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Subchondral bone disturbance in advanced knee osteoarthritis is worsened with co-morbid hypertension: does endothelin-1 matter?

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Purpose: Knee osteoarthritis (OA) and hypertension are prevalent in elderly patients. A close relationship between arterial stiffness and hand OA has been demonstrated in epidemiological studies. Emerging evidence suggests roles of vascular pathology in the pathogenesis of OA. However, the relationship between hypertension and knee OA remains unclear. Hence, this study aims to explore the functional and structural alterations in knee OA with regard to the co-occurrence of hypertension, and look into the hypothesis that ET-1 is involved in the association between hypertension and knee OA.
Methods: A cohort of 76 advanced primary knee OA patients (59 females, 17 male, aged 52-87) were recruited. Knee functions and subchondral bone alterations of patients with medical history of systemic hypertension were compared with the non-hypertensive patients. Functional disabilities of knees were assessed using knee society knee score and knee society functional scale. Axial alignment of the lower extremities was inspected on radiograph. Tibial plateaux resected during total knee arthoplasty were collected with informed consent and examined for the microstructural parameters in subchondral bone using micro-CT.
To investigate the circulating ET-1 level, blood samples were collected from 20 knee OA patients attending outpatient clinic (15 females, 5 females, aged 51–77). The plasma ET-1 level was evaluated using a commercially available ELISA kit (DET100).
To explore the association between osteoblastic cells ET-1 expression and microstructure of OA subchondral bone, explant culture was performed using bone chips collected from medial and lateral compartments of tibial plateaux from 15 advanced primary knee OA patients. Relative gene expressions were studied using qPCR and were correlated to micro-CT results.
Results: When compared to 36 non-hypertensive subjects, 40 hypertensive subjects were observed to have worsened walking functional score (24±7 compared to 21±6), more severe varus deformities (genu varum) (169°±6° compared to 164°±9°) and reduced lateral compartment subchondral bone connectivity densities (7.86±3.52 mm-3 compared to 6.23±2.50 mm-3) when compared to non-hypertensive knee OA patients.
Particularly, decrease in lateral compartment connectivity density (7.67±3.57 mm-3 compared to 5.85±2.54 mm-3) and increase in medial compartment porosity (0.15±0.11 compared to 0.07±0.05) were found in subchondral bone of hypertensive female subjects compared to non-hypertensive female subjects. In male hypertensive subjects, a reduction in medial compartment subchondral bone intersection surface (76.27±29.21 mm2 compared to 37.04±14.06 mm2) was found.
Plasma ET-1 levels were found to be elevated in our cohort of knee OA patients (2.65±1.58 pg/mL) relative to reference value (1.17±0.32 pg/mL). After adjusting for patients' age, gender and body mass index (BMI), the increase in plasma ET-1 in knee OA patients was found to be positively associated with co-morbid hypertension ($\beta = 0.588$, $p = 0.030$) and BMI ($\beta = 0.866$, $p = 0.003$).
In terms of local transcription level, it was found that ET-1 expression positively correlates to TGF-β expression (Pearson's $r=0.666$, $p=0.001$) and NGF expression (Pearson's $r=0.613$, $p=0.025$), while negatively correlates to RUNX2 expression (Pearson's $r=-0.484$, $p=0.026$).

Also, ET-1 expression was found to negatively correlate to connectivity density (Pearson's r=−0.578, p=0.019), bone surface density (Pearson's r=−0.523, p=0.038), trabecular number (Pearson's r=−0.499, p=0.049) while positively correlate to trabecular separation (Pearson's r=0.585, p=0.017) in OA subchondral bone.
Conclusions: Functional and structural alterations were observed in knee OA in the presence of hypertension, and a potential association of ET-1and bone remodeling. Since this is a cross-sectional study, no causative relationship could be indicated. We postulate that high level of ET-1 impairs subchondral bone remodeling evidenced by the poor connectivity of trabecular bone, and thus contributes to more severe gross joint deformity and worse knee function. This prompts the needs of further longitudinal study of the relationship among knee OA, hypertension and ET-1.