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Letter to the Editor

CC chemokines CCL2, CCL3, CCL4 and CCL5 are elevated in osteoporosis patients

Dear Editor:

Osteoporosis is defined as a disorder associated with low bone mineral density (BMD). Evidence indicates that the immune system is strongly related to bone metabolism in terms of osteoimmunology, noticeably, interplay between the skeletal and immune system like cellular and non-cellular components, including innate and adaptive immune responses and cytokines and chemokines[1]. Very few studies are available that investigated the role of chemokines in osteoporosis[2]. In the current study, we sought to determine whether if pro-inflammatory and angiogeneic/angiostasis CC chemokines were altered in patients with osteoporosis. The current cross sectional study was performed in the Rafsanjan University of Medical Sciences during 2012. Signed informed consent form was obtained prior to enrolment from all study participants. The Dual X-ray absorptiometry (DXA) BMD and WHO (World Health Organization) criteria were used for diagnosis. BMD was determined using Lexxos DMS equipment. According to the WHO classifications the bone density T-score at the left femoral neck or lumbar vertebral equal to -1 or more was considered as normal group. Any obtained T-score lower than -1 and -2.5 was regarded as osteopenia and patients showing a T-score equal to or lower than -2.5 were assigned as osteoporosis. Patient demographic characteristics are shown in ***Table 1***. Postmenopausal women were excluded. Subjects with chronic diseases and conditions which may potentially affect either bone mass or chemokine expression were excluded from the study. The approval of the study protocol was granted by the ethical committee of Rafsanjan University of Medical Sciences. Circulating chemokines were detected by ELISA using commercial kits (R and D Systems, UK) immediately after blood collection according to the manufacturer's guidelines. The kits were sensitive at the level of ±2 pg/mL and both inter- and intra-assay assessments were done. The SPSS software version 18 was applied to analysze the data. The significance of differences among individual groups of the tested populations was evaluated with the *t*-test. Any $P<0.05$ was considered significant. Present findings evidenced that the circulating CCL2 level was increased in osteoporosis. The levels of CCL2 were significantly elevated in osteoporosis patients *vs*. healthy controls ($P<0.001$). The mean contents of CCL2 were (1,386.38±3) pg/mL, (221.04±86) pg/mL in osteoporosis patients and controls, respectively (***Fig. 1A***). The circulating level of CCL3 in osteoporosis patients was increased as well. It was significantly elevated in osteoporosis patients compared to controls ($P<0.001$). The mean contents of CCL3 were (936.39±204) pg/mL and (134.5±4.58) pg/mL in osteoporosis patients and controls, respectively (***Fig. 1B***). CCL4 was also increased in osteoporosis patients and was significantly different from controls ($P<0.001$). The mean contents

Table 1 **The demographic characteristics of the study population**

	Osteoporosis	Control
Sex		
Male	3	3
Female	18	18
Age range, years	20-76	27-68
Height, cm	137-185	135-181
Weight, Kg	45-100	53-98
Smoking	0	0
Drinking	0	0

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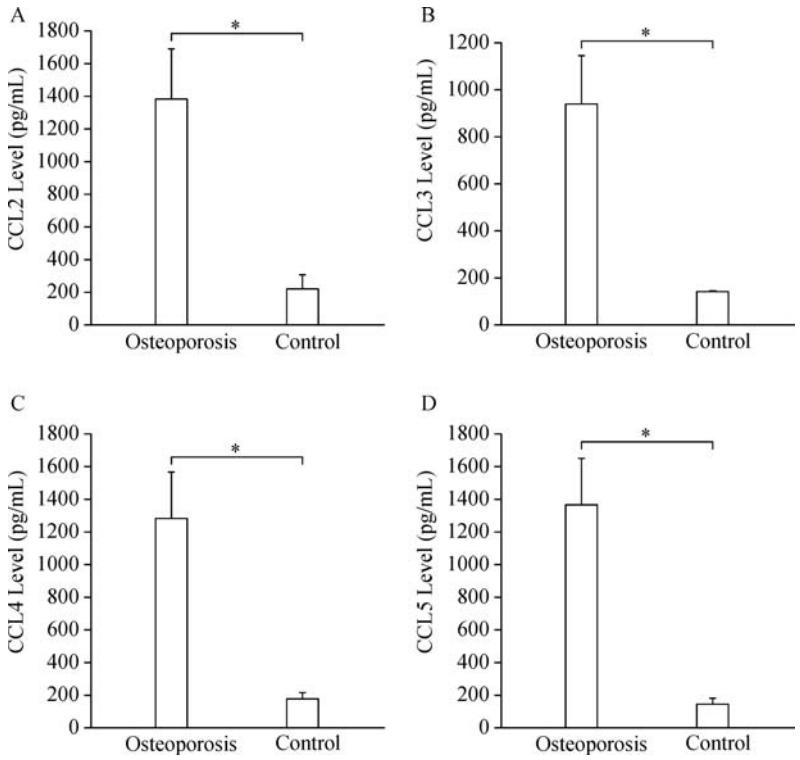

Fig. 1 **The circulating levels of CCL2 (A), CCL3 (B), CCL4 (C) and CCL5 (D) in osteoporosis patients and controls.** Data are presented as mean±SEM for 21 osteoporosis patients and 21 controls. $^{*}P<0.05$.

of CCL4 were (1,287.61±280) pg/mL and (175.66±38) pg/mL in osteoporosis and controls, respectively (***Fig. 1C***). Regardingly, the CCL5 circulating contents were increased in osteoporosis patients. The serum levels of CCL5 were significantly elevated in osteoporosis subjects, when compared to control ($P<0.001$). The mean levels of CCL5 were (1,368.06±280) pg/mL and (156.28±34.04) pg/mL in osteoporosis subjects and controls, respectively (***Fig. 1D***). Cytokines and chemokines are also involved in skeletal remodeling[2]. In the present study, we determined pro-inflammatory and angiogeneic/angiostasis CC chemokines in patients suffering from osteoporosis. The contents of CCL2, CCL3, CCL4, and CCL5 were all increased in osteoporosis with different extents. Evidence suggests that CCL2 had limited effects on both osteoclast fusion and bone resorption of $CD11b^{+}$ cells *in vitro*. The presence of CCL3 receptors (CCR1 and CCR5) on osteoblasts may indicate that this chemokine is involved in bone formation; however, this chemokine has been recently reported to inhibit osteoblastic function in myeloma[8]. CCL5 is an osteoblast chemoattractant and a survival-promoting molecule whose regulation in osteoblast is varied. Furthermore, CCL5 is secreted from osteoclasts and induces osteoblast chemotaxis. Therefore, the expression of CCL5 and its receptors in both osteoblasts and osteoclasts could enable this chemokine to act in an autocrine/paracrine mode[8]. Furthermore, another β-chemokine, CCL3, which acts by binding to CCR1 and CCR5, induced CCL5 secretion from osteoblasts. CCL3 secretion is high in osteoclasts and their precursor cells, compared with osteoblasts. Moreover, a concentration-dependent increase in CCL5 by CCL3 showed that CCR1 and CCR5 receptors are functional in osteoblasts. Finally, because CCL5 regulates several important osteoclast functions and CCL3 is secreted predominantly by osteoclasts, it is conceivable that communication between osteoclasts and osteoblasts could be regulated by these two chemokines[8]. Overall, more investigations are needed to examine the expression of these mediators and their respective receptors at the mRNA level in patients suffering from osteoporosis and osteopenia. We also plan to investigate the role of upstream signals which may control the expression of these chemokines and maybe other members of chemokine subfamily, especially CXC chemokines that are involved in angiogenesis/angiostasis balance such as CXCL10 and CXCL12.

Yours Sincerely,

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