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REVIEW – OPEN ACCESS

Serum Prolidase Activity in Cardiovascular Disease

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ABSTRACT

Serum prolidase activity (SPA) plays a vital role in plaque stabilization in collagen turnover in atherosclerotic plaques. Thus, SPA has an essential role in the diagnosis and prevention of coronary artery disease. SPA values may be higher in hypertension, atrial fibrillation, coronary artery ectasia, and aneurysmatic diseases than average values due to collagen turnover and oxidative stress. We aimed to present a review to show the role of SPA based on cardiovascular diseases and how it will contribute to prognosis with the most recent data.

Keywords: Atrial fibrillation, hypertension, coronary artery disease, collagen turnover, serum prolidase activity

INTRODUCTION

Although matrix metalloproteinases (MMPs) generally initiate collagen degradation, prolidase (peptidase D) mediates the final stage of collagen degradation and the first stage of collagen biosynthesis. Therefore, prolidase is considered to be one of the primary regulators of the collagen cycle (Fig. 1) (1, 2). Collagen is the primary extracellular matrix (ECM) component, which accounts for 60% of the total protein content in atherosclerotic plaques, and possibly, serum prolidase activity (SPA) will regulate plaque stability by affecting the collagen cycle in atherosclerotic plaques (1). With this hypothesis, it has been shown that the SPA is significantly higher in coronary artery disease (CAD) and correlates with the severity of CAD (3). The prolidase enzyme is tested 40 times, normally diluted with serum 2.5 mmol/L Mn^{2+}, and the trizma is buffered with HCl (pH 8.0). Pre-incubation occurs at 37°C for 2 h. Proline levels are measured with a spectrophotometer using the modified Chinard method (4). Intra- and inter-assay coefficient of variations were <8% and <10%, respectively. Results are shown as U/L. We aimed to review this subject since we have not previously encountered, to the best of our knowledge, a review of the diagnostic and prognostic values of prolidase in cardiovascular diseases (CVDs) in the literature. [The articles in this review were added from Google Scholar, published in the last 20 years, using keywords such as “atrial fibrillation,” “hypertension,” “coronary artery disease,” “collagen turnover,” and “serum prolidase activity”].

Clinical and Research Consequences

Relationship Between Myocardial Infarction and SPA

Acute myocardial infarction (MI) is one of the pioneers of overall mortality worldwide (5). Particularly crucial in plaque stability is the durability of the fibrous head, which depends on the balance between ECM synthesis and degradation (6). Proteolytic enzymes such as MMPs have been identified in coronary atherosclerotic plaques (7). Regulation of the cycle of ECM components mediates vascular remodeling (1). Furthermore, rupture-prone thin-cap fibroatheromas have higher MMP levels than stable plaques with a thicker fibrous cap (8).

In a study comparing patients with acute MI and stable CAD, SPA levels were lower in patients with acute MI (9). This finding suggests that low SPA levels during acute MI indicate severe stress rather than plaque rupture.

Demirtas et al. (10) found that SPA is significantly lower in patients receiving anticoagulants and antiplatelet agents than in the control group. Angiotensin convertase inhibitor, such as enalapril, has also been shown to affect prolidase activity by affecting the collagen cycle, such as antiplatelet agents (11). Patients with acute coronary syndrome undergoing percutaneous transluminal coronary angioplasty have lower levels of prolidase activity due to routine acetylsalicylic acid and anticoagulant treatment (9).

SPA has been shown to be independently related to left ventricular diastolic dysfunction (LVDD), hypertension (HT), coronary artery aneurysm, aortic dilatation, and coronary slow flow (12).

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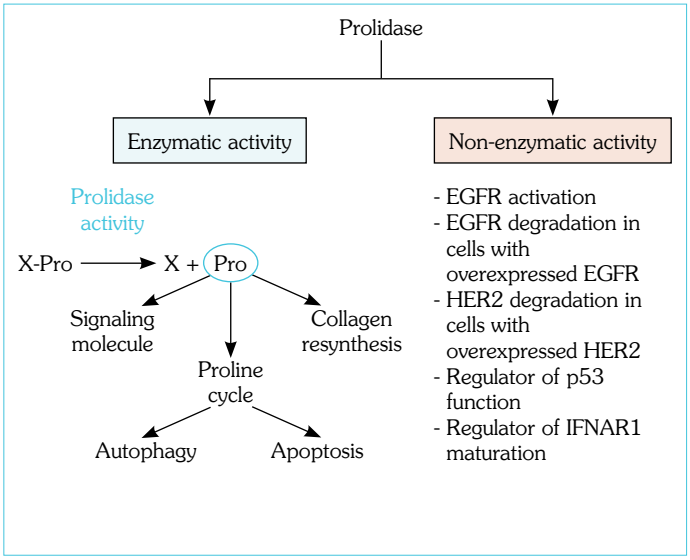

Figure 1. Serum prolidase activity

SPA in Patients with Hypertension

HT has a dramatic effect on cardiac remodeling. Left ventricular hypertrophy (LVH), which develops with mechanisms such as myocyte hypertrophy and increased interstitial fibrosis, is one of the causes of heart failure (13). Fibronectin, laminin, and elastin contribute to the etiopathogenesis of LVH (14).

Increased metalloproteinase activity causes increased collagen turnover and impaired systolic cardiac functions in HT. The tissue inhibitor of metalloproteinase-1 is associated with ECM fibrosis and increases (15). SPA is a Mn^{2+}-dependent cytosolic exopeptidase that clones imidodipeptides containing C-terminal proline or hydroxyproline and affects collagen metabolism, matrix remodeling, and cell growth (16). LVH occurs as a result of increased fibrosis in myocytes and an increase of collagen deposits. Hydroxyproline increased with LVH (17).

Elevated MMP expression and high ECM fibrillary collagen degradation occur at an early age in HT (18). Varo et al. (19) demonstrated that in the left ventricle, antagonism of angiotensin II type 1 receptor with losartan leads to reversal of fibrosis, stimulating MMP-1 activity, and inhibition of metalloproteinase-1 expression by tissue inhibitors in hypertensive adult rats.

A possible explanation for high SPA in patients with HT is that the detrimental effects of increased blood pressure trigger the increase SPA in patients with HT. The large endothelial area in the whole arterial tree is a target for the detrimental effects of HT. In HT, high blood pressure and medial hypertrophy increase arterial wall ECM through hypertrophy of tight collagen fibers and smooth muscle cells and reduction of elastic fibers. Higher subendothelial ECM collagen turnover in arteries is associated with higher SPA levels in patients with HT. Demirbağ et al. (20) attributed the relationship between SPA and HT to a chronic increase in ECM destruction with disease duration.

SPA in Patients with Atrial Fibrillation (AF)

Tissue fibrosis increases atrial tissue anisotropy in AF. The mechanism of different expressions of ECM components is not yet fully understood in AF forms (21). The link between AF and atrial tissue fibrosis is obvious. The fundamental changes of the atrial ECM form are the basis of AF. Interstitial fibrosis may be the cause of electrophysiological or structural modifications of AF (22). A previous study showed that ECM collagen type III increased in patients with AF (23). SPA is known to be very important for the ECM collagen type I turnover rate (22). Rabus et al. (24) attributed the low level of SPA in patients with mitral stenosis to irregular collagen metabolism of the different releases of ECM components.

Decreased SPA levels may indicate collagen metabolism irregularity and the onset of atrial remodeling in paroxysmal atrial fibrillation (PAF). P wave dispersion interatrial conduction delay, and decreased SPA may be predictive for PAF (25).

Association of SPA with Other Cardiovascular Diseases

Lipid hydroperoxide (LOOH) is an oxidative marker characterized by peroxidative reactions with oxidative stress consisting of unsaturated phospholipids, glycolipids, and cholesterol components (26). LOOH (oxidized low-density lipoprotein) leads to the development of atherosclerosis (26). Free sulfhydryl (SH) groups of proteins have been shown to be a crucial antioxidant component of serum and related to the presence and severity of CAD (27). Increased serum LOOH levels and decreased serum SH levels with SPA show the link between collagen turnover and oxidative stress in the atherosclerotic process. Yildiz et al. (28) showed that increased SPA has an independent association with increased collagen turnover in CAD.

Akcakoyun et al. (29) demonstrated the association between ascending aortic aneurysm and low SPA. Lower SPA level is the reason for reduced collagen synthesis and aneurysm formation (30). In patients undergoing coronary artery bypass grafting for multiple vessel disease, an independent association between prolidase activity and aortic stiffness beta index has been found (31).

Increased oxidative stress, increased SPA levels, and decreased antioxidant levels are frequently seen in obesity. The consistent association between oxidative stress and SPA may be one of the important components of atherosclerosis etiopathogenesis in obesity (32). In addition, the biochemical role of oxidative stress rather than mechanical factors contributes to the development of primary varicose veins. Oxidative stress induced by SPA may play an essential role in the etiopathogenesis of primary varicose veins. The possible reason for increased SPA in patients with varicose veins may be oxidative stress. Clinical studies may be conducted to understand the contribution of oxidative stress and SPA relationship to varicose vein formation (33).

Akturk et al. (4) showed that higher levels of SPA in patients with coronary artery ectasia (CAE). This increase in SPA may support the hypothesis that CAE may be related to development.

Jackson et al. (34) showed that collagen-related defects due to hereditary prolidase deficiency can be explained by the inhibitory effects on collagen turnover. The magnitude of the collagen deficiency revealed is best estimated by the clearance rate of the Gly–Pro dipeptide.

SPA in Patients with Left Ventricular Diastolic Dysfunction

The major mechanism of the formation of LVDD is expressed as impairment in myocyte functions and changes in ECM integrity (35). Collagen type I and type III, which are commonly found in the myocardial interstitium, are among the main targets of MMPs (7).

Erkus et al. (12) demonstrated that in a defined population, SPA has a positive and independent effect on the severity of LVDD. Prolidase is a key exopeptidase that affects collagen transformation: the increase in prolidase activity suggests a higher fibrotic process (12). Sezen et al. (36) found lower SPA in patients with dilated cardiomyopathy. In addition, patients with ischemic cardiomyopathy had lower SPA levels than patients without ischemia.

Significant variations in SPA levels were determined in diseases such as coronary atherosclerosis, LVDD, cardiomyopathy, arrhythmias, and HT. SPA is a promising marker and should be used for further investigation in these diseases. We need more clinical studies to realize the importance of the SPA. Due to the pronounced effects of SPA on the collagen turnover, it would be beneficial to focus more on diseases related to the balance of both lysis and synthesis.

CONCLUSION

Currently, CVDs are among the most common causes of death worldwide. SPA may play an active role in the physiopathogenesis of many diseases, usually through the collagen cycle and oxidative stress. Several studies have shown that SPA is independently associated with diseases such as LVDD, HT, coronary artery aneurysm, aortic dilatation, and coronary slow flow. SPA may be a promising new therapeutic agent in CVDs. Studies on the effect of SPA on CAD prognosis are limited; therefore, more comprehensive studies are needed in the future.

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