Review of Ten Biomarkers of Coronary Artery Diseases

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ENDOTHELIN-1 (ET-1)

Endothelin-1 (ET-1) is one of the main vasoconstrictors identified [1]. ET-1 elicits its effects via two receptors including: ETA receptors that is located in vascular smooth muscle cells (VSMC) and cardiomyocytes and mediate contraction, and ETB receptors which is located on vascular endothelial cells (EC), mediate dilation and ET-1 uptake, and regulate ET-1 production [2-4]. ET-1 is mostly released from EC, by a constitutive pathway and contributes to the regulation of the vascular tone [5, 6]. Nitric Oxide (NO) intensely prohibits the release of ET-1 from the endothelium [7]. It has been suggested that NO and ET-1 regulate each other via an autocrine feedback loop [8]. In addition to EC, ET-1 is also produced by VSMC, leukocytes, macrophages, cardiomyocytes, various neurons, and other cells [9]. ET-1 is also proinflammatory and promotes VSMC proliferation [10, 11] therefore, ET-1 by regulating basal vascular tone and remodeling contributes to the cardiovascular homeostasis [5, 9].

ET-1 is considered to play a significant role in the progression of CAD [12]. It seems that the blood flow is the main stimulus for regulation of ET-1 synthesis and release. A reduced blood flow as a result of artery stenosis elevated the production of ET-1 [13]. Many studies have revealed a strong association between ET-1 and CAD [13, 14]. A study indicate that the plasma big ET-1 level is a useful predictor of the severity of new-onset stable CAD associated with significant stenosis. Big ET-1 has a circulating half-life of 23 minutes and could be a better reflect of the true ET-1 value, whereas ET-1 has a half-life of only 3.5 minutes [15, 16].

INTERFERON-INDUCIBLE PROTEIN OF 10 KD (IP-10)

Human interferon-inducible protein 10 (IP-10) is a member of the α chemokine family which inhibits bone marrow colony formation, and is chemoattractant for human monocytes and T cells, and promotes T cell adhesion to endothelial cells [17]. Interferon-inducible protein of 10 kD (IP-10) is a chemokine which activates the CXC chemokine receptor (CXCR) and increases the production of interferon-γ from T-helper 1 cells. IP-10 is expressed by macrophages, endothelial cells, and smooth muscle cells in the atherosclerotic plaque [18]. It has been shown that CXCR3 deletion and IP-10 deficiency modulate early formation of atherosclerotic lesion in ApoE−/− mice [19, 20]. IP-10 was also reported to participate in the formation of atherosclerotic lesions by mediating inflammatory cell invasion [21]. Another study have shown that serum levels of IP-10 were increased in patients with coronary artery disease [21].

SMALL DENSE LOW DENSITY LIPOPROTEIN (SDLDL)

Increased levels of LDL cholesterol are a main risk factor for coronary artery stenosis [22]; however, in several studies it was demonstrated that patients with coronary artery stenosis have a normal range of LDL-cholesterol levels [23]. LDL particles are considered as heterogeneous particles because of their size, density, and lipid composition [24]. Two evident phenotypes were defined for LDL particles by gradient gel electrophoresis. Phenotype A consists of large, buoyant LDL particles with a size of more than 25.5 nm, and phenotype B is comprised of small dense LDL (sdLDL) and is 25.5 nm or less [25]. Small dense LDLS are considered to be atherogenic because they easily penetrate the arterial wall and have a low affinity for LDL receptor [26]. They are also susceptible to oxidation. In many studies, it was shown that coronary artery disease (CAD) risk was increased 2 to 3 fold in patients with sdLDL. Therefore, sdLDL is considered as a new marker for coronary artery stenosis [27, 28].
UROKINASE PLASMINOGEN ACTIVATOR (uPA)

Urokinase plasminogen activator (uPA) is a serine protease that by binding to its receptor, urokinase plasminogen activator receptor (uPAR) generate plasmin [29]. uPA is produced by vascular endothelial cells, smooth muscle cells, macrophages, fibroblasts, monocytes, and epithelial cells [30]. uPAR plays a role in development of atherosclerosis by arranging cellular adhesion, migration, and proliferation and plasma suPAR probably effects on cellular shedding of a section of uPAR from inflammatory or endothelial cells [30]. suPAR is extremely stable during storage and can be measured precisely even after frequent series of freezing and melting [31]. The relation of suPAR to CVD has been recently explored. Most of these studies carried out in Europe have examined the relationship between suPAR and incidence of CVD in healthy community-based populations [32, 33]. In a study by Eapen et al. it was shown that the levels of plasma suPAR were increased by the presence and severity of CAD and are independent predictors of death and MI in patients with suspected or known CAD [34].

ENOCAN

Endocan, which was previously known as endothelial cell specific molecule-1 (ESM-1), is a novel endothelium derived soluble dermaminate sulfate proteoglycan which is secreted by vascular endothelium. It is a potential immunoinflammatory marker and has principally distinct biological functions. Both the protein core and glycosaminoglycan of endocan have been implicated in interactions with extracellular matrices components, intracellular molecules, cell surface proteins, and soluble mediators which regulates cell differentiation, migration, and adhesion [35, 36]. In a study by Kose et al. demonstrated that Endocan is significantly increased in patients with acute coronary syndrome [37]. Balta et al. have shown that Endocan is a potential inflammatory and CVD marker [38].

TOLL-LIKE RECEPTORS (TLRs)

The immune system is composed of two sections including the innate and adaptive systems. The innate immune system is the first line of defense against invading organisms. Pathogens are recognized according to their molecular structures by pattern recognition receptors (PRRs). Toll-like receptors (TLRs) are one of the main family of PRRs. Currently 12 TLRs have been identified in mammals and they are categorized into two groups based on their localization. TLR1, 2, 4, 5, 6, and 11 are found within the cell membrane and recognize components of the microbial cell wall. TLR3, 7, 8, and 9 are expressed internally in compartments including endoplasmic reticulum, endosomes and lysosomes where they bind to nucleic acids of microbial or viral origin [38]. Toll-like receptors have recently been revealed to play a key role in coronary artery disease, especially Toll-like receptor (TLR) 3 and TLR4. In a study by Shao et al. it was found that the expression of TLR4 and TLR3 significantly correlated with the severity of coronary artery disease as reflected by the number of coronary artery stenosis. They believed that TLR3 and TLR4 have the potential to be a useful biomarker of cardiovascular risk [39]. Mizoguchi et al. showed that TLR2 and TLR4 expression in monocytes correlated with the extent and severity of coronary artery diseases in patients with stable angina [40].

OSTEOPONTIN (OPN)

Osteopontin (OPN) is a macrophage chemotactic protein which was identified as a mediator involved in bone remodeling, chronic inflammatory and autoimmune disorder. OPN is synthesized by monocytes/macrophages, endothelial cells, and vascular smooth muscle cells, and it was found to express in neointima and calcified atherosclerotic plaque [44]. In a study by Mohamadpour et al. it was found that there is a positive association between circulating OPN concentrations and the presence of CAD but not the extent of it [45]. Tousoulis et al. study suggests that serum Osteopontin and osteoprogerin levels are associated with arterial stiffness, and the extent of CAD. These results suggest that Osteopontin and osteoprogerin levels are meaningfully associated with vascular function which contributes to the pathogenesis of atherosclerosis in CAD [45].

CHOLINE PLASMALOGENs

Plasmalogens (Pls) are a subclass of glycerophospholipids. They have a vinyl-ether bond and an ester bond at the sn-1 and sn-2 positions, respectively, of the glycerol backbone. Plasmalogens are classified into either choline Pls (PlsCho) or ethanolamine Pls (PlsEtN) according to their polar head groups at the sn-3 position. Choline Pls are localized in cardiac muscle and blood plasma, while ethanolamine Pls are distributed in a wide variety of cells and tissues [46]. Serum levels of Pls are known to correlate positively with HDL-cholesterol. Nishimukai et al. determined serum levels of each ether glycerophospholipids, and scrutinized their associations with clinical parameters. They found that the proportion of choline Pls among total serum phospholipids was meaningfully lower in the male group over 40 years old and was related to some risk parameters more strongly than...
HDL-C. The abundance of serum PlsCho with oleic acid (18:1) in sn-2 showed the most positive association with serum concentrations of adiponectin and HDLC-C, whereas inversely associated with the serum levels of TG and small dense LDL-cholesterol. They revealed that PlsCho, mostly the ones with 18:1 in sn-2, can be considered as a sensitive biomarker for the atherogenic state [47]. It was determined that Pls have antioxidant property [48]. The number and the capability of peroxisome decrease with aging [49], which may reduce the biosynthesis Pls. Decreased antioxidant Pls level may cause predominant oxidative status in redox balance that may cause the diseases associated with aging or oxidative stress such as atherosclerosis [50].

HOMOCYSTEINE

Homocysteine is a sulphhydril-containing amino acid and is an intermediate product in the normal biosynthesis of the methionine and cysteine amino acids. It is produced by de- methylation of dietary methionine that is frequent in animal protein. It has four forms in plasma: 1% as free thiol, 70–80% remains disulphide-bound to plasma proteins mostly albumin and 20–30% form the dimer homocysteine [51]. When homocysteine level in serum is high, a major by-product is formed which is called homocysteine thiolactone. It reacts with low-density lipoprotein (LDL) to form LDL-homocysteine thiolactone aggregates. Macrophages take up these products and then incorporated into foam cells in early atherosclerotic plaques. In these plaques, homocysteine thiolactone acylates proteins and alters the oxidative processes of the vessel and promoting atherothrombosis. Moreover, auto-oxidation of homocysteine leads to formation of superoxide and hydrogen peroxide. These oxygen-derived molecules can lead to oxidation of LDL and endothelial dysfunction and stimulate proliferation of vascular smooth muscle cells [51].

In Gu et al. study homocysteine levels were raised in patients with early-CAD and with high risk factors. They demonstrated that Hyperhomocysteinemia plays a significant role in the pathogenesis of CAD [52]. Another study by Abraham et al. a cumulative analysis have showed a rise in homocysteine lev- els among patients with CAD [51].

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