Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.2182-18
Intern Med 58: 1373-1374, 2019
http://internmed.jp

【 EDITORIAL 】

Rheumatoid Arthritis and Vascular Failure - Rheumatoid Arthritis Is a Risk Factor for Cardiovascular Disease-

Jun-ichi Oyama[1] and Koichi Node[2]

Key words: rheumatoid arthritis, endothelial function, inflammation

(Intern Med 58: 1373-1374, 2019)
(DOI: 10.2169/internalmedicine.2182-18)

Rheumatoid arthritis (RA) is the most common chronic systemic autoimmune disease and is characterized by persistent synovitis, systemic inflammation and autoantibody. The risk of cardiovascular diseases (CVD) has been reported to be increased in autoimmune disease, especially in RA. There is growing evidence that RA contributes to the promotion of atherogenesis secondary to endothelial dysfunction. Indeed, half of all deaths among RA patients are considered to be due to CVD. Furthermore, the CVD risk and cardiovascular mortality in RA patients are about 1.5- to 2.0-fold that in the general population (1). Endothelial dysfunction is thought to reflect the early phase of atherosclerosis. The endothelial function decreased in RA patients to an extent similar to that in patients with type 2 diabetes mellitus (T2 DM), and RA is almost equivalent to T2DM as a cardiovascular risk factor (2-4). Therefore, although diabetes is a well-known cardiovascular risk factor, it is necessary to pay close attention to the onset of cardiovascular events in RA patients.

Endothelial function tests have changed over time, and the forearm blood flow response to acetylcholine infusion by strain-gauge plethysmography or flow-mediated dilatation (FMD) after transient ischemia of upper arm has been conventionally used. However, the use of peripheral arterial tonometry for reactive hyperemia (RH-PAT) has become common recently. Many manuscripts have conventionally reported that the endothelial function using FMD is impaired in patients with RA. Mori et al. observed a reduced endothelial function in patients with RA, which is similar to the findings in patients with T2DM (5). The report by Mori et al. is the first to describe that the endothelial dysfunction was recognized using RH-PAT.

Patients with RA usually receive anti-rheumatic drugs, but do these drugs affect the endothelial function? Glucocorticoids were initially used for RA and are still used often today (6, 7). Some articles have reported that methotrexate improves the endothelial function (8, 9), but others have described opposite results (10), and one report suggests that methotrexate may cause endothelial dysfunction through hyperhomocysteinemia, direct injury to the endothelium or by increasing the oxidative stress. Anti-TNF-α therapy is now widely applied and can improve the endothelial function (8, 11, 12). Taken together, these findings suggest that anti-inflammatory treatments may improve the endothelial function in patients with RA by decreasing the inflammatory responses and endothelial activities.

Whether or not therapeutic interventions can reduce the cardiovascular risk is unclear at present, but as with traditional risk factors, efforts to reduce cardiovascular events with adequate therapeutic intervention are required.

Author's disclosure of potential Conflicts of Interest (COI).
Jun-ichi Oyama: Others, Fukuda Denshi. Koichi Node: Honoraria, Boehringer Ingelheim, Daiichi Sankyo, Astellas, MSD, Takeda, Mitsubishi Tanabe and Sanofi; Research funding, Sanwa Kagaku Kenkyusho, Astellas, Takeda, Boehringer Ingelheim, Bayer, Teijin and Mitsubishi Tanabe.

References

1. Steyers CM 3rd, Miller FJ Jr. Endothelial dysfunction in chronic inflammatory diseases. Int J Mol Sci **15**: 11324-11349, 2014.
2. van Halm VP, Peters MJ, Voskuyl AE, et al. Rheumatoid arthritis versus diabetes as a risk factor for cardiovascular disease: a cross-sectional study, the CARRE Investigation. Ann Rheum Dis **68**: 1395-1400, 2009.
3. Peters MJ, van Halm VP, Voskuyl AE, et al. Does rheumatoid arthritis equal diabetes mellitus as an independent risk factor for cardiovascular disease? A prospective study. Arthritis Rheum **61**: 1571-1579, 2009.
4. Sarwar N, Gao P, Seshasai SR, et al.; Emerging Risk Factors Collaboration1. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet **375**: 2215-2222, 2010.

[1]Department of Circulation Regulation, Saga University, Japan and [2]Department of Cardiovascular Medicine, Saga University, Japan
Received for publication September 25, 2018; Accepted for publication October 2, 2018
Correspondence to Dr. Jun-ichi Oyama, junoyama@cc.saga-u.ac.jp

5. Mori H, Okada Y, Kawaguchi M, et al. A study of the vascular endothelial function in patients with type 2 diabetes mellitus and rheumatoid arthritis. Intern Med **58**: 1383-1390, 2019.
6. Verhoeven F, Prati C, Maguin-Gaté K, Wendling D, Demougeot C. Glucocorticoids and endothelial function in inflammatory diseases: focus on rheumatoid arthritis. Arthritis Res Ther **18**: 258, 2016.
7. Verhoeven F, Totoson P, Maguin-Gaté K, et al. Glucocorticoids improve endothelial function in rheumatoid arthritis: a study in rats with adjuvant-induced arthritis. Clin Exp Immunol **188**: 208-218, 2017.
8. Deyab G, Hokstad I, Whist JE, et al. Methotrexate and anti-tumor necrosis factor treatment improves endothelial function in patients with inflammatory arthritis. Arthritis Res Ther **19**: 232, 2017.
9. Hjeltnes G, Hollan I, Førre Ø, et al. Endothelial function improves within 6 weeks of treatment with methotrexate or methotrexate in combination with a TNF-α inhibitor in rheumatoid arthritis patients. Scand J Rheumatol **41**: 240-242, 2012.
10. Bordy R, Verhoeven F, Tournier-Nappey M, Wendling D, Demougeot C, Totoson P. Methotrexate did not improve endothelial function in rheumatoid arthritis: a study in rats with adjuvant-induced arthritis. Clin Exp Rheumatol 2018 (Epub ahead of print).
11. Hürlimann D, Forster A, Noll G, et al. Anti-tumor necrosis factor treatment improves endothelial function in patients with rheumatoid arthritis. Circulation **106**: 2184-2187, 2002.
12. Tikiz H, Arslan O, Pirildar T, Tikiz C, Bayindir P. The effect of anti-tumor necrosis factor (TNF)-alpha therapy with etanercept on endothelial functions in patients with rheumatoid arthritis. Anadolu Kardiyol Derg **10**: 98-103, 2010.