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POSSIBLE ASSOCIATION OF PSORIASIS AND REDUCED BONE MINERAL DENSITY DUE TO INCREASED TNF-α AND IL-6 CONCENTRATIONS

SUMMARY

Psoriasis is a chronic erythematosquamous disease affecting about 2-3% of the population. It is generally considered to be a T cell-mediated disorder. Psoriasis is characterized by Th1-type cytokine pattern with the predominant secretion of IL-2, IL-6, IFN-α and TNF-α. Such cytokine pattern is sufficient in inducing keratinocyte hyperproliferation, a hallmark of psoriasis. It seems that development of psoriatic lesions is mediated by TNF-α and proliferation of local T cells is dependent on local TNF-α production. IL-6 enhances activation, proliferation and chemotaxis of T cells into psoriatic lesions. It is also a direct keratinocyte mitogen that could directly stimulate keratinocyte proliferation. Data of possible association between psoriasis and reduced bone mineral density (BMD) are limited and therefore not fully conclusive. The major limitation of two studies reported so far was small sample size. Based on increased concentrations of TNF-α and IL-6 in psoriasis we hypothesised that these patients are more prone to osteoporosis than healthy subjects. TNF-α enhances bone resorption via stimulating osteoclast development and activity and bone formation. On the other hand, IL-6 is also a potent stimulator of bone resorption. Moreover, increased production of TNF-α and IL-6 has been found in postmenopausal women with osteoporosis. Several lines of evidence support our hypothesis; higher value of IL-6 was recorded in children with idiopathic osteoporosis than in healthy controls; TNF-α knock-out mice do not lose bone after ovariectomy; polymorphism of TNFRSF1B gene which encodes 75Kd TNF receptor is associated with BMD; treatment with anti-TNF-α antibody exert beneficial effect on bone metabolism in patients with rheumatoid arthritis and finally, raloxifene inhibit osteoclast activity by reducing TNF-α and IL-6 synthesis. However, our

hypothesis raised number of questions. Are increased serum concentrations of TNF-α and IL-6 mirrored by increased concentrations of these cytokines on the local level? Furthermore, do other cytokines relevant in the pathogenesis of the psoriasis, first of all IFN-α, could modulate the risk of osteoporosis? Thus, a large prospective, case-control study with the data on BMD, biochemical parameters of bone turnover and fractures have to be done to test our hypothesis.

Psoriasis is a chronic erythematosquamous disease affecting about 2-3% of the population (1). It is generally considered to be a T cell-mediated disorder (2). In psoriasis, T lymphocytes affect epidermal growth homeostasis inducing increased keratinocyte proliferation and abnormal differentiation. Systemic T cell activation is followed by the local accumulation of CD4+ lymphocytes in the dermis and activation of CD8+ lymphocytes in the epidermis of psoriatic lesions (3). Thus, it seems that activation of T cells is a key step in the development of psoriasis. Psoriasis is characterized by Th1-type cytokine pattern with the predominant secretion of IL-2, IL-6, IFN-α and TNF-α (4). Such cytokine pattern is sufficient in inducing keratinocyte hyperproliferation, a hallmark of psoriasis. The source of these cytokines is not only T cells but also keratinocytes itself (5). T cells are the likely source of IFN-α, TNF-α and IL-2, whereas keratinocytes produce IL-6 and TNF-α. Thus, psoriasis is a consequence of persistent dialogue between keratinocytes and T lymphocytes in an appropriate cytokine milieu.

Altered cytokine network seems to have a central role in the pathogenesis of psoriasis. Among previously mentioned cytokines, TNF-α is crucial for local T cell proliferation (6). It seems that development of psoriatic lesions is mediated by TNF-α and proliferation of local T cells is dependent on local TNF-α production. The importance of TNF-α in psoriasis is further stressed by the efficacy of anti-TNF-α monoclonal antibodies in the treatment of psoriatic patients (7).

In psoriasis, IL-6 enhances activation, proliferation and chemotaxis of T cells into psoriatic lesions (8). It is also a direct keratinocyte mitogen that could directly stimulate keratinocyte proliferation. IFN-α, produced by activated T lymphocytes, has a major growth-producing effect on psoriatic keratinocytes. Although, IFN-α is a potent inhibitor of keratinocyte proliferation in vitro, in psoriasis IFN-α in cooperation with other growth factors enhances keratinocyte proliferation (9).

Data of possible association between psoriasis and reduced bone mineral density (BMD) are limited and therefore not fully conclusive. Reduced BMD has been linked to palmoplantar pustular psoriasis (10), but has not been found in chronic plaque form of the disease although patients with joint affection have significantly lower BMD than those without arthropathy (11). However, the major limitation of these studies was small sample size.

Based on previously mentioned increased concentrations of TNF-α and IL-6 in psoriasis we suggest that these patients are more prone to osteoporosis than healthy subjects. It is well known that various cytokines influence bone remodelling. Specifically, TNF-α enhances bone resorption via stimulating osteoclast development and activity and bone formation (12). On the other hand, IL-6 is also a potent stimulator of bone resorption (13). It has been suggested that mechanism of postmenopausal osteoporosis is, at least partly, mediated by modulation of cytokine production due to estrogen deficiency (14). Zheng and colleagues observed increased production of TNF-α, IL-1β and IL-6 in postmenopausal women with osteoporosis (15).

Several lines of evidence support our hypothesis in terms of key role of TNF-α and IL-6 in bone remodelling; higher value of IL-6 was recorded in children with idiopathic osteoporosis than in healthy controls (16); TNF-α knock-out mice (TNF-α -/-) do not lose bone after ovariectomy (17); polymorphism of TNFRSF1B gene which encodes 75Kd TNF receptor is associated with BMD and bone loss (18); treatment with anti-TNF-α antibody has been shown to exert beneficial effect on bone metabolism in patients with rheumatoid arthritis (19). Finally, raloxifene, drugs approved for treatment of osteoporosis, inhibit osteoclast activity by reducing TNF-α and IL-6 synthesis (20).

Although above mentioned evidences suggest association of psoriasis and osteoporosis risk our hypothesis raised number of questions. Are increased serum concentrations of TNF-α

and IL-6 mirrored by increased concentrations of these cytokines on the local level, in the bone microenvironment seem to be the most important one. Furthermore, do other cytokines relevant in the pathogenesis of the psoriasis, first of all IFN-α, could modulate the risk of osteoporosis? Thus, a large prospective, case-control study with the data on BMD, biochemical parameters of bone turnover and fractures have to be done to test our hypothesis.

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