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DISCUSSION FORUM

Does epicardial fat contribute to COVID-19 myocardial inflammation?

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This Commentary referes to 'COVID-19-related myocarditis in a 21-year-old female patient', by I.-C. Kim *et al.*, doi:10.1093/eurheartj/ehaa288.

We read with great interest the report by In-Cheol Kim *et al.* describing the case of myocarditis in a young COVID-19 patient.[1] The authors provided a timely observation that may open up previously unexplored clinical and research scenarios. We also applaud the authors for their unique finding and excellent description of the case. Cardiac computed tomography (CT) and magnetic resonance imaging showed normal coronary arteries, but a hypertrophic and oedematous myocardium. Interestingly, a significant thickness and increased echogenicity of the epicardial and pericardial layers with subendocardial and pericardial effusion can be noted from the echocardiographic image provided.[1]

Cardiac involvement during COVID-19 infection, previously overlooked, became more prevalent, and a few cases of myocarditis have been reported.[2] The causative mechanism of COVID-19 myocarditis is the subject of debate and discussion.[3] We believe that epicardial adipose tissue (EAT), due its direct anatomical and functional contiguity with the myocardium, could be implicated in the physiopathology of COVID-19 myocarditis. In fact, no muscle fascia separates EAT from the underlying myocardium, and the two tissues share the same microcirculation.[4] More interestingly, EAT is a highly inflammatory depot with dense macrophage infiltrates, highly enriched in pro-inflammatory cytokines, such as interleukin-6 (IL-6), highly overexpressed in COVID-19 patients with cardiac and lung diseases. The EAT inflammatory secretome can reach the myo-pericardium directly via the vasa vasorum or through paracrine pathways.[4]

Angiotensin-converting enzyme 2 (ACE2) is recognized as the entry ligand receptor of COVID-19. Data from autopsied human heart samples showed that down-regulation of the myocardial ACE2 system could mediate myocardial inflammation. The presence of ACE2 in EAT further makes this visceral fat depot a potential player in myocardial inflammation. Interestingly, reduction in ACE2 has been associated with EAT inflammation.[5] Down-regulation of ACE2 increases EAT polarization to pro-inflammatory M1 macrophages, whereas angiotensin-(1-7) treatment reduced EAT macrophage polarization and preserved cardiac function in obese ACE2 knockout mice. The imbalance between anti- and pro-inflammatory adipokine secretion from EAT can play a role in the cytokine storm described in patients with severe COVID-19. The innate inflammatory response of EAT can cause an up-regulation and higher release of IL-6, leading to myocardial inflammation.

Obesity is emerging as a major risk factor for COVID-19 cardiopulmonary complications. Visceral adipose tissue depots, such as EAT, can be considered to be functional reservoirs of COVID-19. In highly vascularized adipose tissue, endothelial and smooth muscle cells as well as resident macrophages exhibit additional perturbations in response to an activated renin–angiotensin system (RAS). Adipose tissue is a potential target for further immune amplification by external pathogens such as viruses.

It is noteworthy that EAT can be clinically measured with CT or standard echocardiography. CT-measured EAT density could serve as a reliable and accurate marker of EAT inflammation. EAT is a direct target of medications modulating adipose tissue, such as ACE inhibitors and dipeptidyl peptidase 4 (DPP4) inhibitors, recently shown to be involved in COVID-19.

EAT can play a role in COVID-19 myocarditis and become a clinically measurable and modifiable therapeutic target.

Conflict of interest: none declared.

References

1. Kim I-C, Kim JY, Hyun AK, Kim AH, Han S. COVID-19-related myocarditis in a 21-year-old female patient. *Eur Heart J* 2020;doi:10.1093/eurheartj/ehaa288.
2. Hu H, Ma F, Wei X, Fang Y. Coronavirus fulminant myocarditis saved with glucocorticoid and human immunoglobulin. *Eur Heart J* 2020;doi:10.1093/eurheartj/ehaa190.
3. Dare RK. Is fulminant myocarditis caused by circulating human coronaviruses? *Eur Heart J* 2020;–doi:10.1093/eurheartj/ehaa330.
4. Iacobellis G. *Epicardial Adipose Tissue: From Cell to Clinic*. Cham, Switzerland: Springer Nature; 2020.
5. Patel VB, Mori J, McLean BA, asu R, Das SK, Ramprasath T, Parajuli N, Penninger JM, Grant MB, Lopaschuk GD, Oudit GY. ACE2 deficiency worsens epicardial adipose tissue inflammation and cardiac dysfunction in response to diet-induced obesity. *Diabetes* 2016;**65**:85–95.

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