

Editorial

Oxidative stress may be a common mechanism linking major depression and osteoporosis

Introduction

Chronic conditions constitute the bulk of the disease load, particularly in Western societies. The prevalence and consequences of such conditions are becoming better appreciated, although the intricacies of their pathogenesis and interrelationships are largely not definitively determined. Major depressive disorder and osteoporosis are two pertinent examples of increasingly prevalent disorders that appear to be related. Several epidemiological studies have reported diminished bone mineral density among depressed men and women compared with controls (1–10), dysregulation of bone turnover (3,5,8) and increased risk for fracture (11–13). Data from animal models show that stress-induced depression leads to altered rates of bone remodelling (14) and loss of trabecular bone volume, trabecular number and connectivity (15). Although these studies are heterogeneous in design, they reveal a consistent association between depression and indices of osteoporosis. The nature of this association remains to be clarified, but a number of pathophysiological pathways are potential mediating mechanisms. Among these, oxidative stress stands out as a plausible candidate, given the fundamentality of oxidation physiology, and the newly emerging evidence for an intrinsic role of oxidative stress in both major depression and osteoporosis.

Oxidative stress

At higher concentrations, free radicals and non-radical reactive species are hazardous for living organisms and damage major cellular constituents. At lower concentrations, however, nitric oxide and reactive oxygen species (ROS, including superoxide, singlet oxygen, hydrogen peroxide and the highly reactive hydroxyl radical) play important roles as

regulatory mediators in signalling processes (16,17). Many ROS-mediated responses protect cells against exposure to oxidants and re-establish reduction/oxidation (redox) homeostasis. Excess ROS disrupt cellular redox status, leading to a net oxidative overbalance ('oxidative stress'), which causes cellular dysfunction, and has been implicated in the pathogenesis of disease including cancer (18), diabetes mellitus (19), atherosclerosis (20) and rheumatoid arthritis (21). Progressive changes in free-radical-mediated regulatory processes may also play a role in the aetiology of both depression and osteoporosis and may, in part, mediate their association.

Oxidative stress and depression

Altered levels of antioxidative enzymes (22–25) and the lipid peroxidation product malondialdehyde (22–24) have been reported in major depression, especially in cases with melancholic features (22). Normalisation of oxidative stress markers with antidepressant treatment has been demonstrated (22,23,25), and a positive correlation was reported between oxidative stress index values and severity of depression (26). These findings strengthen the hypothesis that oxidative stress is inherent in active depressive illness processes.

Further support for the relevance of oxidative stress behind depressive illness pathogenesis can be found in pharmacology studies. Established antidepressants have been shown to possess antioxidant properties in cellular and animal studies. For instance, the monoamine oxidase (MAO) inhibitor phenelzine has been observed using *in vitro* cell studies to modulate oxidative stress pathways via several mechanisms that included hydrogen peroxide scavenging and the prevention of MPP⁺-induced decrease in mitochondrial membrane potential, cytochrome *c* release, formation of ROS and depletion of

glutathione (27). The reversible inhibitor of MAO-A, moclobemide, has been shown to significantly increase the survival of rat neuronal-astroglial cultures using *in vitro* models of brain ischaemia, with decreased free radical formation through MAO-A inhibition being the hypothesised mechanism (28). Venlafaxine reduced levels of oxidative stress in a rat model of depression (induced by chronic mild stress), as indexed by increased glutathione peroxidase activity and glutathione and vitamin C levels and by lower nitric oxide levels and lipid peroxidation in the brain (29). Both venlafaxine and fluoxetine have been shown to modulate antioxidant proteins, among others, in a proteomic study (30).

Oxidative stress and osteoporosis

Bone loss occurs as a result of imbalances in bone remodelling, whereby osteoclastic bone resorption exceeds osteoblastic bone formation (31). Adult ageing is accompanied by bone loss (32), decreases in plasma antioxidant enzymes (33) and reduced antioxidant intakes in the diet (34). The rate of bone remodelling and negative bone balance increases after menopause in women, accelerating bone loss and trabecular and cortical thinning, and increasing bone porosity and fragility (35).

There is compelling *in vitro* and *in vivo* evidence to suggest that oxidative stress is involved in bone cell biology. Antioxidant defences were found to fall in the bone marrow of female rats after ovariectomy, and the response was rapidly normalised by exogenous 17- β oestradiol and prevented by the antioxidants *N*-acetylcysteine (NAC) and ascorbate (36). By contrast *L*-buthionine-(SR)-sulphoximine (BSO), a specific inhibitor of glutathione, the major intracellular antioxidant, caused substantial bone loss. Furthermore, depletion of antioxidants by BSO, like ovariectomy, caused bone loss through tumour necrosis factor- α (TNF- α) signalling, and in ovariectomised mice treated with soluble TNF- α receptors, antioxidant defences in bone remained low, despite inhibition of bone loss (37). The authors concluded that low levels of antioxidants in bone following ovariectomy were the cause of increased bone resorption.

The antioxidant vitamins are vitamins C and E and the β -carotene form of vitamin A. Guinea pig studies have shown that low vitamin C intake in growing animals is associated with high rates of bone turnover (38). Epidemiological studies have found a positive association between dietary vitamin C intake and bone mineral density in postmenopausal women (39–41), and low dietary intakes of vitamins C and E have been linked to an increased

risk of hip fracture in smokers (42). Diminished dietary and endogenous antioxidants have been reported among elderly osteoporotic women compared with age-matched controls (43), with differences significant for dietary vitamins A, C and E, and for endogenous molecules with scavenging activity (specifically uric acid, superoxide dismutase and glutathione peroxidase). Antioxidant vitamin supplements have been associated with reduced rates of bone resorption in non-smoking postmenopausal women (44), and a recently reported randomised controlled trial showed progressively reduced bone resorption in early postmenopausal women treated with the potent orally administered antioxidant, NAC (45). Vitamin intake may, however, be associated with other risk factors.

It should be noted that excess dietary retinol intake has been identified as a risk factor for hip fracture and associated with accelerated bone loss (46,47). It has been suggested that serum concentrations of vitamin A at both ends of the spectrum (high and low) increase the risk of hip fracture (48). The role of retinol, in addition to other forms of vitamin A (including β -carotene), remains unclear. However, taken in aggregate, the findings suggest a positive role for antioxidants in protecting against bone loss.

Oxidative stress connecting depression and osteoporosis

An initial hypothesis for the association between osteoporosis and depression related to hypercortisolaemia, which has been observed in major depression and is known to be detrimental to the skeleton (49). However, this seems more suitable in explaining a unidirectional relationship and is unlikely to be the sole mechanism of the association between these two conditions, given the complexities of their aetiologies and pathogenic processes.

An advantage of examining pathogenesis from the oxidative stress perspective is the explanatory power afforded by its fundamental placement in the hierarchical aetiopathogenic framework, which extends from gross extrinsic influences to basic molecular biology. Hence, regardless of the initial insults responsible for the illness, oxidative stress may be a common trunk pathogenic pathway, which may become a self-perpetuating process that progressively induces disease states in susceptible individuals. Because of this basic role and its ubiquitous involvement in all bodily systems, oxidative stress stands out as a prime candidate mediator in the pathophysiology of comorbid diseases. As there is already evidence that

establishes an active role for oxidative stress in the development of both major depression and osteoporosis, the extension of this role to a mediating one seems most plausible on both theoretical and empirical grounds.

It would of course be simplistic and unconvincing to assert that oxidative stress is the only mediating mechanism, when most diseases including major depression and osteoporosis involve multiple pathological paths. The capacity for the oxidative stress hypothesis to incorporate the action of other mechanisms through the confluence of oxidative pathways with other biopathways is one of its strengths. Immunological pathways provide a useful example for this discussion. For major depression and osteoporosis, each has individually accrued literature on immunological changes that seem intrinsically related to the disease process. In major depression, these include the acute-phase response, comprising raised haptoglobin, interleukin (IL)-6, complement factors and C-reactive protein (50–53), impaired lymphocyte proliferative response to mitogens and reduced lymphocyte phagocytosis (54). Elevated serum high-sensitivity C-reactive protein (hsCRP) has been reported in a large sample of women with osteopenia or osteoporosis and has been positively correlated with serum alkaline phosphatase levels, indicating states of accelerated bone turnover (55). Serum hsCRP has recently been identified as a prognostic marker of fracture (56–58). Various anti-inflammatory and proinflammatory cytokines including IL-1, IL-6, TNF- α and - β , transforming growth factor- α and - β , granulocyte-monocyte colony-stimulation factor, monocyte-macrophage-stimulating factor and prostaglandin E₂ are understood to be important in the normal bone remodelling process (59,60). There is abundant evidence that cytokines and the inflammatory response are closely linked to oxidative stress states (61–63), and this might provide a further nexus in the mediating role of oxidative stress for depression and osteoporosis.

Although oxidative stress is unlikely to be the sole mediator between major depression and osteoporosis, it offers an attractive hypothesis for further study for several reasons. Its omnipresent role in human physiology and its applicability to diverse, if not universal, pathological processes suggest that it may be comparatively dominant among different biological pathogenic mechanisms. Furthermore, it may have important practical implications in that antioxidants may have undiscovered preventive and therapeutic values. The oxidative stress hypothesis raises the possibility that sustaining antioxidant defences during

ageing may be protective against these diseases. Antioxidant defences may be sustained through antioxidant intake, body habitus and lifestyle, and this field of research warrants further investigation. Nutritional epidemiology has already suggested that dietary antioxidants are crucially involved in the prevention of certain degenerative diseases, but at this time, the scientific data do not justify the use of antioxidants for risk reduction of depression or osteoporosis. We anticipate data for developing evidence-based recommendations for new methods of intervention using available tolerable, safe and affordable antioxidant approaches.

Conclusions

We have postulated and explored the concept that development of major depression and deterioration of the skeleton are both influenced by increased oxidative stress levels. Indeed, markers of oxidative stress within depression and osteoporosis may play a vital role in disease expression and suggest a mediating link between these disorders. In addition to pathological understanding, this hypothesis introduces opportunities to investigate novel treatment approaches, which may be of benefit to the outcomes of debilitating chronic diseases.

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