·Opinion·

8-iso-prostaglandin-F2α: a possible trigger or accelerator of diabetic retinopathy

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INTRODUCTION

Diabetes mellitus (DM) is a global disease, the number of patients of which is predicted to rise to about 380 million by 2025 by the World Health Organization (WHO)[1]. Diabetic retinopathy (DR) is one of the most sigificant complications in DM [1], and the first cause of irreversible blindness of adults in the world[2]. It occurs in 90% of patients after 20-30y from the diagnosis of DM[1], and about 5 million individuals have DR, which is responsible for approximately 5% of blindness worldwide [3]. There are two main stages of DR: proliferative diabetic retinopathy (PDR) and non-PDR (NPDR) [2]. The hallmark of the presence of PDR is neovascularization, while no neovascularization means NPDR [4]. About 60% of diabetic patients suffer from PDR, which is the advanced form of DR[1].

Oxidative stress is defined as the increased generation of free radicals and impaired antioxidant defense which induces imbalance[5]. Because it activates other pathway (*e.g.* polyol pathway flux, and activation of diacylglyceol-protein kinase C pathway, *etc*) and leads to other structural and functional changes, it plays a leading role in the progression of DM and its complications [6]. Oxidative stress can be measured by many indicative parameters, such as lipoperoxidation, protein oxidation, and changes in antioxidant defence system status[7]. Lipid peroxidation biomarkers included malondialdehyde, lipoperoxides and lipid hydroperoxides [7]. However, 8-iso-prostaglandin-F2α (8-iso-PGF2α), as one of the stable products of non-cyclooxygenase peroxidation of arachidonic acid, has proved to be the most available and reliable marker of lipid peroxidation *in vivo* [8-9], and it appears more sensitive and specific than other markers of oxidative stress[8]. Furthermore, 8-iso-PGF2α induces vasoconstriction, mitogenesis and persistent platelet activation [9-10], which can contribute to the progression of diabetes and/or its complications. Some previous studies showed that the concentration of 8-iso-PGF2α is associated with the level of acute and chronic glucose fluctuation [11-12], the level of hemoglobin A1c (HbA1c), and fasting glucose [13], which might lead to the onset and/or progression of DR. To the best of our knowledge, however, there has been no studies about the relationship between the level of plasma 8-iso-PGF2α and the onset and/or progression of DR so far.

HYPOTHESIS

As reported by Monnier *et al*[12], relationship between 8-iso-PGF2α excretion rates and mean amplitude of glycemic excursions was still significant after adjusting for other markers of diabetic control. As a case-control study of Chang *et al* [14] showed, there was positive correlation between 8-iso-PGF2α and mean amplitude of glycemic excursions which estimated for an episode of 24h or the standard deviation of HbA1c levels after adjustment for other markers of diabetic control. In a word, acute or chronic glucose fluctuation could cause more severe oxidative stress [12,14], which will be accompanied with the elevation of the level of 8-iso-PGF2α as an oxidative stress marker. And then or simultaneously, acute or chronic glucose fluctuation may lead to DR or more severe DR. Accordingly, we postulated that there may be positive correlation between the level of plasma 8-iso-PGF2α and the severity of DR, and 8-iso-PGF2α may contribute to the onset or progression of DR in patients with Type 2 diabetes.

Evaluation of the Hypothesis 8-iso-PGF2α is the marker of oxidative stress as mentioned above, and possibly contributes to the onset or progression of DR. We speculated that there may be three possible pathogenic mechanisms (Figure 1).

Firstly, an experiment by Yura *et al* [15] showed that physiological concentration of 8-iso-PGF2α stimulated DNA synthesis, cell proliferation, endothelin-1 mRNA and protein expression in bovine aortic endothelial cell. 8-iso-PGF2α, as a vasoconstrictor itself [16], could help to stimulate the production of endothelin-1 *in vitro* [15], which also promotes

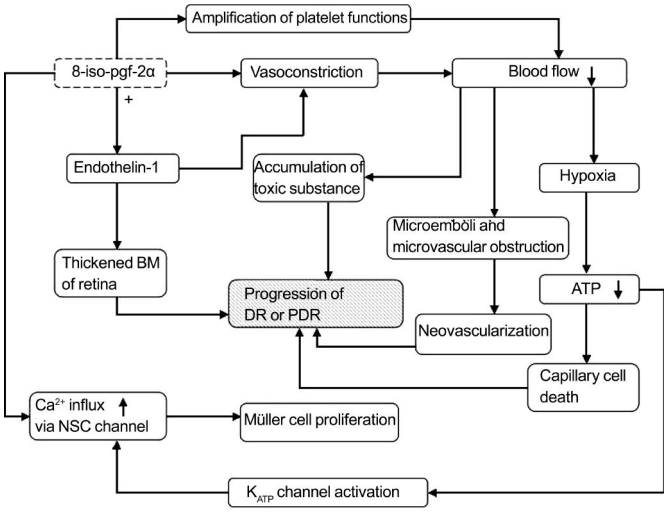

Figure 1 Schematic figure of three possible pathogenic mechanisms that 8-iso-PGF2α contributes to the progression of DR BM: Basement membrane; NSC: Nonspecific cation; CICR: Calcium induced calcium release; ATP: Adenosine triphosphate.

vasoconstriction, therefore slows down the blood flow in the retina [16]. It may cause accumulation of toxic substances and serious consequences that we will mention in the third point. Endothelin-1 could also lead to the increase of extracellular matrix protein through regulation of its gene expression [17], and thus cause the thickening of basement membrane in the retina [6,8], which may contribute to the progression of DR, if the same happens in human.

Secondly, 8-iso-PGF2α could cause persistent platelet activation [10,18], platelet shape change in the concentration raging from 1 nmol/L to 1 μmol/L [10,18], enhance platelet adhesion and attenuate the antiadhesive and antiaggregatory effects of nitric oxide [19]. 8-iso-PGF2α causes irreversible platelet aggregation in a dose-dependent manner (10 nmol/L-10 μmol/L) in the presence of concentrations of collagen, ADP, arachidonic acid, and analogues of prostagladin H2 and thromboxane A2 which could not aggregate platelets when acting alone [18]. The amplification of platelet functions (activation, adhesion and aggregation) that mentioned above may slow down blood flow, or even cause microemboli and microvascular obstruction, and finally lead to neovascularization in retina.

Thirdly, 8-iso-PGF2α leads to the release of calcium from intracellular stores in the concentration raging from 1 nmol/L to 1 μmol/L [18], which can increase the concentration of intracellular calcium. Consequently, it can increase the lethality of the oxidative stress especially in the microvasculature of retina [20]. Moreover, the increased intracellular calcium and the consequent activation of potassium channels lead to Müller cell proliferation[21], which might cause PDR [6,21-22]. In addition to the boosting of the intracellular calcium, 8-iso-PGF2α could slow down the blood flow as it is metioned above, so there may be more deaths of capillary cells of retina through the polyamine/ K_{ATP} channels/Ca^{2+} influx/calcium induced calcium release pathway[23].

Though there were studies which reported that there was no relationship between plasma/urinary 8-iso-PGF2α and glucose variability for Type 1 DM [24-25], we should consider the effect of insulin analogue[26] and different dietary intake[24].

Testing the Hypothesis In order to make sure the hypothesis, we can suppress the expression of specific gene which can decrease the production of 8-iso-PGF2α by Gene targeting. The gene knocked-out mice are purchased from Cyagen Biosciences Inc. (USA) [27]. We will use streptozotocin to induce the gene knocked-out mice as diabetic experimental model [28]. Simaltaneously, another group of age-matched wild-type mice will be also made diabetic with streptozotocin. Both groups will be killed 2mo after initiation and each retina will be removed immediately [28]. Immunohistochemistry, tunnel staining, and ELISA are needed for evaluating cell deaths, and the onset or progression of DR. The rest of retina of each groups will be obtained for analyzing the level of 8-iso-PGF2α by the approach of gas chromatography-mass spectrometry [9]. This will elucidate whether there is an effect of 8-iso-PGF2α in the onset or progression of DR *in vitro*.

In order to prove the hypothesis *in vivo*, the plasma 8-iso-PGF2α will be detected by specific ELISA in different groups of people. Four groups of participants, including those with both Type 2 diabetes and NPDR, those with Type 2 diabetes and PDR, those with Type 2 diabetes but without DR, and healthy volunteers will be included. The exclusion criteria will be strictly set to make the hypothesis confirmed. Exclusion criteria include pregnancy, a body mass index (BMI) >30 kg/m^2, a glomerular filtration rate of less than 60 mL/min per 1.73 m^2 according to the Cockcroft-Gault formula, recent history of ketosis, cardio-vascular disease, blood system disease, liver disease, cancer, systemic inflammatory disease and other metabolism disease, being treated with steroid, non-steroid anti-inflammatory drugs, insulin, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, anti-platelet drugs, or anti-oxidant agents to avoid influence of the concentration of 8-iso-PGF2α[12].

In order to give an exact analysis by synthesis, the clinical parameters of all subjects will be measured as below: BMI, blood pressure, fasting plasma glucose, postprandial glucose, the serum levels of HbA1c, mean amplitude of glycemic excursions, triglyceride, total cholesterol, low density lipoprotein, high density lipoprotein, high sensitivity C-reaction protein. This will elucidate whether the association between the level of 8-iso-PGF2α and the severity of DR is a single factor analysis in the study, and by affecting which factor the level of 8-iso-PGF2α affects the severity of DR *in vivo*.

Consequences of the Hypothesis 8-iso-PGF2α may contribute to the onset or progression of DR in patients with Type 2 diabetes. It is important for us to know whether 8-iso-PGF2α initiated DR at the onset or deteriorated DR during the progression. It could tell us whether we need high physiological antioxidant requirement to prevent DR before the onset of DR, and whether antioxidant requirement still makes sense when DR already existed, especially when local application of antioxidant requirement or local application that prevents the production of 8-iso-PGF2α matures.

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