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Is subchondral bone cyst formation in non-load-bearing region of osteoarthritic knee a vascular problem?

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ABSTRACT

Subchondral bone cyst is common in the progressive knee osteoarthritis yet its underlying mechanism remains unclear. In addition to the existing theories such as synovial fluid influx and mechanical contusion, we identified the potential link between vascular pathology and osteoarthritic bone pathologies including cystic lesion formation, particularly in the non-load-bearing region. This new hypothesis for SBC formation in non-load-bearing region for knee, which cannot be explained by the existing theories, will provide us a new angle to understand the pathomechanism and pathophysiology of subchondral bone disturbance in osteoarthritis in addition to the classical biomechanical overloading theories. It might guide us to develop a novel diagnostic and therapeutic approach to treat progressive osteoarthritis via targeting vascular pathology.

Introduction

Subchondral bone cyst (SBC), also known as “pseudo-cyst” and “geode” to orthopaedic surgeons, is one of textbook radiological features in osteoarthritis (OA) of the knee and shoulder. Previous reports stated SBCs commonly occurred underneath the joint surface subject to major mechanical loading where the articular cartilage were severely damaged. Given the evidence that the presence of SBCs is associated with greater loss of articular cartilage and increased risk of joint replacement surgery [1], it is obvious that the underlying pathomechanism of SBCs warrants further studies.

Two conflicting theories were proposed to address the aetiology of SBCs. One is the synovial intrusion theory – according to which synovial fluid is believed to be pumped into subchondral trabecular bone through microcracks on worn articular cartilage and damaged subchondral bone plate. This theory is widely accepted by orthopaedic surgeons and to a large extent veterinarians, as lollipop-shape synovial invaginations are sometimes observed in navicular bone of horses [2]. Another postulation is the bony contusion theory – in which bone bruising upon repetitive mechanical loading of subchondral trabecular bone is believed to be a prerequisite, and subsequent bone marrow oedema that fail to resolve due to chronic injuries and inflammation would further progress into SBCs. Whilst these theories may explain occurence of SBCs in load-bearing-regions caused by repetitive load-bearing and mechanical insults, both of them cannot explain the entire spectrum of SBC pathophysiology in OA. From our observations, SBCs do exist in non-load-bearing regions, like the tibial eminence and lateral compartment without apparent damage on overlying cartilage or fractures of the subchondral bone plate in addition to the usually reported load-bearing area with overlying cartilage defects (Fig. 1) [3], and in our previous cross-sectional study which analysed 144 tibial plateau specimens, for every 10 SBC identified, 5 were found in the tibial eminence and 1 would be in the lateral compartment. Some researchers also found SBCs in the tibial eminence [4] and lateral compartment [1,5,6] without visible overlying cartilage defects. Since articular cartilage has poor regeneration capacity, it is very unlikely that the surface heals itself post SBC formation, and whilst the lateral compartment SBCs may still be accounted for by the bony contusion theory to a certain extent since the compartment takes approximately 30% of the total load of the knee, SBCs present in the tibial eminence cannot be easily explained by this hypothesis, rendering these biomechanics-based theories far less sound and applicable. Furthermore, there is still no consensus on the existing hypotheses since there is adequate supporting evidence for both hypotheses, suggesting microcrack formation and bone bruising do occur at a certain stage of SBC formation in load-bearing compartments, but whether there are factors other than biomechanical forces that may predispose the subchondral bone to these events remain unknown, and whether the two existing hypotheses are mutually exclusive or not is yet another unanswered question. Apart from mechanical factors, excessive bone resorption in rheumatic

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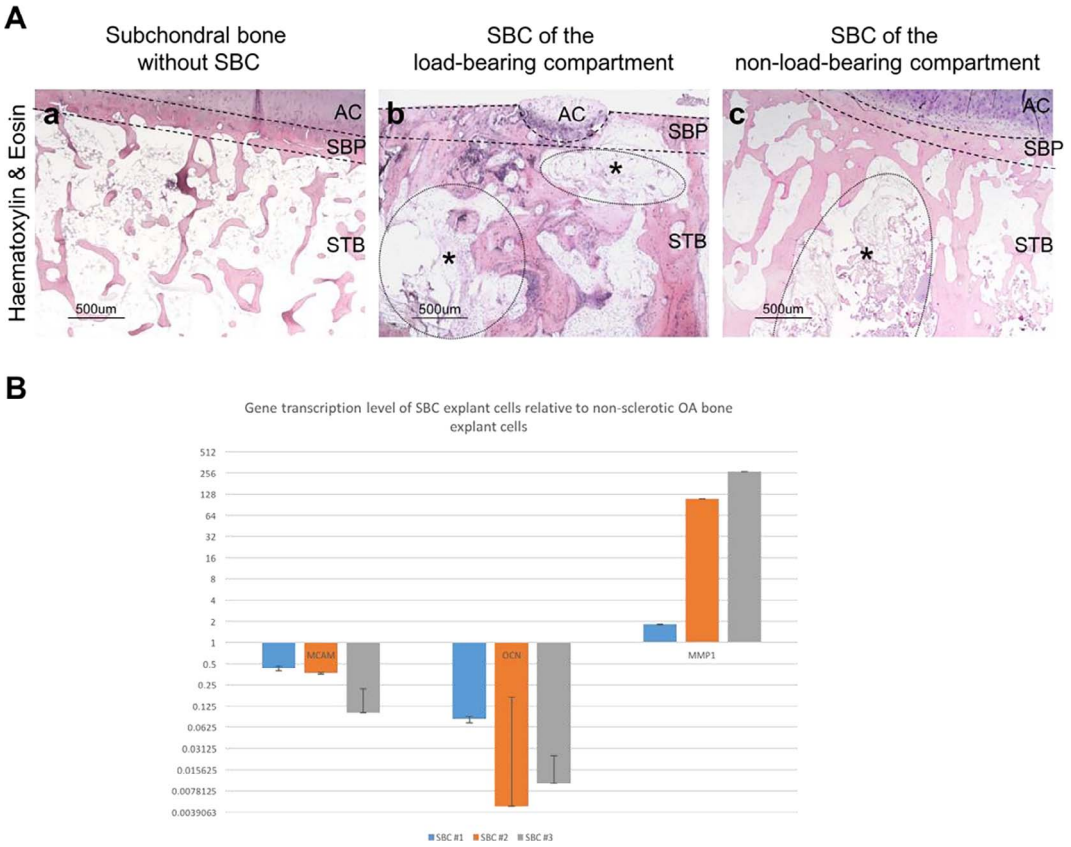

Fig. 1. (A) representative histological images of **lateral compartment** tibial plateau in advance knee osteoarthritis without subchondral bone cyst (a), with SBC of the load-bearing compartment **i.e. medial compartment** (b) and of the non-load-bearing compartment **i.e. lateral compartment** (c). The articular cartilage is labelled as AC, subchondral bone plate as SBP, and STB stands for subchondral trabecular bone. The SBCs are denoted by asterisk and demarcated by round dotted lines. We observed more fibrous tissue with higher cellularity in the case of load-bearing region SBC, and loosely filled void with some de novo bone fragments in the case of non-load-bearing region SBCs. (B) Relative Gene transcription levels of MCAM (CD146), Osteocalcin (OCN) and Matrix metalloprotease 1 (MMP1) of SBC explant cells. Numbers are expressed in fold difference relative to non-sclerotic tibial plateau subchondral bone explant cells from the same patient.

patients is a plausible contributing factor to the development of giant geodes in the subchondral bone. Moore et al. demonstrated that SBCs can originate as an isolated structure beneath the subchondral bone yet communicate with the synovial joint as it progresses based on an MRI-based case study of a RA patient [7]. Although RA is out of the scope of our study, this information does illustrate SBC formation could be a lot more complicated than otherwise thought.

To solve the mysterious occurrence of SBC in non-load-bearing region, our research group looked into systemic and local factors related to SBCs formation in knee OA and found hypertension, rather than obesity or weight, is a risk factor for SBC formation in these regions of the tibial plateau. However, this alone is insufficient in explaining the aetiology. Hence we would like to look deeper into how vascular pathology may lead to SBC formation in the non-load-bearing region.

Hypothesis

Currently, despite the synovial intrusion theory and the bony contusion theory are well established, and in our opinion, sufficient for explaining the occurrence of SBC in the load-bearing region, neither theories can provide satisfactory explanation for the occurrence of SBC in the non-load-bearing region. We believe the aetiology of these non-load-bearing SBCs could be remarkably different from the load-bearing SBCs and that other non-mechanical factors may cause development of SBC in the non-load-bearing region. The subchondral bone is a highly vascularised tissue, any disruption to the blood supply into the subchondral bone may cause detrimental consequences to the structure, one of them being bone resorption, which is a necessary step of bone geode formation. Angiotensin, which is the main vasoconstrictor and a major target for anti-hypertensive treatments, was found to be released by endothelial cells and act on osteoclasts thus leading to bone resorption [8]. In addition, it is known that bone marrow oedema (BMO) could be caused by reperfusion injury and that BMO can progress into SBCs [9], and given that our previous findings suggested a link between essential hypertension and SBC presence in the non-load-bearing region (Table 1), *we hypothesise SBCs in the non-load-bearing region are primarily caused by ischaemic episodes of insufficient vascular supply in the subchondral bone area as a result of vascular ageing and endothelial dysfunction.*

To test our hypothesis, we must first proof the occurrence of vascular ageing. Apart from the altered vessel structure and relaxation response to nitric-oxide and enhanced endothelin-mediated contraction, vascular ageing and endothelial dysfunction have been characterised by reduced endothelial cell senescence, endothelial migration and proliferation, thus compromised angiogenesis for repairing [10]. This inability in tissue repairing results in chronic ischaemia of the tissue, compromised neo-angiogenesis and plausibly depletion of perivascular cells (pericytes) in the injured site compared to the case of normal vasculature. Three separate sets of experiments are listed below to confirm tissue ischaemia and vascular ageing of the subchondral bone.

Firstly, to demonstrate previous ischaemic episodes, immunohistochemical staining of hypoxic markers regulated by HIF-1 and with longer half-life like Glut-1 and PAI-1 [11] should be appropriate. Whilst the gold standard for demonstrating vascular ageing would be functional analysis of vascular response upon addition of relaxation and contraction factors, it is not feasible to harvest intact vessels from the subchondral bone. To demonstrate signs of endothelial senescence,

Table 1
Comparison of systemic and organ-specific functions in knee osteoarthritis patients with or without subchondral bone cyst formation.

Parameters			OA patients without bone cyst	OA patients with bone cyst in non-load-bearing regions	*p* value
Demographic Data	Age (years old)		72 ± 11	72 ± 9	.980
	Gender	Male	5	8	.731
		Female	11	26	
	Height (Meter)		1.51 ± 0.05	1.52 ± 0.06	.602
	Body Weight (kg)		63 ± 12	63 ± 9	.824
	Body Mass Index (kg/m2)		28 ± 5	26 ± 3	.325
Blood pressure	Systolic blood pressure (mmHg)		167 ± 23	167 ± 12	.961
	Diastolic blood pressure (mmHg)		72 ± 11	72 ± 9	.731
	Mean arterial pressure (mmHg)		112 ± 14	113 ± 9	.719
	Pulse pressure (mmHg)		**56 ± 20**	**69 ± 13**	**.027**
	Heart Beat (/min)		98 ± 10	97 ± 15	.773
Blood	Hemoglobin (g/dL)		12 ± 1	12 ± 2	.943
Kidney	Urea (2.9–8.0 mmol/L)		6 ± 2	7 ± 3	.080
	Creatinine (49–82 umol/L)		75 ± 29	82 ± 24	.431
Liver	Total protein (67–87 g/L)		75 ± 6	75 ± 5	.863
	Albumin (39–50 g/L)		41 ± 3	42 ± 3	.375
	Globulin (26–40 g/L)		34 ± 6	33 ± 6	.444
	Alkaline phosphatase (47–124 U/L)		81 ± 29	71 ± 21	.244
	Alanine transaminase (8–45 U/L)		28 ± 21	24 ± 15	.617
	Aspartate transaminase (15–37 U/L)		37 ± 7	25 ± 8	.647
Glucose (< 7.8 mmol/L)			6.3 ± 1.1	7.8 ± 2.9	.087
Electrolytes	**Calcium (2.24–2.63 mmol/L)**		**2.25 ± 0.09**	**2.35 ± 0.10**	**.033**
	Phosphate (0.88–1.45 mmol/L)		1.13 ± 0.18	1.06 ± 0.15	.367

histochemical staining of senescence-associated-β-galactosidase (SA-β-gal) would be required.

Secondary, vascular supply has been known to be a vital and indispensable component in osteogenesis ever since the discovery of roles of VEGF as a growth factor essential for bone development in addition to vessel ingrowth. Kusumbe et al. first classified endosteal vessels into L-type ($CD31^{lo}$, $EMCN^{lo}$) and H-type ($CD31^{hi}$, $EMCN^{hi}$) vessels and found H-type vessels, despite being present in low percentage, are responsible for angiogenesis and modulating osteoblastic cells [12]. These findings have been successfully replicated by other authors and were first validated in the context of OA progression by Cui et al. [13], in which excessive H-type vessel ingrowth into the subchondral bone is found to cause osteosclerosis. A recent report also demonstrated that H-type vessels indeed play a role in maintaining bone mass in humans, and the depletion in such vessels results in bone loss, causing osteopenia [14]. We hypothesise insufficient H-type vessel ingrowth results in formation of SBC. This can be evaluated by immunofluorescent staining of CD31 & EMCN and subsequent histomorphometric analysis used in Wang and colleagues' study [14].

Pericytes around vessels is a source of potent mesenchymal stem cells and possibly osteoprogenitors [15], a cut-off could lead to osteopenia if not void formation. Rather than resulting in total collapse of subchondral bone in the case of "spontaneous osteonecrosis of the knee" (SPONK), the subchondral bone is temporarily stabilized by the formation of thickened trabeculae around the SBC to bear the load. To explore this hypothesis, SBCs and bone chips can be harvested from patients during total knee arthroplasty or subchondralplasty surgery and the cells can be harvested for flow cytometry analyses. Endothelial markers, mesenchymal markers, osteoprogenitor markers can be employed for general profiling of cell populations. Western blot and proteome can be used for testing the protein expression levels. A comparison study utilising transwell co-culture of normal pericytes with endothelial cells from the SBC explant against co-culture of normal pericytes with normal endothelial cells may be useful in investigating roles of defective endothelial cells in SBC formation. In an attempt to understand how cellular composition of the SBC differ from normal subchondral bone tissue, we have performed a pilot qPCR study in which we have harvested SBC soft tissue and the cyst wall as well as non-sclerotic OA bone chips for cell explants, SBC cell explants has shown significantly decreased transcription levels of pericyte marker (MCAM) & osteoprogenitor marker (OCN) in the SBC compared to non-sclerotic OA bone explants (Fig. 1B), indicating stem cell & progenitor cell exhaustion. The increased matrix metalloprotease I (MMP1) expression in SBC explant cells showed senescence-associated secretary phenotype and degradation of the bone extracellular matrix. We believe this imbalance between bone resorption and formation contributes to SBC formation.

Through demonstrating occurrence of previous ischaemic episodes, endothelial senescence, insufficient H-type vessel ingrowth and loss of pericyte and osteoprogenitors in OA patients with SBC in the non-load-bearing regions, our hypothesis that vascular dysfunction may cause SBC in non-load-bearing region of the joint can be validated.

On the other hand, regarding how the load-bearing SBCs differ from the non-load-bearing SBCs discussed in the above hypothesis, given that the existing hypotheses suggest load-bearing region SBCs are caused by overloading of the subchondral bone, the load-bearing SBCs should in theory have a different histological morphology, at least in the early phase of SBC formation. Apart from being located close to articular cartilage in the case of synovial intrusion and filled with cartilage and necrotic bone fragments, the cellularity should also be higher and there should be more inflammatory cells infiltration since bone marrow oedema is involved. On the other hand, the vasculature in load-bearing SBCs should be relatively normal compared to the non-load-bearing SBCs. However, in advanced or end stage of the disease, it may become hard to tell the difference simply through histological observations. Nonetheless, we still believe the SBC content may provide us some hints, e.g. more fibrous tissue with higher cellularity in the case of load-bearing SBC and loosely filled void with some de novo bone fragments as demonstrated in the case of non-load-bearing region in Fig. 1A (b) & (c) respectively.

Discussion

Currently, there is insufficient understanding for aetiology of SBCs in OA knees. Whilst previous theories may be able to explain formation of SBCs caused by overloading of the knee, the formation of SBCs in

non-load-bearing region is another story and attempt to study them is like venturing in totally unknown waters due to lack of previous reports. In our recent cross-sectional study, we found hypertension to be a possible predictor of SBC formation in non-load-bearing region, which leads us to think about vascular pathology in SBC formation.

The linkage between vascular pathology and bone homeostasis has long been studied – vascular dysfunction is a proven risk factor of osteoporosis [16,17]. Given both osteoporosis and SBC formation involves excessive bone resorption and insufficient repairing, we believe the molecular mechanisms behind could be similar if not directly translatable from one to another. But since previous correlational studies show inverse relationship between osteoporosis and OA [18], it would seem counterintuitive to look into relationships between vascular dysfunction and OA. More recent evidence however proves this assumption to be wrong. Findlay's review [9] provided insights in how vascular pathology may contribute to OA pathogenesis and progression. We think the molecular mechanism behind osteoporosis may even be applicable in SBC.

The idea that ischaemia may contribute in OA pathogenesis is not an entirely novel idea [19,20]. Studies on hip joints in the past two decades revealed a distinct form of fracture of the subchondral bone termed "subchondral insufficiency fracture", which is different from osteonecrosis in a way that no sign of osteonecrosis can be seen prior to the collapse. This insufficiency fracture is caused by a normal or physiological stress loading to bone with suboptimal elastic resistance which tend to be osteopenic or osteoporotic [21]. However, the majority of past knee joint studies focused on ischaemia-induced osteonecrosis as a precursor of secondary OA rather than osteopenic bone due to chronic low-grade ischaemia as a primary cause of OA, or in our hypothesis a cardinal OA feature. There could be a blurred fine line between SPONK and subchondral insufficiency, a term coined by Bangil et al. in 1996 [22]. It is plausible that this precise condition would result in partial collapse of the subchondral bone and thus SBC formation, rather than total collapse of trabecular structure as seen in osteonecrotic fracture which precedes secondary OA.

It would be counterintuitive to debride SBCs in order to treat OA because they would always come back if the problem cannot be nipped in the bud. Demonstrating vascular diseases could be the root of non-load-bearing region SBCs however, may provide clinicians with the opportunity to prevent their development, if not OA progression, with a conservative treatment that is not only cost-effective but also safer and less unpleasant to the patient. Apart from its value as an imaging biomarker for OA, the sight of non-load-bearing region SBC may also be seen as an indicator that flags underlying vascular disorder. Maybe SBC is still a relevant radiological sign after all?

Contributions

PMB Chan and CY Wen drafted the manuscript; WC Yang, CH Yan and KY Chiu collected the clinical samples; all authors involved in data interpretation and proof-reading of manuscript before submission.

Conflicts of interests

None.

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