

# Marfan Syndrome and Early-Onset Diabetic Retinopathy: A Case Report

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**D**iabetic retinopathy is characterized by the proliferation of fibrovascular tissue extending from the retina into the vitreous cavity. MFS is an autosomal dominant disorder of the elastic tissue. Although MFS clearly manifests with multiple ocular problems, there is no reported association between MFS and diabetic retinopathy. Reported here is the case of 32-year-old male with Marfan Syndrome (MFS) and type 2 diabetes mellitus (DM) presented with an accelerated onset of diabetic retinopathy. Our patient developed diabetic retinopathy only 4 years following the diagnosis of type 2 DM, despite excellent glucose control. We suggest that there may be a pathophysiological link between MFS and diabetes involving extracellular matrix components that accelerates and/or augments the retinopathic processes in MFS patients. Specifically, we postulate that increased levels of matrix metalloproteinases (MMP) and transforming growth factor beta (TGF- $\beta$ ) in diabetic retinas facilitate the proteolysis of an already weakened ocular connective tissue in MFS, ultimately leading to early development of ophthalmologic manifestations such as diabetic retinopathy.

**Key Words:** Marfan syndrome, Diabetic retinopathy, Type 2 diabetes, Matrix metalloproteinases

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## Introduction

Marfan Syndrome (MFS) is an autosomal dominant disorder of the connective tissue characterized by a wide spectrum of phenotypic manifestations, primarily involving cardiovascular, ophthalmic and skeletal systems. The gene presumed to be most responsible, FBN-1, encodes a glycoprotein in the extracellular matrix called fibrillin-1.<sup>1-3</sup> Fibrillin-1 is an important structural component of elastic tissue that provides strength and elastic recoil in the heart, kidney, blood vessels, lungs, ligaments, dermis, ocular structures and skeletal muscles.<sup>4</sup> Fibrillin-1 also binds to and sequesters the inflammatory cytokine transforming growth factor beta (TGF- $\beta$ ). The reduced levels of fibrillin-1 can cause an increase in the levels of TGF- $\beta$  and the inflammatory effects of TGF- $\beta$  are believed to be responsible for some of the features of MFS.<sup>5</sup> There is also evidence that shows mutations in the gene encoding TGF- $\beta$ R2 (transforming growth factor beta receptor 2) are involved in the pathogenesis of MFS.<sup>5</sup> In fact, the importance of the TGF- $\beta$  pathway was confirmed with the discovery of a similar syndrome,

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the Loeys-Dietz syndrome, involving mutations in the genes encoding TGF- $\beta$ R2 and TGF- $\beta$ R1.<sup>5</sup>

The ocular manifestations of MFS include lentis ectopia, open angle glaucoma, axial myopia, corneal flattening, strabismus, pre-senile cataract iris and ciliary muscle hypoplasia, elongation of ciliary processes, and retinal detachment.<sup>4,6</sup> It is supposed that various mutations of fibrillin-1 are central to the pathophysiology of these defects.<sup>3,7,8</sup>

We performed a literature search with PubMed database and used the keywords Marfan Syndrome, Type 2 Diabetes, and diabetic retinopathy in different permutations. Although it is clear that MFS manifests with multiple ocular problems, to date, there is no known association between MFS and proliferative retinopathies such as diabetic retinopathy. Diabetic retinopathy is characterized by the proliferation of fibrovascular tissue extending into the vitreous cavity, and is thought to involve extracellular matrix degradation.<sup>1</sup> Given that both MFS and diabetic retinopathy involve extracellular matrix components; it is plausible that there is a commonality in their pathophysiologies. In this article, we present the first case, to our knowledge, of MFS and early onset diabetic retinopathy.

## Case Report

The patient was a 32-year-old East Indian male with MFS, type 2 DM, and Schizophrenia. Demographic information and lab investigations are summarized in Table 1. His family history included a mother and sister both with type 2 DM and MFS, however, neither had reported early diabetic retinopathy.

In 1988, (age 13), the patient he was diagnosed with MFS. Manifestations included a dislocated crystalline lens in the right eye, astigmatism, arachnodactyly and pectus carinatum. The aortic diameter was within the upper limit of normal. The patient was started on prophylactic Atenolol.

**Table 1. Demographic characteristics and laboratory investigations upon admission**

Variable	Values
Age	32
Height (m)	1.85
Weight (kg)	72.6
BMI (Kg/m <sup>2</sup> )	21.1
Blood pressure (mmHg)	110/70
Laboratory findings	
HbA1c (%)	5.3
Creatinine ( $\mu$ mol/L)	85
eGFR (ml/min)	111
Urea (mmol/L)	4.2
Cholesterol (mmol/L)	2.92
Triglyceride (mmol/L)	0.87
HDL-C (mmol/L)	1.48
LDL-C (mmol/L)	1.04

BMI: Body mass index, HbA1c: Hemoglobin A1c  
eGFR: Estimated glomerular filtration rate  
HDL-C: High density lipoprotein cholesterol  
LDL-C: Low density lipoprotein cholesterol

In 1998 (age 23), the patient developed schizophrenia and was subsequently treated with Clozapine, an atypical antipsychotic.

In 2002, (age 27), he was diagnosed with type 2 DM. The etiology was thought to be an adverse effect of Clozapine compounded by a family history of type 2 DM. Oral medications alone maintained steady tight control of his serum glucose, with an A1C well below 7%, ranging between 5.2% and 6%. He was on maximum doses of oral anti-diabetic medications including Metformin immediate release 3000 mg, Pioglitazone 45 mg, and Glyburide 10 mg. He showed no evidence of macrovascular or microvascular complications of diabetes such as coronary artery disease, stroke, peripheral vascular disease, nephropathy or neuropathy.

In 2006, (age 31), the patient received bilateral refractive laser surgery. Subsequently, he began to complain of blurred vision in the left eye and was immediately referred to an ophthalmologist.

Ophthalmologic examination revealed an uncorrected visual acuity of 20/40 in the right eye and 20/20 in the left eye. IOP was 10

mmHg. Auto refraction showed myopic astigmatism on the right eye. Slit lamp examination did not show neovascularization of the irises. Slight superior dislocation of the right crystalline lens was seen. Both of his optic nerves were healthy with cup to disc ratio of 0.3. The right macula was healthy, but the left macula showed single microaneurysm at the centre. No retinal thickening, IRMA formation or neovascularization were observed; in essence, the patient demonstrated mild non-proliferative diabetic retinopathy in his left eye, without macular edema. Laser treatment was not performed. Given his excellent visual acuity in the left eye, his symptom of blurred vision was thought to be secondary to recent refractory laser surgery.

## Discussion

Major predictors of diabetic retinopathy include hyperglycemia, hypertension, and duration of diabetes.<sup>1</sup> Although 10-20% of type 2 DM patients have retinopathy at diagnosis, our patient did not fall under this category. Rather, he clearly developed diabetes after taking Clozapine, and was kept on constant glucose monitoring following the diagnosis of type 2 DM. Contrary to the major risk factors, our patient developed diabetic retinopathy only 4 years following his diagnosis of type 2 DM, despite documented, well controlled glycemic levels.

The most widely accepted pathogenesis of MFS involves the extracellular matrix protein fibrillin-1, an important structural component of microfibrils in elastic fibers.<sup>3,7,8</sup> Various mutations in the gene encoding for fibrillin-1 result in an altered amount and/or strength of fibrillin-1 in the extracellular matrix.<sup>3,7,9</sup> One proposed explanation to account for this phenomenon involves a calcium binding mechanism. Calcium serves to protect fibrillin-1 from proteolysis via serine proteinases such as matrix metalloproteinases, neutrophil elastase, chymotrypsin, and trypsin that are secreted by inflammatory cells.<sup>4,8,10</sup> In MFS, mutations that reduce the binding affinity of

calcium may lead to conformational changes that expose cryptic protease cleavage sites on fibrillin-1. The exposed fibrillin-1 is more susceptible to degradation, which ultimately results in a weakened connective tissue.

Previous research suggests that a number of matrix metalloproteinases (MMP) are involved in the pathogenesis of MFS.<sup>4,7</sup> MMPs are zinc-dependent proteinases widely expressed by fibroblast and inflammatory cells. They are involved in the breakdown and remodelling of the extracellular matrix and are important in angiogenesis, tumour invasion and wound healing. MMPs are secreted as zymogens (proMMPs) requiring the presence of activators such as membrane type-MMPs (MT-MMP), and inhibited by Tissue Inhibitors of Metalloproteinases (TIMPs). In the eyes, MMPs are involved in corneal ulceration and healing, postoperative conjunctival wound healing, scleral remodeling, lens remodeling, and vitreous liquefaction.<sup>11</sup> In addition, MMPs are expressed by retinal pigment epithelium and are suggested to have a role in retinal revascularization in proliferative diabetic retinopathy.<sup>10-12</sup>

Proliferative diabetic retinopathy is a microvascular complication of diabetes resulting in 1) the breakdown of the blood-retinal barrier (BRB), 2) neovascularization and 3) fibrovascular proliferation of retina into the vitreous cavity. Research indicates that MMPs are involved in each of these three aspects of diabetic retinopathy.

First, data suggests that MMPs are involved in the breakdown of the BRB, an early phenomenon of diabetic retinopathy.<sup>13</sup> Giebel et al. showed that the mRNA levels for MMP-2, MMP-9 and MMP-14 are increased in the retinas of early diabetic rats. Additionally, bovine retinal endothelial cells and human retinal pigment epithelial cells exhibit increased production of MMP-9 when treated with high concentrations of glucose in vitro, as well as abnormal tight junctions when treated with MMP-2 or MMP-9.<sup>2</sup> Second, MMPs appear to play a significant role in neovascularization, which involves remodel-

ling and penetration of the capillary basement membrane into the extracellular matrix. Specifically, both animal<sup>14</sup> as well as human data<sup>12,15</sup> indicate that MMP-2 and MMP-9 are significantly increased in both expression and activity in the epiretinal neovascular membranes of individuals with proliferative diabetic retinopathy compared to individuals with normal retinas. In addition, MMP-2 and MMP-9 are elevated in the vitreous samples of patients with diabetic retinopathy compared to patients with epiretinal membranes or macular holes without diabetic retinopathy.<sup>16</sup> Third, the fibrovascular tissues of patients with diabetic retinopathy exhibit elevations in both the activation ratios of MMP-2 and MMP-9 as well as in the level of MT1-MMP, a substance that activates proMMP-2, compared to controls without diabetic retinopathy.<sup>15</sup> This suggests the potential role of MMP-2 in fibrovascular proliferation of diabetic eyes.

In addition to the increased level of MMPs in the eyes, individuals with diabetes also demonstrate increased levels of MMPs in the serum. Jacqueminet et al. report that individuals with type 1 diabetes exhibit significantly higher levels of MMP-9, TIMP-1, and MMP-9/TIMP-1 ratio in the serum compared to nondiabetic controls.<sup>17</sup> Similar findings are seen when individuals with both diabetes and retinopathy are compared to individuals solely with retinopathy, possibly reflecting the increased production and release of MMP-9 from the retinopathic eyes into the periphery.

Furthermore, an important protein involved in both MFS and diabetic retinopathy is the inflammatory cytokine TGF- $\beta$ . Studies have shown that a deficiency of fibrillin-1 in the extracellular matrix leads to excessive signaling by TGF- $\beta$ , which may be responsible for the disease manifestations of MFS such as the cardiovascular complication of aortic-root enlargement.<sup>5</sup> Furthermore, the role of TGF- $\beta$  in MFS was confirmed by use of TGF- $\beta$  antagonists to treat the pathologic changes in the aortic wall and the progressive dilation of the aortic root.<sup>18</sup> TGF- $\beta$  is also involved in

the control of endothelial cell proliferation, adhesion and deposition of extracellular matrix, thus TGF- $\beta$  may play a role in the control of endothelial cell proliferation seen in diabetic retinopathy.

In a study done by Ye et al., the levels of serum TGF- $\beta$ 1 were measured in patients with nonproliferative diabetic retinopathy and compared to diabetic patients without diabetic retinopathy and healthy patients. It was found that the levels of TGF- $\beta$ 1 increased as the severity of diabetic retinopathy increased.<sup>19</sup> In another study done by Hirase et al, the levels of TGF- $\beta$ 2 was measured and compared in 49 vitreous specimens obtained from eyes of patients with proliferative diabetic retinopathy (PDR) undergoing vitrectomy, and 19 vitreous specimens from nondiabetic subjects. It was found that the levels of TGF- $\beta$ 2 were significantly higher in the vitreous of patients with PDR compared to the controls, suggesting that TGF- $\beta$ 2 plays an important role in the pathogenesis of PDR.<sup>20</sup> It is not clear how elevated levels of TGF- $\beta$  would be causing the specific pathologies seen in MFS and diabetic retinopathy, however the inflammatory reactions can cause release of proteases that can degrade components of the extracellular matrix such as the elastin fibers.

We present a patient with MFS and early onset diabetic retinopathy. Given that matrix metalloproteinases and TGF- $\beta$  play a role in both MFS and diabetic retinopathy, the disease processes may influence one another via MMP and/or TGF- $\beta$ . It is important to consider the possibility that increased levels of MMPs and TGF- $\beta$  in the retinas of individuals with type 2 DM facilitate the proteolysis of already weakened connective tissues in MFS, ultimately accelerating the development of ophthalmologic pathologies such as diabetic retinopathy. This postulation has significant clinical implications in MFS patients with diabetes as they may manifest early retinopathy and thus there may be a potential benefit from therapy targeting MMPs and/or TGF- $\beta$ . Future research investigating the role of MMPs and TGF- $\beta$  in MFS and di-

abetic retinopathy will help to elucidate our understanding of both the physiology be-

tween the two disease processes and of possible treatments.

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