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EDITORIAL COMMENT

Chronic Pain at Multiple Sites Increases Myocardial Infarction

If So, Why?*

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Many individuals suffer from extensive musculoskeletal pain at multiple sites.[1-4] Cardiologists have investigated whether cardiovascular disease could be the cause of such pain, mainly chest pain and/or back pain.[5] Once potentially serious cardiovascular diseases have been ruled out, however, these patients are not generally followed by cardiologists but are likely under the care of general practitioners. In some cases, they may obtain prescriptions from general practitioners or take over-the-counter drugs. Although recent studies suggest an association between musculoskeletal pain and cardiovascular disease,[6,7] no longitudinal studies have been performed and the causes are unclear. The increased prevalence of chronic musculoskeletal pain and/or widespread pain is an important medical issue that must be addressed, and cardiovascular mortality in these patients is attracting increased attention.

In this issue of *JACC: Advances*, Tian et al[8] report that musculoskeletal pain at multiple sites causally increases the risk of myocardial infarction (MI), highlighting the importance of considering musculoskeletal pain when assessing an individual's MI risk. The authors found that the higher the number of painful sites, the greater the association with a higher risk of incident MI and stroke. Multivariate analysis showed that individuals with chronic multisite musculoskeletal pain had a high risk of both MI and stroke. A 2-sample Mendelian randomization (MR) analysis supported a causal effect of multiple site pain on MI risk, but not stroke risk. Tian et al[8] therefore suggest the need for pain treatment and management toward ameliorating MI risk. MR analyses are applied to overcome the limitation of observational studies that examine only the relationship between some risks and diseases. Due to the increasing availability of data from genome-wide association studies (eg, the UK Biobank), epidemiological studies are applying MR analysis to the field of cardiology to examine the causal risk factors of cardiovascular disease.[9-13] Importantly, in addition to using 2-sample MR to assess genetic causality of multisite pain with MI and stroke, Tian et al applied other MR methods to confirm their conclusions. The results indicated that multiple pain sites increase the incidence of MI, but not stroke, over an approximately 12-year follow-up.

How does chronic musculoskeletal pain increase the risk of cardiovascular disease, particularly MI? Potential mechanisms include chronic low levels of inflammation, endothelial dysfunction, and sympathetic activation.[14-16] Blood pressure elevation and/or large fluctuations may also occur in relation to chronic pain due to sympathetic dysregulation.[14,15] Tian et al[8] found the levels of high-sensitivity C-reactive protein as a marker of inflammation were higher in those with greater number of musculoskeletal painful sites than those without pain. The relationship between pain and autonomic function is certainly relevant to sympathetic activation. The influence of somatic reflexes on the sympathetic nervous system is well known.[17,18] The involved pathways, including afferent, efferent, and brain

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nuclei, have been examined in mainly experimental animal studies. In the central nervous system, the midbrain periaqueductal gray matter and brainstem nuclei play important roles in sympathetic activity-related blood pressure alterations.[18] An imbalance of nitric oxide and the generation of reactive oxygen species in the brain may also be involved.[15] Examining and following changes in autonomic function in individuals with multiple chronic pain sites and other known cardiovascular risk factors will provide important information. Endothelial function examined by flow-mediated vasodilation testing is feasible to perform and will also be interesting to investigate in these individuals.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used to treat pain but are associated with gastrointestinal, cardiovascular, and renal adverse effects.[19] Thus, it is possible that the increased MI risk in individuals with chronic pain is related to the use of NSAIDs. Tian et al, however, did not find a relationship between NSAID use and an increased risk of MI associated with chronic pain at multiple sites. Many other anti-pain drugs, such as pregabalin, are now widely prescribed for individuals with chronic pain and may be better at controlling chronic pain without the adverse effects of NSAIDs.[4]

The study by Tian et al[8] suggests the importance of follow-up care for individuals with multisite musculoskeletal pain, even in those with no history of MI. If multisite pain is a causal factor for MI, other risk factors should be carefully controlled by general physicians. Pain control must be addressed. Finally, the mechanisms underlying how musculoskeletal pain causes MI should be investigated, including neural efferent-afferent networks, central nervous system circuits, endothelial dysfunction, increased oxidative stress, and chronic inflammation/immunological changes. Neuro-inflammation in humans with chronic diseases and states is a current hot topic in the field of neuroscience.[20] Chronic and widespread pain is maintained in part by central sensitization, which consists of synaptic plasticity mediated by neuronal and glial alternations.[20] Neuro-immune communication, including immune cells, inflammatory mediators, and signaling pathways activated by pain-induced tissue injury, is being actively studied.[21] Damage-associated molecular patterns contribute to inflammation and are related to high mobility group box-1, which mediates inflammatory cytokines such as interleukin-6 and matrix-metalloproteinase-1.[22] Thus, clarification of the mechanisms involved will lead to the development of novel biomarkers and diagnostic methods as well as appropriate therapeutic approaches.

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