YKL-40 and its complex association with metabolic syndrome, obesity, and cardiovascular disease

Advances in acute cardiovascular care have rebutted the old paradigm that diabetics without previous myocardial infarction have the same cardiovascular risk as non-diabetics with myocardial infarction (1). The prognosis of diabetes patients is better determined by long-term medical management than acute interventions (2). The cardiovascular event and death risk of diabetics remains twice as that of non-diabetics (3).

Thus, the investigation of new and additional pathways that account for the increased atherosclerosis burden, which in turn causes cardiovascular events, is mandatory.

In this issue of The Anatolian Journal of Cardiology, Akboğa et al. (4 entitled "Increased serum YKL-40 level is associated with the presence and severity of metabolic syndrome.") showed that YKL-40 is associated with metabolic syndrome as defined by NCEP-ATP III criteria. Levels of YKL-40 correspond with the numbers of individual components of the metabolic syndrome (4). Furthermore, ROC analysis revealed a comparable power of YKL-40 [AUC: 0.785 (0.718–0.853), p<0.001] to hs-CRP [0.804 (0.735–0.872), p<0.001] (4).

Till date, the association of YKL-40 with obesity, metabolic syndrome, morbid obesity, and cardiovascular disease is complex.

YKL-40, produced by the gene chitinase 3-like 1 (CH3L1) (5, 6), is a heparin- and chitin-binding lectin without chitinase activity and a member of the mammalian chitinase-like protein cluster (6). YKL-40 belongs to the glycosyl hydrolase family 18, which consists of enzymes and proteins, and includes hydrolytic enzymes from various species, including mammalian, bacteria, fungi, nematodes, insects, and plants (6). YKL-40 is secreted by activated macrophages, activated neutrophils, arthritic chondrocytes, fibroblast-like synovial cells, osteoblasts, and differentiated vascular smooth muscle cells (5).

Minor researches have been conducted on the exact functions of YKL-40 so far. Several studies have suggested that YKL-40 is an essential factor in extracellular tissue remodeling. It controls mitogenesis via MAP kinase and PI-3K signaling cascades in fibroblasts (7, 8). Those initial observations led to a first identification of the involvement of YKL-40 in cancer (7) and rheumatoid disorders (9).

YKL-40's association with migration, reorganization, and adhesion of endothelial cells and smooth muscle cells suggests a role in angiogenesis (7, 8).

Indeed, stimulated by an initial review of Rathcke et al. (10), numerous investigators have studied the influence of YKL-40 on cardiovascular disease. Recently, a Mendelian analysis in 96 110 individuals from the Danish general population revealed that elevated YKL-40 is associated with a 34% increase in triglycerides and a two-fold increased risk of ischemic stroke (11). Noteworthy, genetically elevated YKL-40 was not a cause of stroke (11).

Thus, risk factor-related increase of YKL-40 might be a simple measure of risk increase but may also be independently involved in associated pathways. Thus, the findings that YKL-40 is linked to metabolic syndrome (4), morbid obesity (12), type 2 diabetes mellitus (13), type 1 diabetes mellitus (14), and albuminuria (13, 15) suggests an interaction in the development and progression of atherosclerosis in patients with those comorbidities.

Because YKL-40 synergistically acts with IGF-1 and initiates MAPK and PI3K signaling in fibroblasts, it might be of interest to investigate those pathways (7, 8) in cells, such as endothelial cells or smooth muscle cells.

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