

COMMENTARY

# Matrix metalloproteinases in diabetes

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## ABSTRACT

Diabetes, the Obesity-Diabetes Epidemic, is one of the major global health problems. Complications associated with it resulted in serious complications and need urgent attention for new therapeutic approaches. In recent years, evidence supporting role of Matrix metalloproteinases and their inhibitors in development of diabetes associated complications are increased. Due to their role in diabetes associated complications they may be potential therapeutic targets.

**Keywords:** *Matrix metalloproteinases, diabetes, obesity, therapeutic target, complications*

## Introduction

Diabetes, the term denotes diabetes in the context of obesity, is one of the foremost epidemic problems. [1] In the recent time prevalence of obesity and type two diabetes had a rapid rise worldwide. They are mainly contributed to sedentary lifestyle and diet apart from genetic susceptibility [2, 3]. Both of these conditions diabetes and obesity leads to an increase risk of developing complications and comorbid disease conditions like cardiovascular disease, hypertension and stroke, which can complicate disease management. Evidence from the recent studies associated matrix metalloproteinases (MMPs) with the development and advancement of diabetic microvascular complications [4]. In cardiomyopathy associated to diabetes, MMPs play important role in breakdown of collagen and elastin, remodelling of myocardium as well as the coronary plaque vulnerability. Further altered MMPs expression leads to extracellular matrix deposition resulted in glomerular hypertrophy that ultimately lead to renal complications [5]. Altered levels of MMPs causes impaired angiogenesis thus the development of diabetic peripheral arterial disease [6]. Studies reported role of MMPs in cerebral circulation, stroke volume in diabetes and impairment in diabetic wound healing [7-9]. Table 1 showed activity of various MMPs in obesity and diabetes.

## MMPs in obesity

For the role of MMPs pattern in obesity conflicting observations are reported. In experimental animal models increased level of mRNA levels of MMP-2, MMP-3, and other MMPs have been reported in adipose tissue [10]. It has been hypothesized that

MMPs may be associated with adipose tissue remodeling and differentiation of pre-adipocytes [11-13]. Neutrophils and endothelial cells produced MMP-8 is a collagenase that is involved in collagen breakdown resulted in increased vulnerability of atherosclerotic plaques [14]. In another study significantly increased levels of MMP-9 were observed obese hypertensive children compared to normotensive; in the same study correlation of MMP-9 with BMI, systolic blood pressure and fasting plasma insulin was also established [15]. Furthermore higher levels of plasma MMP-9 and lower levels of MMP-2 in obese women compared to lean ones are also reported [16]. However some authors reported increased levels of MMP-2 and MMP-9 in obese subjects and suggested abnormal extracellular matrix metabolism in these subjects [17].

Table 1. MMPs and TIMPs expression in obesity and type 2 diabetes mellitus

MMP type	Obesity	Diabetes mellitus
MMP-2	↑↓	↑
MMP-3	↑	↑
MMP-7	↓	No data
MMP-8	↑	No data
MMP-9	↑	↑
MMP-10	No data	No data

↑: Increased, ↓: Decreased, ↑↓: Some studies reported increase while other reported decrease

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## MMPs in diabetes

Role of MMPs is widely studied by many researchers and although some authors have reported increase in MMPs levels in diabetes some have not observe any difference in plasma concentrations of MMP-2 and MMP-9 [18]. In diabetic cultured endothelial cells and monocyte derived macrophages, under elevated glucose concentration conditions, increased expression of MMP-1, MMP-2, and MMP-9 is reported [19]. Furthermore in similar conditions decrease in MMP-3, however no significant change on TIMP-1 expression was observed [19]. Some studies reported that MMP activity of mesangial cell controls ECM degradation that leads to pathogenesis of diabetic nephropathy [20, 21]. Different mechanisms are proposed by which hyperglycemia regulate MMP gene expression including protein kinase C (PKC) agonists, cytokines, TGF- $\beta$ , and nuclear factor- $\kappa$ B (NF- $\kappa$ B). It is not clear how hyperglycemia alter MMP expression. For example, glycation of the ECM decreases MT1-MMP expression in diabetics the but at the same time increases MMP-2, TIMP-1, and TIMP-2 expression [22]. Increased level of MMPs in heart failure patients and further increase in level with progression of heart failure have been reported [23]. In another study significant increase in MMPs levels within hours of the precipitation of myocardial infarction have been reported that was followed by local activation of cytokines and infiltration of inflammatory cells [24]. Enhanced MMP-2 activity by high glucose concentrations is observed in human retinal pericytes and decreased by modification with thiamine that controls AGE formation, ROS production, and polyol pathway [25]. MMP-2 and MMP-9, TIMP-1 and TIMP-2 were significantly higher in type 2 diabetes patient compared to controls, especially in those with acute coronary syndrome [26].

## Concluding remarks

MMPs play important role in diabetesity and leads to precipitation of various complications and comorbidities associated with diabetes and obesity. Various MMPs based on their level can be targeted for treatment of diabetesity associated complications.

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