What is the site of pain osteoarthritis? A triple gut-brain-joint microbioma axis

Sirs,

In Europe osteoarthritis (OA) is the most common form of chronic pain condition (34%) reported and entails a high economic and social burden for society. This burden is growing with the increasing and ageing population. The precise aetiology of OA remains unknown thus far, even if various risk factors have been associated with presence of the disease, including age, sex, obesity, and diet, and local joint injury (1).

Pain OA has traditionally been viewed as peripherally mediated nociceptive pain. Many people with symptomatic OA report chronic joint pain, especially if those patients are older than 50 years (2). This condition is progressive and leads to functional decline and loss in quality of life, with important healthcare and society costs. General joint hypermobility may be associated with OA, but differences by physical activity are not known. Particular repetitive activities inherent in certain occupations have long been, and continue to be, associated with greater risk of OA (3). A recent study involving multiple subgroups of people with OA showed that obesity, depression, medical comorbidities, younger generation, lower education, and joint degeneration were correlated with the highest pain intensity (4).

The gap between pain-OA and OA is usually explained by the propensity of some OA patients to develop sensitisation. The pain-OA is becoming increasingly recognised as being related to central sensitisation (CS) mechanisms at both spinal cord and brain levels (5). For example, people with OA are more sensitive to experimental noxious stimuli at body sites distant from their affected joints compared to people without pain-OA (6). Interestingly, CS has been documented in people with knee, hip, low back pain, shoulder and hand OA. The emerging evidence suggests that pain in OA cannot be attributed solely to peripheral nociception. Cognitive and emotional factors associated with CS and chronic pain contribute to the pain experience, suggesting a broader approach to management in these cases. Exercise reduces evidence of CS (*e.g.* hyperalgesia and improvements in endogenous inhibition) in many patients with chronic pain conditions associated with elevated CS (7).

OA is now considered an induced inflammatory condition where the role of the microbiome is emerging as one of the most important factors in the disease. Several publications report a clear demonstration of the link between OA and gut microbiota (8). For instance, the translocation of bacteria or related compounds (*i.e.* LPS, peptidoglycans) across the gut barrier into the systemic circulation was found to mediate OA (9-11). PCR analyses and NGS of osteoarthritic synovial fluid and synovial tissue have also revealed the presence of bacterial DNA, raising the possibility that live bacteria or bacterial products are present in the joint during disease progression (12).

Pain and stress, which are considered threats of homeostasis unbalance and reducing quality of life, can have short- and long-term effects on the body functions. Exposure to stress and pain may lead to the alteration of the brain-gut interactions ("brain-gut axis") by changing gastrointestinal secretion and intestinal permeability, thus causing dysbiosis and increasing rate of intestinal bacterial translocation and inflammatory products (13). The involvement of gut microbiota has been proven to be of crucial importance in the development of several metabolic and inflammatory diseases. Actually, the mechanism and the influence of intestinal microbiota to OA pathogenesis has still not being known and needs to be further explored. Interestingly, emerging evidence leads to the hypothesis that alterations in the gut microbiome could also be considered as possible triggering factors in the onset of inflammatory arthropathies such as OA (14). Though, the health responses of the gut microbiota, show considerable individual variation, which is affected by absorption, metabolism and genetic variations of subjects. Recently, pharmacomicrobiomic science is studying as microbial consortium can modulate the action or the fate of many drugs. Specific (but unknown) gut microbes can modulate the activity of acetaminophene (paracetamol) by producing p-cresol which competes with its drug metabolisms and activity (15). This consequence may lead to an indirect different perception of the pain according to the microbiota composition. This paper shows conflicting evidence for where is the seat of pain in people with OA.

• All non-pharmacological treatments are merely minor variations on those early physical therapy or ortheses methods, pharmacological interventions care is mainly based on alleviating pain symptoms, and surgical interventions which are more expensive; pain in OA is not simply attributable to the structural changes in the local joint.

• Awareness is growing among clinicians that they should integrate the concept of central sensitisation during clinical reasoning and patient management.

• The exact role of gut microbiota involvement in the pathophysiology of OA remains under investigation; all these aforementioned observations raise the possibility that the microbiome or part of it may mediate the pain in people with OA.

We have thought of the "brain-gut-joint marrow" triangular interaction hypothesis as a potential explanation for pain localisation. For these reasons, the associations between OA and gut microbiota is emerging as one of the considerable factors in the disease. The understanding of OA and its manifestations has expanded in recent years; *so what is the site that should be chosen?*

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