

Role of matrix metalloproteinases in the development of vascular complications of diabetes mellitus – clinical implications

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Abstract: Cardiovascular complications are the leading cause of increasing and premature mortality in diabetic patients. Matrix metalloproteinases (MMPs) play an important role in the development and progression of vascular lesions. Matrix metalloproteinases are members of endopeptidases and are capable of degrading many extracellular matrix components. Results of recent studies indicated that non-pharmacological and pharmacological treatment of diabetes influenced disturbed system of metalloproteinases and their inhibitors. Clinical trials are being performed in hope that the selective MMP inhibitors reduce the progression of pathological vascular remodeling in diabetes. Further basic and clinical research is required to confirm this hypothesis.

Key words: diabetic angiopathy, matrix metalloproteinases, treatment of diabetes

INTRODUCTION

Abnormal carbohydrate metabolism is an important and still growing social problem. Cardiovascular complications are the leading cause of increasing premature mortality in diabetic patients despite the progress in the diagnosis and the treatment of this disease [1,2]. In the last few years, considerable progress was observed in our knowledge about the mechanism of the development of diabetic angiopathy. However, our understanding of the precise events involved in the vascular remodeling is far from complete. Recently it has been proven that matrix metalloproteinases (MMPs) play an important role in the atherosclerosis and the rebuilding of vascular wall [3]. Vascular diabetic lesions are directly linked to hypertrophy of smooth muscle cells, extracellular matrix (ECM) expansion, proliferation of endothelium, and thickening of intima-media complex [4]. This article described changes that are likely associated with disturbances in the system of metalloproteinases.

Metalloproteinases belong to the family of Zn-containing endopeptidases. The main function of MMPs is structural rebuilding of extracellular matrix components. Metalloproteinases are secreted as latent proenzymes and require biochemical conversion for their reactivation. Moreover, their activation is controlled by specific tissue inhibitors (TIMPs).

MMPs are expressed in all tissues of the body. However, their synthesis is initiated in endothelial and smooth muscle cells of vascular walls [5].

Expression of MMPs is controlled by the neuro-immuno-hormonal system and maintained physiologically in tissues at a low grade, constant level. The activation and inhibition of MMPs are complex and rely on the phenomenon of cascade regulation. Expression of MMPs is increased by proinflammatory cytokines (interleukin-1 [IL-1], interleukin-6 [IL-6], tumor necrotic factor alpha [TNF- α]), as well as hormones and growth factors (transforming growth factor [TGF β], endothelial growth factor [EGF], plates growth factor [PDGF] or basic fibroblast growth factor [bFGF]). Meanwhile, corticosteroids, retinoic acid, heparin and IL-4 have an inhibitory effect [6]. Direct activation of MMPs is proceeded through proteases (plasmin, trypsin, chymase, elastin) and some metalloproteinases (MMP-1, MMP-2, MMP-8, MMP-9). However, the membrane type metalloproteinases (MT-MMPs) are responsible for their local activation [7].

In the 1990s, the substrate specification of metalloproteinases was divided into four classes. Numeric classification is now used (tab.) [5].

Role of matrix metalloproteinases and their inhibitors in the development of vascular complications of diabetes mellitus

Diabetic macroangiopathy

In the recent years, more reports have been published and they indicate the role of metalloproteinases and their inhibitors (MMP/TIMP) in the pathophysiology of cardiovascular

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disease. Thus, rebuilding of extracellular matrix is observed amongst others in dilated cardiomyopathy after myocardial infarction and heart failure [5,8].

Metalloproteinases also participate in the formation and destabilization of the atherosclerotic plaque. A key role in this phenomenon plays the activation of MMP-1, MMP-2, MMP-3, MMP-7 and MMP-9 within atherosclerotic arteries [9,10]. It was proved that the polymorphism of MMP-9 gene contributes to the occurrence of acute coronary events.

It has been suggested that a high serum concentration of MMP-9 combined with a low HDL- cholesterol concentration is the important risk factor for myocardial infarction [11].

In comparison with the general population, atherosclerosis in diabetic patients manifests earlier, is more severe and has a more disseminated character. Moreover, diabetic patients die more frequently of myocardial infarction, suffer from recurrent coronary events and are more prone to the development of heart insufficiency. A reason for this adverse prognosis could be a disturbed balance in MMPs/TIMPs [12]. Signorelli et al. have observed considerably higher concentrations of MMP-2 and MMP-9 in the serum of patients with type 2 diabetes and atherosclerosis of lower extremities [13]. It is known that the risk of stroke in patients with abnormal carbohydrate metabolism is from 4 to 6 times higher than those without diabetes. It has been suggested that pathological remodeling of brain vessels in diabetes is initiated by endothelin-1 (ET-1), which also contributes to the metalloproteinase system- increases

activity of MMP-2 and decreases MMP-1 concentration. As a result, hypertrophy of intima-media by increased deposition of collagen is initiated, which progressively decreases the lumen of the vessels [14]. Compared with subjects without carbohydrate imbalance, diabetic patients are more likely to have impaired collateral circulation in the ischemic region of the myocardium. Moreover, unfavorable remodeling of the heart wall deteriorates cardiac function. In 2006, investigators have shown that the reason for this phenomenon could be associated with increased activity for TIMP-1 and TIMP-2, along with the glycation of matrix extracellular protein in diabetes. Thus, this change in the ECM protein structure makes them more difficult to degradation by proteolytic enzymes [15].

Diabetic microangiopathy

Disturbances of physiological balance between metalloproteinases and their inhibitors seem to play an important role in the development and progression of diabetic microangiopathy. Increased expression of MMP-2, MMP-9 and MMP-14 was confirmed in the early stage of retinopathy [16]. It was indicated that production of MMP-9 in retinal cells increases in the response to high serum glucose concentration. It then leads to an increase in vascular permeability by the mechanism involving proteolytic degradation of basement membrane proteins. Selective apoptosis of pericytes and disruption of the tight junction complex in the basement membrane are the reason

Tabele. Classification of matrix metalloproteinases

Traditional classification	Numeric classification	Substrate specificities of collagenases
Collagenases		
interstitial collagenase	MMP-1	collagens (I, II, III, VII, VIII, X), gelatin, IL-1β, L-selectin, proteoglycans, MMP-2 i MMP-9, fibronectin
neutrofil collagenase	MMP-8	
collagenase-3	MMP-13	
Gelatinases		
gelatinase A (neutrophil gelatinase)	MMP-2	gelatin, collagens (I, IV, V, VII, X), elastin, fibronectin, proteoglycan, IL-1β, MMP-1, MMP-9, MMP-13, plasminogen
gelatinase B	MMP-9	
stromelysin		
stromelysin-1	MMP-3	proteoglycan, fibronectin, laminin, elastin, gelatin, vitronectin, plasminogen, fibrinogen, fibrin, collagens (III, IV, V), antithrombin, MMP-1, MMP-2, MMP-8, MMP-9, MMP-13
stromelysin-2	MMP-10	
stromelysin-3	MMP-11	
matrylisin	MMP-7	
metalloelastase	MMP-12	
Membrane type metalloproteinases (MT-MMP)		
MT-MMP-1	MMP-14	collagens (I, II, III), gelatin, elastin, fibronectin, laminin, vitronectin, proteoglycan, MMP-2, MMP-13
MT-MMP-2	MMP-15	
MT-MMP-3	MMP-16	
MT-MMP-4	MMP-17	

MMP – matrix metalloproteinases, MT – membrane type, IL – interleukin

for microaneurismatic dilation of the capillaries in which blood components accumulate. Disturbed microcirculation in these conditions results in the disclosure and formation of ischemic areas in the retina. Furthermore, the damage of physiological blood-retinal barrier leads to hard exudates. Hypoxia of the retina deepens disturbances in the MMPs/TIMPs started by hyperglycaemia. Imbalance between MMPs and their inhibitors is the reason of excessive extracellular matrix synthesis and proliferation of pathological vessels in the retina. This process is followed by the production of angiogenetic factors, such as the vascular-endothelial growth factor (VEGF). This factor is one of the main mediators of new vessel formation. It increases additional expression of matrix metalloproteinases. Not surprisingly, the serum activity of MMP-2 and MMP-9 increases in proliferative retinopathy. High concentration of these proteinases (after excluding other reasons) could be considered as a marker of active proliferation in the retina [17,18].

The hypertrophy of the glomerulus and increased volume of the kidney is observed in the early stage of the diabetic nephropathy. Long duration of this glucose metabolism disturbance results in a characteristic progressive thickening of basement membrane with increased mesangial volume. Advanced stage of diabetic kidney disease leads to fibrosis and hyalinization of glomerulus. Increased activity of metalloproteinases has been already observed in the early phase of diabetic nephropathy without features of structural damages of kidneys. Proteolytic enzymes secreted by neutrophils digest proteins and glycosaminoglycans of the basement membrane of glomeruli. In the aftermath of decreased heparin sulphate content, the negative charge repulsion alterations on the basement membrane leads to excessive permeability of negative charge particle like albumins. The recent research has even indicated that higher serum concentration of MMP-9 in diabetic patients anticipate on several years of microalbuminuria and can be prognostic in its character [19,20]. Disturbed balance between ECM synthesis and degradation in the next stage of diabetic renal damage leads to excessive production of material of basement membrane including type IV collagen and fibronectin. Thus, in the late period of diabetes, decreased activity of MMP-2 and MMP-9 is observed, but there is increased activity of TIMP-1 [21]. This is because the prolonged hyperglycaemia can alter the blood concentration of angiotensin II, TNF- β , connective tissue growth factor (CTGF) and the expression of plasminogen activator inhibitor of (PAI-1). These factors decrease the synthesis of MMPs in the mesangium, and they also increase the activity of their inhibitors [22,23]. Glycation of ECM protein makes them additionally more resistant to degradation by proteolytic enzymes. As a result of the ECM depositions formation in the glomerulus, the surface area involved in the filtration is decreased. Clinically, a decrease of glomerular filtration rate correlates with pathological changes in the mesangium, even fibrosis.

In the literature, there is only a few data about the role of metalloproteinases in the development of diabetic neuropathy. However, it is possible to expect that metabolic distur-

bances in diabetes contribute to the damage of the peripheral and central nervous system. Therefore, chronic hyperglycaemia induces the range of pathological processes influenced on the neuron function. Additionally, disturbed balance between metalloproteinases and their inhibitors have an effect on nerve conduction. Hence, it was proven that metalloproteinases participate in process of demyelination and regeneration of axons [24].

Factors affecting MMPs/TIMPs in diabetes

Development of chronic diabetic complication is associated with metabolic, hormonal, genetic and environmental factors [1,2]. In chronic and acute hyperglycaemia, nonenzymatic protein glycation, poliol pathway and oxidative stress activation are all effected. Atherogenic lipid profile in diabetes is characterized by high concentrations of triglyceride, low concentrations of HDL-cholesterol and presence of small high density LDL and HDL particles. Then, those particles undergo modification initiated by reactive oxygen species and increased blood glucose concentration. In these conditions the amount of glycated and oxydated LDL particles increase, which is harmful for the endothelium [25]. Haemodynamic changes in diabetes due to increased blood pressure, apart from those initiated by hyperglycaemia, lead to adverse remodeling of the vascular wall. This phenomenon is linked to the renin-angiotensin system (RAS) activity. Angiotensin II activates vascular NADH/NAD(P)H oxydase through the AT₁ receptor. The confluence point of above-mentioned processes is the elevated intracellular kinase activation including: protein kinase C (PKC) and mitogen activated phosphokinase (MAPK). It comes in the activation of transcription factors, including nuclear factor NF- κ B, which participates in the induction and modulation of inflammatory response. This factor influences the up-regulation of genes coding cytokines, growth factors, and metalloproteinases. This phenomenon contributes to several disturbances in the endothelium, in addition to decreased bioavailability of nitrogen oxide and increased level of endothelin-1, which impairs the diastolic function of the vessels. This pathological cascade activates disturbances in MMPs/TIMPs [27]. Therefore, in the low-grade chronic inflammatory state induced by hyperglycaemia, expression of MMPs is subject to compound regulation of many hormones and growth factors. Disturbed balance between metalloproteinases and their inhibitors becomes the reasons of pathological rebuilding of vascular wall, proliferation of endothelium and impairment arteriogenesis in diabetes.

Metalloproteinases and their inhibitors-therapeutic implications

The Diabetes Control and Complications Trial (DCCT) in type 1 diabetic patients and United Kingdom Prospective Diabetes Study (UKPDS) in type 2 diabetes have clearly shown that improvement of metabolic control decreases development

and progression of chronic complication of diabetes [28,29]. The STENO-2 study has paid attention to the specific complex treatment of hyperglycaemia, hyperlipidaemia, and hypertension for people with type 2 diabetes [30]. The advantages of behavioral and pharmacological treatment of diabetes seem to be related with positive modulation of a balance between metalloproteinases and their inhibitors.

Diet

It was shown that limitation in diet of simple carbohydrates and saturated fats along with increased content of fiber, not only enables the reduction of body mass and correction of metabolic parameters, but also decreases the concentration of pro-inflammatory cytokines, adhesion molecules, and MMP-9 [31]. It is known that polyphenols influence the MMPs/TIMPs balance particularly favourably. Their protective effect was observed in prevention of cancer, cardiovascular diseases and diabetes. Vitamins and flavonoids, present in vegetables and fruits, exert antioxidant and antiinflammatory effects because they favorably influence the decreased expression and activation of matrix metalloproteinases [32].

Physical activity

Systematic, moderate physical activity represents an important component of the treatment of diabetes. Prescribed regular, aerobic exercises not only improve insulin-sensitivity of the tissues, but positively correct glucose and insulin blood concentration, lipid profile and moreover, serum fibrinolytic activity. The antiatherosclerotic role of physical activity is connected probably with its anti-inflammatory effect as well as favorable modulation of metalloproteinases and their inhibitors.

Smoking cessation

Cigarette smoking is recognized as an important risk factor of diabetic macro- and microangiopathy. Tobacco smoke affects the inflammatory reaction through activation of polynuclear neutrophils and monocytes, increasing their migration and adhesion to the vascular wall, release of proinflammatory cytokines, proteolytic enzymes, and start-up of the metalloproteinase cascade. Smokers are therefore at a higher risk of atherosclerotic plaque rupture and development of acute coronary syndrome. Smoking cessation by diabetic patients can limit progression of vascular complications started by the disturbed balance in the MMPs/TIMPs system [33].

Pharmacological treatment

Treatment of type 2 diabetes, aside from changing eating habits and increasing physical activity, usually requires the use of pharmacotherapy. During a one-year period, observa-

tion of type 2 diabetic patients, who were intensively treated with metformin, acetylsalicylate acid, statins, angiotensin covering enzyme (ACE) inhibitors and others antihypertensive agents, gained not only the improvement of metabolic control (decrease of HbA1c, blood pressure and lipid parameters), but also there was observed reduction of serum TIMP-1 concentration. Correction of metabolic parameters in diabetes has led to decreased expression of connective tissue growth factor (CTGF) and TIMP-1 in the kidneys [34].

It has been observed that treatment of thiazolidinediones is associated with decreased serum concentrations of MMP-2 and MMP-9. This phenomenon can be explained by the influence of PPAR- γ receptors on transcription of metalloproteinases genes [35]. It has been shown, that in addition to already proven favorable metabolic effect, metformin decreases also the pathologic activation of MMPs cascade and therefore exerts direct effect on the course of inflammatory reaction [36]. Currently, there is insufficient data in the medical literature regarding influence of sulphonylurea derivatives on expression and activation of MMPs. However, effective treatment of hyperglycaemia applied by this group of agents probably influences also in the disturbances in MMPs/TIMPs balance observed in diabetes. It is emphasized that the possible role of glyclazide in this range is that of the sulphonylurea derivative with proven antioxidant effect [37].

Statins and fibrates are the most common agents using in therapy of hyperlipidaemia in diabetes. It is known that they exert also antiinflammatory and antioxidant effect. They cause the improvement of endothelium function and stabilization of atherosclerotic plaque via modulation of extracellular matrix homeostasis by decreasing the concentration and activity of metalloproteinases and their inhibitors. Moreover, they limit remodeling initiated in the ischemic myocardium [38,39].

The ACE inhibitors are the treatment of choice of hypertension in diabetes, but in case of their intolerance, the angiotensin receptor blockers (ARB) are indicated. Blockade of RAS has become an important therapeutic strategy to reduce renal and cardiovascular events. Earlier consideration about the role of metalloproteinases and their inhibitors in development and progression of diabetic kidney disease can be related with RAS. It is known that angiotensin promotes the oxidative stress and affects expression and activation of metalloproteinases. Ebihara et al. have proven that after a 6-month treatment of ACE-inhibitors, reduction of microalbuminuria and decrease of serum MMP-9 concentrations were observed [19]. Gradual decrease of metalloproteinases activity in kidneys coincides with progression of diabetes. However, it is important to note that treatment of low doses of perindopril have decreased deposits of type IV collagen in the basement membrane of glomerulus. ACE inhibitors also limit the formation of advanced glycation end-products (AGE) [21]. Multicenter clinical trials have demonstrated, that the inhibition of RAS due to ACE inhibitors reduces the risk of myocardial infarction, sudden death, ischemic heart disease and left ventricle insufficiency in patients with diabetes. ACE inhibitors and

ARBs are characterized as having protective properties on the vascular wall. They are able to induce regression of vascular structural alterations and decrease thickness of intima-media membrane through increase of proteolytic activity of MMP-9 and decrease of contents of type-1 collagen [40].

Another group of medicines that have favorable effects on the metalloproteinases system are calcium channel blockers (Ca-blockers). It has been demonstrated in the in-vitro studies that Ca-blockers reduce the secretion of MMP-9 and TIMP-1 by macrophages [41]. Moreover, positive results of the aspirin's use in primary and secondary prevention in diabetes could be related to aspirin's influence on the TIMP-1/MMP-9 system [42]. Therefore, acetylsalicylic acid blocks the cyclooxygenase, decreases the synthesis of prostaglandins and then controls the pathologic activation of metalloproteinases [43].

The proven participation of MMPs in mechanisms involved in remodeling of the vessel and heart wall has important clinical implications. Synthetic inhibitors of metalloproteinases are currently being assessed in the cancer and rheumatoid diseases. Control of MMPs by their specific inhibitors seems to restrict the ischaemic area in the heart as well as decreases the risk of development of heart failure initiated by pathologic remodeling of the myocardium [43]. MMP-2 inhibitors could also be used as potential vasodilators and antiagregatic agents [5,45]. Although it seems that synthetic inhibitors of metalloproteinases limit progression of pathological vascular remodeling in the future, it does not solve the problem of chronic diabetic complications altogether.

The disturbed balance between metalloproteinases and their inhibitors plays an important role in the development and progression of chronic complications in diabetes. Our knowledge of mechanisms responsible for rebuilding of vessel wall and associated changes in the extracellular matrix may have important clinical and therapeutic implications.

However, it requires further experimental and clinical research.

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