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COMMENTARY

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Understanding the phenotypical representations of temporomandibular osteoarthritis for effective management

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Osteoarthritis (OA) or Degenerative Joint Disease (DJD) is the most prevalent form of arthritis, producing a progressive deterioration of the articular structures, chronic disability and joint pain.[1] From a pathophysiological perspective, OA is considered to be a 'whole joint' disease, including deterioration and loss of the cartilage and meniscal structures, changes in bony structures including the subchondral bone and synovial inflammation.[2] Over the last four decades, many different mechanisms of degenerative temporomandibular joint (TMJ) disease have been proposed in the literature. Most of these alleged mechanisms are based on the premise that overloading of the joint, excessive forces and trauma play a central role in disrupting the structural integrity of the TMJ structure.[3,4] Theoretically, non-physiological loads, trigger the production of free radicals through hypoxia-reperfusion cycles, micro bleeding, and consequently, reactive oxygen species (ROS) formation, producing the induction of neuropeptides, inflammatory cytokines (including IL-1, IL-6, IL-10 and TNF-alfa), the degradation of the extracellular matrix and synovial fluid hyaluronic acid, and the activation of catabolic enzymes such as metalloproteinases and aggrecanases.[5] Even though this pathophysiological mechanism of injury is widely cited in dental literature, there is no evidence to support or reject the hypothesis that hypoxia/reperfusion occurs in OA of the temporomandibular joint and/or other joints.[6]

Three critical aspects of joint biology are neglected by the current theoretical construct: (a) Articular surfaces are comprised of avascular tissue, obtaining most of their nutrition and oxygen supply from the synovial fluid. Consequently, the different cells of the TMJ fibrocartilage must adapt to low oxygen tensions.[7] (b) Experimental data have shown that low tension oxygen environments stimulate collagen and glycosaminoglycans chondrocytic biosynthesis, as well as chondrogenic differentiation and chondrogenesis. Oxygen levels seem to play an important role in the modulation of chondrocytic metabolism.[7] (c) Approximately 25% of the joint cartilage ATP production is through mitochondrial oxidative phosphorylation.[8] In diseased osteoarthritic chondrocytes, the hormetic process of remodelling, necessary to maintain cartilage integrity, is disturbed. Additionally, inflammatory mediators and oxidative stress contribute to compromise the energetic viability of chondrocytes.[8,9] This significant metabolic burden, affects the serine/threonine kinase AMPK system, decreasing its activity; mechanism crucial for adjusting the cellular energetic balance, and it is essential in adapting the metabolic demand.[9] Moreover, inflammation cytotoxicity drives an increase in nitric oxide and ROS, which impairs mitochondrial ATP generation and damages the mitochondrial respiratory chain complexes resulting in mitochondrial dysfunction, thus further increasing mitochondrial ROS production.[8] Indeed, ROS overproduction may not only be a result of static/intermittent overloading over the TMJ but rather the result of diverse pathological circumstances, such as oxidative stress, expression of inflammatory mediators, chondrocytic pro catabolic phenotypic changes and impaired bioenergy production.[9]

It is reasonable to assume that the pathophysiological mechanisms, described in rheumatologic literature, occur in TMJ OA. In striving towards the production of a comprehensive model for understanding the pathophysiology of TMJ OA, we must first acquire an understanding of the succession of biological events leading to degenerative disease of the temporomandibular joints. Mechanisms such as the activation of innate immunity such as the role of damage-associated molecular patterns, alarmins, and the complement system, the role inflammatory mediators, mitochondrial damage and dysfunction, catabolic cellular reprogramming, the role of synovitis, and the changes within the osteochondral unit. All of these factors require further investigation in TMJ degenerative diseases. Notably, two recent research articles published in the Journal Oral Rehabilitation seem to be heading in that direction:

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- Monasterio et al., studied the association of Th1/Th17/Th22 immune response with joint pain and radiographical bone loss.[10]
- Alstergren et al. studied the concentration of inflammatory mediators on the synovial fluid (inflammatory activity) and its diagnostic correlation with TMJ arthritis.[11]

Clarification of the fundamental aspects of the underlying pathogenic mechanisms of TMJ OA is imperative to build a robust theoretical framework. Without a solid foundation, it is not surprising that the exact aetiologic factors involved in TMJ osteoarthritic changes are still not well understood. Currently, the primary therapeutic goal when treating TMJ OA remains palliative and symptomatic, solely attempting to modify the disease progression, with varying degrees of success. The absence of validated clinical guidelines, the modest effectiveness of therapeutic interventions, and the lack of disease-modifying strategies should serve as a signal that a change of strategy is required.

A plausible explanation that underlies such poor therapeutic outcomes may be that TMJ OA is, indeed, a heterogeneous disease. A recent investigation that compared the somatosensory function between TMJ arthralgia and TMJ OA patients, uncovered that TMJ OA patients present an array of somatosensory abnormalities with variable degrees of central and peripheral sensitisation.[12]

Recognising the disease heterogeneity, consisting basically of distinct subtypes OA or clinical phenotypes, is probably the milestone needed to develop treatment strategies that would be earmarked to modify, stop or reverse the disease progression.

OA Phenotypes can be defined as subtypes of OA that share distinct underlying pathobiological and pain mechanisms, each phenotype producing a set of different functional and structural consequences.[13]

Somatosensory profiling, the inflammatory burden of the disease (eg biomarkers/cytokines), genomics (ie risk of developing the disease), metabolic status (ie metabolomics), molecular endotypes, environmental factors, and the extracellular matrix turnover may all serve as phenotyping tools.[14]

Treatment of TMJ OA should take the leading example from the field of rheumatology,[15] identifying well-defined phenotypes to comprehensively explain the wide variety of clinical presentations, aetiologies, the inter-individual variability in the progression of the disease, and the diverse clinical responses to treatment. Indubitably, recognising different subgroups of TMJ OA will help explain the driving factors related to TMJ degeneration, recognise clinical characteristics, and design tailored and targeted treatments for specific biologic aspects of TMJ OA phenotypes by a disease-modifying approach, and not just as palliative therapy. The call for well-identified TMJ OA phenotypes is necessary for a comprehensive assessment and proper management of the disease.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

All of the authors contributed to the conception, drafting, and critical revision of the article.

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