

Editorial / Editöryal Yorum

Increased serum pentraxin-3 levels; a novel cardiovascular marker

Artmış serum pentraxin-3 seviyeleri: Yeni bir kardiyovasküler belirteç

Ercan Varol, M.D.

Department of Cardiology, Suleyman Demirel University Faculty of Medicine, Isparta

Cardiac syndrome X (CSX) is a clinical entity that has three characteristic features: 1) angina or angina-like chest pain with exertion; 2) ST segment depression that can be induced by treadmill exercise testing, or alternatively, a pathological thallium scan with normal coronary arteriography; and 3) no spontaneous or inducible epicardial coronary artery spasm upon ergonovine or acetylcholine provocation.^[1] Although the exact mechanism by which CSX develops, remains unclear, coronary microvascular abnormalities, silent atherosclerosis and endothelial vasomotor dysfunction have been suggested as possible contributing factors.^[2] Abnormal coronary arteries with atheromatous plaques and intimal thickening have been observed in intravascular ultrasonographic studies of patients with CSX.^[3] Therefore, the etiopathogenesis of CSX may be similar to that of coronary artery disease (CAD). Inflammation has also been accepted as one of the important mechanisms in pathogenesis of CSX like CAD. High-sensitivity C-reactive protein (hs-CRP), intercellular cell adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1) were found to be elevated in patients with CSX.^[4,5]

Pentraxin-3 (PTX-3) has emerged as a novel marker and is thought to be more specific to vascular inflammation than other proteins in the pentraxin family such as CRP.^[6]

Pentraxin-3 is synthesized locally at the inflammatory sites by endothelial and smooth muscle cells or

by monocytes/ macrophages upon exposure to primary inflammatory signals.^[7] PTX-3 is a biomarker of atherosclerosis and correlates with the risk of vascular events.^[8] Serum PTX-3 levels have been found to be elevated in patients with unstable angina and non-ST elevation myocardial infarction,^[9] ST elevation myocardial infarction^[10] and heart failure,^[11] and adverse cardiovascular outcomes.^[6,11]

Abbreviations:

CAD Coronary artery disease

CSX Cardiac syndrome X

hs-CRP High-sensitivity C-reactive protein

PTX-3 Pentraxin-3

In the study by Buyukkaya et al.,^[12] they measured and compared serum PTX-3 and hs-CRP levels in patients with CSX, CAD, and controls. The CSX group had significantly higher PTX-3 levels than the control group. However, there were no differences in serum levels of PTX-3 between the CSX and the CAD groups. Similarly, the CSX group had significantly higher hs-CRP levels than the control group and there were no differences in levels of hs-CRP between the CSX and CAD groups. Serum PTX-3 levels were positively correlated with hs-CRP levels. In summary, they concluded that PTX-3, as well as the known inflammatory marker hs-CRP, was elevated in patients with CSX. This was the first study showing the role of PTX-3 in patients with CSX. A limitation to their study was that they used a hyperventilation test instead of ergonovine or acetylcholine provocation to rule out coronary artery spasm. It is less sensitive in

Correspondence: Dr. Ercan Varol. Süleyman Demirel Üniversitesi Tıp Fakültesi, Kardiyoloji Anabilim Dalı, Isparta, Turkey.

Tel: +90 246 - 232 44 79 e-mail: drercanvarol@yahoo.com

© 2013 Türk Kardiyoloji Derneği



detecting coronary artery spasm when compared with ergonovine or acetylcholine provocation.

Endothelial dysfunction and impaired coronary microcirculation are two main entities speculated to be responsible for CSX. The association of inflammation with endothelial dysfunction has been well established. The study highlighted above showed that inflammation plays an important role in pathogenesis of CSX. It can be speculated that PTX-3 is important marker and it may have an important role in a variety of cardiac diseases like valvular heart diseases, hypertension, atrial fibrillation, and stroke. More studies are needed to determine the role of PTX-3 in cardiac disease.

The mechanism whereby PTX-3 is associated with cardiovascular diseases and cardiovascular outcomes is unclear. CRP is a short pentraxin produced in the liver in response to interleukin-6, whereas PTX-3 is a long pentraxin produced by inflammatory and immune cells in the presence of interleukin-1.^[7] In addition, PTX-3 is also distinct from CRP in ligand recognition and innate immunity function.^[7] It has been shown that, unlike CRP, PTX-3 may be part of a protective mechanism in vascular repair.^[13] PTX-3 binds and inactivates fibroblast growth factor-2, an angiogenic growth factor responsible for smooth muscle proliferation in atherosclerosis.^[14] PTX-3 may be elevated in vascular injury as a protective mechanism. Very high levels of PTX-3 may indicate a more severe vascular disease state, explaining its ability to detect increased risks for adverse outcomes.^[6]

In comparison with hs-CRP, PTX-3 seems to be a more specific and sensitive marker in cardiovascular diseases. Recent findings indicate that measurement of plasma PTX-3 represents a more effective means for early risk stratification compared to hs-CRP in patients with myocardial infarction^[15] and chronic heart failure.^[16] The superior prognostic value of PTX-3 might result from a higher specificity of PTX-3 for localized inflammation and damage in the cardiovascular system. In a recent large scale study, rosuvastatin lowered hs-CRP levels but, significantly raised PTX-3 levels.^[11]

In conclusion, elevated plasma PTX-3 is a potential cardiovascular risk factor. More large-scale prospective studies are mandatory to determine the cause and effect relationship between elevated plasma PTX-

3 and cardiovascular diseases. In the future, PTX-3 might be an effective target point for the prevention and treatment of cardiovascular diseases.

Conflict-of-interest issues regarding the authorship or article: None declared

REFERENCES

1. Panting JR, Gatehouse PD, Yang GZ, Grothues F, Firmin DN, Collins P, et al. Abnormal subendocardial perfusion in cardiac syndrome X detected by cardiovascular magnetic resonance imaging. *N Engl J Med* 2002;346:1948-53. [\[CrossRef\]](#)
2. Al Suwaidi J, Higano ST, Holmes DR Jr, Lerman A. Pathophysiology, diagnosis, and current management strategies for chest pain in patients with normal findings on angiography. *Mayo Clin Proc* 2001;76:813-22. [\[CrossRef\]](#)
3. Wiedermann JG, Schwartz A, Apfelbaum M. Anatomic and physiologic heterogeneity in patients with syndrome X: an intravascular ultrasound study. *J Am Coll Cardiol* 1995;25:1310-7. [\[CrossRef\]](#)
4. Tousoulis D, Davies GJ, Asimakopoulos G, Homaei H, Zouridakis E, Ahmed N, et al. Vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 serum level in patients with chest pain and normal coronary arteries (syndrome X). *Clin Cardiol* 2001;24:301-4. [\[CrossRef\]](#)
5. Cosín-Sales J, Pizzi C, Brown S, Kaski JC. C-reactive protein, clinical presentation, and ischemic activity in patients with chest pain and normal coronary angiograms. *J Am Coll Cardiol* 2003;41:1468-74. [\[CrossRef\]](#)
6. Dubin R, Li Y, Ix JH, Shlipak MG, Whooley M, Peralta CA. Associations of pentraxin-3 with cardiovascular events, incident heart failure, and mortality among persons with coronary heart disease: data from the Heart and Soul Study. *Am Heart J* 2012;163:274-9. [\[CrossRef\]](#)
7. Garlanda C, Bottazzi B, Bastone A, Mantovani A. Pentraxins at the crossroads between innate immunity, inflammation, matrix deposition, and female fertility. *Annu Rev Immunol* 2005;23:337-66. [\[CrossRef\]](#)
8. Norata GD, Garlanda C, Catapano AL. The long pentraxin PTX3: a modulator of the immunoinflammatory response in atherosclerosis and cardiovascular diseases. *Trends Cardiovasc Med* 2010;20:35-40. [\[CrossRef\]](#)
9. Matsui S, Ishii J, Kitagawa F, Kuno A, Hattori K, Ishikawa M, et al. Pentraxin 3 in unstable angina and non-ST-segment elevation myocardial infarction. *Atherosclerosis* 2010;210:220-5. [\[CrossRef\]](#)
10. Peri G, Inrona M, Corradi D, Iacuitti G, Signorini S, Avanzini F, et al. PTX3, A prototypical long pentraxin, is an early indicator of acute myocardial infarction in humans. *Circulation* 2000;102:636-41. [\[CrossRef\]](#)
11. Latini R, Gullestad L, Masson S, Nymo SH, Ueland T, Cucovillo I, et al. Pentraxin-3 in chronic heart failure: the CO-RONA and GISSI-HF trials. *Eur J Heart Fail* 2012;14:992-9.

12. Buyukkaya E, Karakas MF, Kurt M, Motor S, Akcay AB, Buyukkaya S, et al. The serum pentraxin-3 is elevated in patients with cardiac syndrome X. *Turk Kardiyol Dern Ars* 2013;41:290-5.
 13. Norata GD, Marchesi P, Pulakazhi Venu VK, Pasqualini F, Anselmo A, Moalli F, et al. Deficiency of the long pentraxin PTX3 promotes vascular inflammation and atherosclerosis. *Circulation* 2009;120:699-708. [\[CrossRef\]](#)
 14. Camozzi M, Zacchigna S, Rusnati M, Coltrini D, Ramirez-Correa G, Bottazzi B, et al. Pentraxin 3 inhibits fibroblast growth factor 2-dependent activation of smooth muscle cells in vitro and neointima formation in vivo. *Arterioscler Thromb Vasc Biol* 2005;25:1837-42. [\[CrossRef\]](#)
 15. Latini R, Maggioni AP, Peri G, Gonzini L, Lucci D, Mocarelli P, et al. Prognostic significance of the long pentraxin PTX3 in acute myocardial infarction. *Circulation* 2004;110:2349-54.
 16. Suzuki S, Takeishi Y, Niizeki T, Koyama Y, Kitahara T, Sasaki T, et al. Pentraxin 3, a new marker for vascular inflammation, predicts adverse clinical outcomes in patients with heart failure. *Am Heart J* 2008;155:75-81. [\[CrossRef\]](#)
-
- Key words:** Cardiac syndrome X; C-reactive protein/metabolism; coronary artery disease; PTX3 protein.
- Anahtar sözcükler:** Kardiyak sendrom X; C-reaktif protein/metabolizma; koroner arter hastalığı; PTX3 proteini.