations of each class of drug, it seems that the most efficient way of prevention and treatment of osteoporosis is better and deeper understanding of its pathophysiology. The role of inflammation in osteoporosis has been indicated for a long time, yet its exact role is not fully understood. Our search revealed that several cytokines or inflammatory proteins such as interleukin (IL) 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), receptor activator of nuclear factor κB ligand (RANKL), osteoprotegerin (OPG), osteopontin (OPN), bone morphogenic proteins (BMPs), c-reactive protein (CRP), cyclooxygenase (COX) and platelets involve in the pathogenesis of osteoporosis and interaction of these mediators creates different pathological pathways which are connected to each other (Salari and Abdollahi, 2011). In this regard platelets and platelets derived numerous immune and inflammatory factors can be considered as a target for prevention or treatment of the disease (Sharif and Abdollahi, 2010a). According to the possible inflammatory link between osteoporosis and cardiovascular diseases, we hope to find an exact common pathway in preventing both senile chronic diseases. As it was mentioned before and according to the role of COX enzyme in inflammation, several investigators have studied the effect of omega 3 fatty acids on osteoporosis but no conclusive data was provided (Salari et al., 2008b). Another clinical trial was conducted to compare the effect of 900 mg omega 3 fatty acids versus placebo. In this study, we observed that this amount of omega 3 fatty acids reduces pyridinoline (a marker of bone resorption) in the urine sample of osteoporotic patients with no effect on bone formation markers such as osteocalcin (Sharif et al., 2010a). A new review revealed anti-resorptive effects of non-steroidal anti-inflammatory drugs (NSAIDs) on bone that seems mediated by inhibiting COX enzyme, while their impact on bone formation is not obviously addressed (Salari and Abdollahi, 2009).

From the other point of view, the relationship between osteoporosis and cardiovascular diseases was reviewed in several articles which considered the inflammation as the leading cause of both diseases, however the role of homocysteine should not be neglected. Literature review shows that hyperhomocysteinemia negatively affects bone density and increases the risk of fracture in addition to the role of vitamin B in bone metabolism (Salari et al., 2008a).

Although, sympathetic nervous system influences the bone metabolism, its net effect has not been fully known yet. Animal studies show protective effects of beta-blockers on bone while human studies are limiting and not conclusive. In the investigation in the field of beta-blockers the most important things which are of major concern are pharmacokinetic and pharmacodynamic properties of this class of drugs (Sharif and Abdollahi, 2010b).

Other than beta-blockers and NSAIDs, the effect of statins on bone metabolism has been studied in animal and human investigations. The pleiotropic effects of statins and the role of lipid metabolism in bone remodeling provided clues for further investigations. In vitro studies showed their benefits on bone formation however the issue could not be confirmed because of lack of enough evidences (Sharif and Abdollahi, 2011).

Enthusiasm into application of natural products especially in prevention modalities in the recent decade made investigators eager in paying special attention into their impact on bone as phytoestrogens. A meta-analysis on the clinical trials showed that phytoestrogens can prevent bone resorption with non-significant benefit on bone formation (Sharif *et al.*, 2010b); an effect similar to the effect of n-3 fatty acids on bone metabolism.

Taken together it is suggested that more investigations on the role of inflammation in the pathogenesis of osteoporosis and its counterbalance with special biomarkers such as homocysteine highlights the best way of prevention and/or treatment of osteoporosis with less side effects and better efficacy.

REFERENCES

Fraser, L.A., K.N. Vogt, J.D. Adachi and L. Thabane, 2011. Fracture risk associated with continuation versus discontinuation of bisphosphonates after 5 years of therapy in patients with primary osteoporosis: A systematic review and meta-analysis. Ther. Clin. Risk Manage., 7: 157-166.

Green, J., G. Czanner, G. Reeves, J. Watson, L. Wise and V. Beral, 2010. Oral bisphosphonates and risk of cancer of oesophagus, stomach and colorectum: Case-control analysis within a UK primary care cohort. BMJ, 341: c4444-c4444.

Larijani, B., A. Moayyeri, A.A. Keshtkar, A. Hossein-Nezhad and A. Soltani *et al.*, 2006. Peak bone mass of Iranian population: The Iranian multicenter osteoporosis study. J. Clin. Densitom., 9: 367-374.

McGarry, K.A. and D.P. Kiel, 2000. Postmenopausal osteoporosis: Strategies for preventing bone loss, avoiding fracture. Postgrad. Med., 108: 79-91.

Nevitt, M.C., 1994. Epidemiology of osteoporosis. Rheum. Dis. Clin. North Am., 20: 535-559.

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

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

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. and M. Abdollahi, 2011. 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. Int. J. Pharmacol., 7: 552-567.

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

Sharif, P.S. and M. Abdollahi, 2010b. A systematic review on the relationship between β-blockers and bone health. Int. J. Pharmacol., 6: 577-583.

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, 10.1007/s11357-010-9180-6.

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.