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Response to "Spontaneous hypertensive rat exhibits bone and meniscus phenotypes of osteoarthritis: is it an appropriate control for MetS-associated OA?" by Chan and Wen

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We thank Dr Chan and Dr Wen for their interest in our report¹ and their resulting eLetter². We fully agree that, among the different components of metabolic syndrome (MetS), hypertension has very recently been brought out as a critical feature in the development of osteoarthritis (OA) in humans.^{3,4} In these reports using either data from the Framingham OA study³ or the Osteoarthritis Initiative study⁴, it has been emphasized that high blood pressure (diastolic or systolic respectively) was associated with increased incidence of radiographic knee OA.

In order to further experimentally investigate the actual role of hypertension in OA onset and development, Chan and colleagues describe in a yet unpublished study the development of OA features in the spontaneous hypertensive rat (SHR) model, a widely characterized model of systemic hypertension.^{2,5} Although the spontaneous hypertensive heart failure (SHHF) rat strain we employed is deriving from the SHR strain⁶ and suffers high blood pressure likewise, we were not able to identify OA-like lesions in our experimental model of SHHF^{+/+} lean rats.¹ These seeming discrepancies obtained in two related rat strains raised the concerns expressed by Chan and Wen on our recent results.

First, we respectfully disagree on the reservations put forward by Chen and Wen regarding our choice 'to study the mixed components of MetS in one model'.² Indeed, in contrast to their study,^{2,5} our goal was purposely to explore the contribution of MetS as a whole,¹ not to investigate a single and isolated MetS component, such as hypertension. Besides, since SHHF^{+/+} and SHHF^{cp/cp} are both hypertensive,^{7,8} our results demonstrate the contribution of the metabolic components of MetS (obesity, dyslipidemia and insulin resistance) in knee OA development after adjustment for both age and blood pressure. Interestingly enough, the ability of eplerenone to prevent OA development¹ without decreasing blood pressure⁸ further support the role of MetS as a whole, but not that of hypertension, in the OA lesions we observed in SHHF rats.¹

Second, Chan and Wen suggest the inadequate use of SHHF^{+/+} as proper controls in our study.² Because both SHHF^{+/+} and SHHF^{cp/cp} share the very same genetic background, SHHF^{+/+} rats are very appropriate controls to compare to their littermate SHHF^{cp/cp} rats. By contrast, Wistar Kyoto (WK) used as control in Chan's study and SHR rats^{2,5} are more distant genetically and may differ greatly besides the normal vs. hypertensive status, which therefore may force caution in the proposed interpretations of the results. It stands however true that, in contrast to Chan and colleagues' results,^{2,5} we did not observe OA-like lesions in 12.5 month-old SHHF^{+/+} knee joints,¹ when they do report changes in bone and menisci, but no gross cartilage damage, in the knees of 9-month-old SHR rats.^{2,5} The apparent discrepancies may be attributable to the difference in the parameters examined to evaluate OA in the two studies. Indeed, Chan *et al.* mostly evaluated changes in subchondral bone and meniscus,^{2,5} whereas we performed histopathological analysis of synovial and cartilage tissues.¹ Although subchondral remodelling is critical in OA, we have not looked closely at the subchondral bone phenotype as clearly stated in our Letter.¹ So, if as explained above we can exclude that hypertension does cause by itself OA-like phenotype in synovial and articular cartilage tissues of ^{12.5}SHHF^{+/+} rats, we cannot rule out that, similar to what can be observed in SHR rats, SHHF^{+/+} rats (and SHHF^{cp/cp} for that matter) do present significant remodelling of subchondral bone, a highly vascularized tissue, more prone to get affected by systemic pressure modification.

Based on Chan's eLetter comments² and forthcoming study on SHR rats,⁵ we acknowledge that further investigation will be required to study and clarify the role of hypertension in SHHF rats as well. As a matter of fact, beside a comprehensive μ CT analysis of the subchondral bone of both placebo- and eplerenone-treated SHHF^{+/+} and SHHF^{cp/cp} knees, we are also currently analyzing the knee phenotype of 18-month-old SHHF^{+/+} rats. Compared to age-matched Wistar Kyoto normotensive rats as controls, this would allow to answer more directly Chan and Wen concern regarding the independent role played by hypertension in the SHHF model and probably corroborate their findings obtained in the SHR rats.^{2,5}

Again, we appreciate the interest Chan and Wen show in our work and hope we adequately answered their concerns.

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Contributions

HK and AP : concept, writing; CD, AB, NP, DM, MK, CG, HK and AP : final approval.