

Role of Advanced Glycation End Products and Vascular Endothelial Growth Factor in Pathophysiology of Diabetic Retinopathy

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ABSTRACT

Background: The hyperglycemic state occurring in diabetes mellitus is responsible for formation and accumulation of advanced glycation end products (AGEs) that participate with their receptors, receptor for advanced glycation end products (RAGE) in the pathogenesis of vascular complications of diabetes mellitus. Intraocular vascular endothelial growth factor (VEGF) levels have been studied in animal models and human vitreous fluid, where the levels are found to be high in patients with active intraocular neovascularization. **Objective:** To investigate the levels of AGEs, soluble form of RAGE (sRAGE), VEGF and total antioxidants (TAO) in both vitreous and blood of diabetic patients with and without diabetic retinopathy. **Study Design:** Blood and vitreous samples were collected from 30 diabetic patients, 15 with proliferative diabetic retinopathy (PDR), 15 without retinopathy, and 15 non diabetic control subjects. ELISA technique was used for measuring vitreous and blood levels of AGE, sRAGE, VEGF and TAO. **Results:** AGEs, sRAGE and VEGF levels in blood were significantly higher in all diabetic groups compared to controls and in PDR patients compared to diabetic group. There were positive correlations between serum AGEs, sRAGE and VEGF levels in both diabetic groups. Vitreous levels of AGEs and VEGF were significantly increased in all diabetic groups compared to controls and in PDR group compared to diabetic group. Also there were significant correlations between these levels in both PDR and diabetic groups. Serum and vitreous TAO levels were decreased in patients with diabetes compared to controls and in patients with PDR compared to diabetics without retinopathy. Furthermore, Serum TAO levels were inversely correlated with serum levels of AGEs, sRAGE and VEGF in all diabetic patients. TAO levels in vitreous were inversely correlated with vitreous levels of AGEs, and VEGF in all diabetic patients. **Conclusion:** These findings suggest that the interaction of advanced glycation end products (AGEs), with their cellular receptor (RAGE) and oxidative stress is implicated in the pathogenesis of diabetic vascular complications through stimulation of VEGF.

INTRODUCTION

Diabetic retinopathy is a common and potentially devastating microvascular complication in diabetes and is a leading cause of acquired blindness among the people of occupational age. Chronic hyperglycemia is a major initiator of diabetic retinopathy⁽¹⁾. Among various pathways implicated in the pathogenesis of diabetic retinopathy, the process of formation and accumulation of advanced glycation end products (AGEs) and their mode of action are most compatible with the hyperglycemic theory⁽²⁾.

Hyperglycaemia leads to non-enzymatic glycation of intracellular and extracellular proteins with the formation of AGEs. The formation and accumulation of AGE is known to progress during normal ageing, and at an extremely accelerated rate in diabetes mellitus⁽³⁾.

The best-characterised receptor for AGEs is the receptor for AGEs (RAGE, also known as AGE-specific receptor [AGER]). RAGE belongs to the immunoglobulin superfamily of cell-surface molecules⁽⁴⁾. The role of RAGE in diabetic vasculopathy has been investigated in animal and human studies⁽⁵⁾. RAGE has a circulating secretory receptor form, soluble RAGE (sRAGE) which can be measured in peripheral blood, and result from the expression of a RAGE gene⁽⁶⁾. It consists of only the extracellular ligand binding domain and lacking the cytosolic and transmembrane domains. Due to these characteristics, the sRAGE represents a naturally occurring competitive inhibitor of the signaling pathways

induced by the interaction of AGEs with its cellular receptor; by functioning as a decoy, sRAGE may contribute to the removal/neutralization of circulating RAGE-ligands⁽⁷⁾.

Vascular endothelial growth factor (VEGF) is responsible for the growth of new blood vessels by stimulating the endothelial cells which form the walls of the vessels and transport nutrients and oxygen to the tissues. In normal retina, VEGF expression is limited to vessel walls and the retinal pigment epithelium⁽⁸⁾. Angiogenesis (or neovascularization) refers to the development of new vessels from a preexisting vascular bed. During embryonic development and the menstrual cycle, angiogenesis is a physiological process. In the adult, the vascular endothelium is remarkably quiescent, with a turnover time of several years. The retinal vascular endothelium is even more quiescent as its turnover time is 25 years⁽⁹⁾.

Angiogenesis is the major feature in the pathogenesis of proliferative diabetic retinopathy (PDR), in which the retinal neovascularization has a catastrophic effect on vision by causing vitreous haemorrhage, retinal detachment with formation of a fibrovascular membrane and eventual blindness⁽¹⁰⁾.

Oxidative tissue and organ damage may play roles in diabetes and its complications (11). Specifically, in diabetic retinopathy, both the genesis and the advanced stage of proliferative diabetic retinopathy (PDR) have been hypothesized to be a result of increased oxidative species or to be associated with ischemia –

reperfusion injury at the boundaries of perfused and non perfused retina, which leads to both increased oxidative species and neovascularization⁽¹²⁾. Diabetes results in increased oxidative stress, and elevated oxidative stress plays an important role in the pathogenesis of diabetic complications⁽¹¹⁾. Increased oxidative stress in diabetes is postulated to promote the development of neuropathy⁽¹⁴⁾, nephropathy⁽¹⁵⁾, myocardial injury⁽¹⁶⁾, and retinopathy⁽¹⁷⁾.

The aim To evaluate the levels of AGEs, sRAGE, VEGF and total antioxidants in both vitreous and blood of diabetic patients with and without diabetic retinopathy. The motivation behind this study was to determine their possible role in pathophysiology of diabetic retinopathy which may be needed for prophylactic and therapeutic purposes.

PATIENTS & METHODS

This study included 30 persons (14 men & 16 women) with ages ranged from 51-57 years. It was carried in both Ophthalmology and Physiology Departments, Faculty of medicine, Assiut University from January 2007 until October 2008. The protocol was approved by the Faculty of Medicine, Assiut University Human Study Ethics Committee, and informed consent was obtained from each patient before the collection of samples. Diabetic patients were classified into 2 groups:

1-PDR group: included 15 diabetic patients (6 type I & 9 type II) with proliferative diabetic retinopathy.

2-Diabetic group: included 15 diabetic patients (7 type I & 8 type II) without diabetic retinopathy with other vitreo retinal conditions as macular hole (n = 10) and epiretinal membrane (n=5).

Control group: included 15 non diabetic patients with other conditions requiring vitrectomy, as macular hole (n=9) and epiretinal membrane (n=6).

Full ophthalmological examination and medical history was taken for each subject including:

1. Intraocular pressure measurement by applanation tonometry.
2. Slit lamp examination to determine anterior chamber depth and presence of iris neovascularization. Indirect ophthalmoscopy and biomicroscopy to evaluate the grade of vitreous proliferation and determine the presence or absence of macular oedema.

Exclusion criteria: Any patient with local eye disease such as, cataract, glaucoma or uveitis was excluded from the study. Also any patient with serum creatinine > 1.2 mg/dl or urinary albumin excretion > 150 mg/24hrs was not included in this study.

Vitreous collection: Vitreous samples (1– 2ml) were obtained at the onset of vitrectomy by aspiration into a syringe attached to the vitreous cutter before starting intravitreal infusion of a balanced salt solution. The vitreous samples were transferred to a tube, placed immediately on ice, and were frozen at – 70⁰ C until assayed.

Plasma and Serum collection:

Blood samples (4ml) were collected simultaneously with the vitrectomy from healthy controls and patients, the samples were taken from

an anticubital vein and were transferred to chilled sterile disposable tubes. 1ml was heparinized and separated as plasma and the rest was separated as serum after centrifugation at 3,000 *r.p.m.* for 20 min. Plasma and serum were stored immediately at -70°C until assay.

Laboratory assays:

Assay kits for estimation by Enzyme-linked immunosorbent assays (ELISA) with monoclonal antibodies against each substance were used following the instructions supplied with each kit for measuring of:

VEGF: Levels of VEGF (pg/ml) in both vitreous and plasma samples were measured using kits supplied from (Koma Biotech Inc, Seoul, Korea) **AGE:** AGE was measured with a kit supplied from (Sigma, St Louis, MO, USA). **sRAGE:** Serum sRAGE levels were determined using kits of (R&D systems, Minneapolis, MN, USA). **Total antioxidant levels:** Total antioxidant levels were also analyzed with a available ELISA kit (Calbiochem, La Jolla, CA, USA).

Statistical Analysis:

All values were expressed as mean \pm SE for all parameters. These data were analysed by using GraphPad Prism data analysis program (GraphPad Software, Inc., San Diego, CA, USA). Examination of significance was performed with Student Newman-Kleus t-test for unpaired data. For multiple comparisons, one-way analysis of variance (ONE- WAY- ANOVA) test followed with at least significant difference was used. Correlations were assessed using Spearman's non-parametric correlation coefficient p

(11) .Levels of significance (P) was considered as follow: (1) $P > 0.05$, not significant; (2) $P \leq 0.05$, significant (3) $P \leq 0.001$, highly significant (18).

RESULTS

The clinical characteristics of the controls, diabetic and PDR are shown in Table 1. The serum blood sugar levels for diabetic patients were significantly higher than those of control subjects ($p < 0.001$) and in PDR group than in diabetic group ($p < 0.001$).

The plasma levels of VEGF, serum levels of AGEs and sRAGE were significantly higher in all diabetic patients than control subjects ($p > 0.001$, respectively). Also plasma levels of VEGF, serum levels of AGEs and sRAGE in PDR group were significantly elevated compared with diabetic group ($p > 0.001$, respectively). On the other hand, the serum levels of TAO were significantly decreased in all diabetic groups compared to controls ($P < 0.0001$). Also serum levels of TAO in PDR patients were significantly decreased compared to diabetic group ($p > 0.001$). Data are presented in Table (2).

The vitreous levels of both AGE and VEGF were significantly higher in all diabetic patients than in control subjects ($p > 0.001$, respectively). Also these levels were significantly increased in PDR group than diabetic group ($p > 0.001$, respectively).

Total antioxidant levels in the vitreous was decreased in diabetic patients compared with control subjects ($p < 0.001$). Vitreous levels of TAO were decreased in PDR group

than diabetic groups ($p < 0.001$), Data are shown in Table (3).

Figure 1A shows that there were positive correlations between serum levels of AGE and both plasma levels of VEGF and serum levels of sRAGE in all diabetic patients including diabetic and PDR groups ($r = 0.84$, $r = 0.42$, respectively, $p < 0.001$). Positive correlations between plasma levels of VEGF and serum levels of sRAGE in all diabetic patients were found ($r = 0.98$, $p < 0.001$).

Inverse correlations between serum levels of TAO and blood levels of AGE, VEGF and sRAGE in all diabetic patients are presented in Figure 1C ($r = -0.93$, $r = -0.88$, $r = -0.84$, $p < 0.001$, respectively).

There was a significant correlation between the vitreous levels

of AGE and VEGF in all diabetic patients of both diabetic and PDR groups ($r = 0.98$, $p < 0.001$) Table (4).

Furthermore, as shown in table (4) total antioxidant levels in vitreous in both groups were inversely correlated with the vitreous AGE and VEGF levels ($r = -0.92$, $r = -0.87$ respectively, $p < 0.001$).

There were no significant correlations between blood levels of AGE, VEGF, sRAGE and TAO with vitreous levels of studied parameters.

There were no significant correlations between blood and vitreous levels of any of studied parameters with serum levels of glucose in all studied groups.

Table (1): Characteristics of controls, diabetic and PDR groups included in this study

Parameter	Control	Diabetic	PDR
Number	15	15	15
Male/female	5/10	8/7	6/9
Age (years) (mean \pm SE)	51 \pm 6.6	54 \pm 7.7	55 \pm 7.5
Duration of Diabetes (mean \pm SE)	--	11.88 \pm 2.1	11.21 \pm 1.88
Serum glucose (mg/dl) (Type I / type II)	90.7 \pm 0.5	183.4 \pm 1.3 ^a (7/8)	229.5 \pm 0.6 ^{a,b} (6/9)

a: P < 0.001 as compared to the control group

b: P < 0.001 as compared to the diabetic group

Table (2): Blood levels of different parameters in all studied groups

	Control	Diabetic	PDR
VEGF (pg/ml)	20.20± 0.24	28.51± 0.49 ^a	52.75± 1.23 ^{a,b}
AGE (unit /ml)	4.095± 0.10	4.583±0.081 ^a	4.922±0.078 ^{a,b}
sRAGE (pg/ml)	134.9 ± 0.65	245.5 ±1.15 ^a	284.9 ±0.90 ^{a,b}
TAO (mmol/ml)	6.45±0.041	2.63±0.069 ^a	1.94±0.096 ^{a,b}

Data are expressed as mean ± SE, VEGF=vascular endothelial growth factor, AGE=advanced glycation end product, sRAGE=soluble form of receptor for advanced glycation end products, TAO= total antioxidants.

a : P < 0.001 as compared to the control group

b : P < 0.001 as compared to the diabetic group

Table (3): Vitreous levels of different parameters in all studied group

	Control	Diabetic	PDR
VEGF (pg/ml)	37.33± 1.919	82.47±5.788 ^a	1928 ± 148.8 ^{a,b}
AGE(unit/ml)	0.046± 0.001	0.134± 0.001 ^a	0.167±0.002 ^{a,b}
TAO (mmol/ml)	1.816± 0.014	1.399±0.018 ^a	1.032±0.053 ^{a,b}

Data are expressed as mean ± SE, VEGF=vascular endothelial growth factor, AGE=advanced glycation end product, TAO= total antioxidants, a: P<0.001 as compared to the control group, b: P<0.001 as compared to the diabetic group.

Table (4): Multiple correlations analysis between vitreous levels of different studied parameters in diabetic and PDR groups

Parameters	VEGF		TAO	
	Coefficient (r)	P	Coefficient (r)	P
AGE	0.98	<0.0001 ^{***}	-0.92	<0.001 ^{***}
TAO	-0.87	<0.0001 ^{***}	-	-

VEGF=vascular endothelial growth factor, AGE=advanced glycation end product, AO= total antioxidants

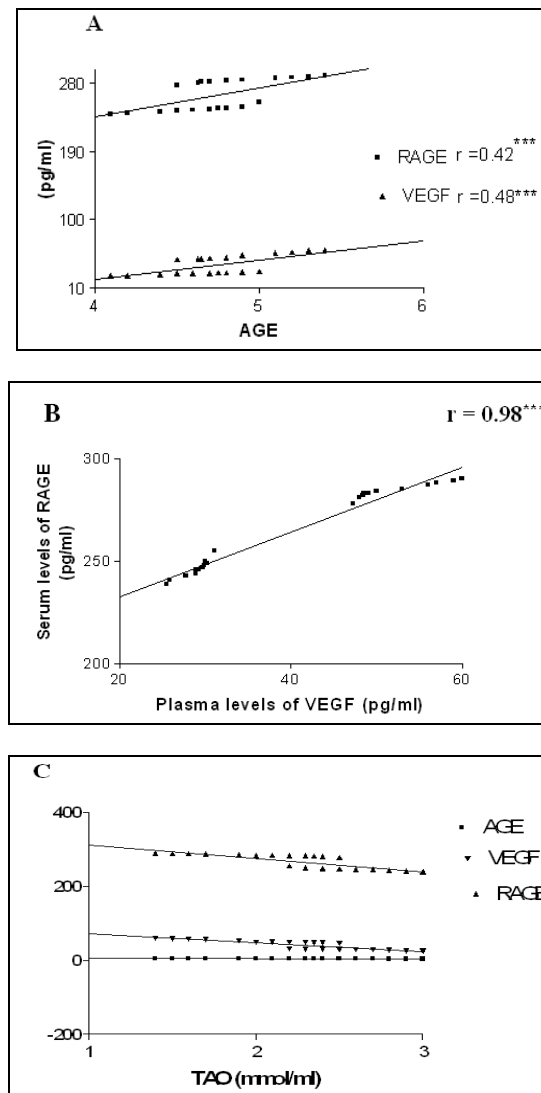


Figure (1): Multiple correlations analysis between blood levels of different studied parameters in all diabetic patients (diabetic and PDR) (A) Positive correlations between serum levels of AGE and blood levels of VEGF and sRAGE. (B) Positive correlations between plasma levels of VEGF and serum levels of sRAGE (C) Inverse correlations between serum levels of TAO and blood levels of AGE, VEGF and sRAGE, VEGF=vascular endothelial growth factor, AGE=advanced glycation end product, TAO= total antioxidants, sRAGE=soluble form of receptor for advanced glycation end products. ***= P<0.001

DISCUSSION

This study showed that the plasma VEGF and serum AGE levels in PDR group were significantly higher than those of diabetic and control groups, there was a positive significant correlation between VEGF and AGE in both PDR and diabetic group. This was explained by that chronic hyperglycemia favors glycation reactions and non enzymatic glycation. Reducing sugars can react non-enzymatically with amino groups of protein. These early glycation products undergo further complex reaction such as rearrangement, dehydration, and condensation to become irreversibly cross-linked, heterogeneous derivatives, which is AGEs. This leads to accumulation of AGEs in diabetes⁽¹⁹⁾ which can stimulate the expression of VEGF leading to increase its levels. This increase is also additive with hypoxia, another well-characterized stimulus for VEGF expression in diabetic retinopathy⁽²⁰⁾.

Also sRAGE serum levels were significantly higher in PDR group than diabetic and control groups and were positively correlated with circulating AGE levels and VEGF in both diabetic and PDR group. This may be explained by that AGEs are positive regulators of cell expression of RAGE, and serum sRAGE levels are in humans. AGEs can stimulate RAGE through activation of nuclear factor- κ B in human vascular endothelial cells⁽²¹⁾. Hence, in states of increased AGEs, RAGE expression is increased⁽²²⁾. The ability of AGEs to modulate RAGE expression is likely

to contribute to the pathological state of chronic activation of full-length RAGE in diabetes. Hence, increased AGEs in the diabetic patients causes increased cell surface RAGE and through that leads to higher levels of sRAGE generated directly from this species. Circulating endogenous sRAGE which reflects tissue RAGE expression may increase as a counter-system against endothelial cells injury in diabetic patients⁽²³⁾.

In the present study it was demonstrated that vitreous levels of both AGE and VEGF were significantly higher in PDR group than diabetic patients and control subjects, and their levels were elevated in association with the severity of neovascularisation in diabetic retinopathy. It was also found that vitreous levels of AGE and VEGF were positively correlated with each other. This is due to that AGE induces VEGF expression in retinal cell culture and animals⁽²⁴⁾. Moreover, local accumulation of AGE could increase vascular permeability in diabetic macula via VEGF, thus being involved in the pathogenesis of PDR, in which vascular permeability is increased⁽²⁵⁾. AGE induces blood-retinal barrier dysfunction by stimulating retinal VEGF expression in rats⁽²⁾, which supports this speculation.

It was found that total antioxidant status was decreased in the serum and vitreous of PDR group than diabetic and control groups, and that serum and vitreous levels of AGE and VEGF were inversely correlated with the total antioxidant status in PDR and diabetic groups. These were explained

by that formation and action of AGE not only induces oxidative stress by generating of reactive oxygen species via the AGE pathway leading to the activation of nuclear transcriptional factor, NF- κ B, and causing further damage to the cells⁽¹⁸⁾, but also inactivate a superoxide scavenging enzyme, Cu-Zn superoxide dismutase, both of which could lead to impairment of antioxidant defense systems. AGE may also contribute to the decreased total antioxidant status in diabetic retinopathy⁽²⁶⁾.

Oxidative stress also has an effect in diabetic retinopathy: it regulates vascular inflammation, gene expression of growth factors and cytokines, such as VEGF⁽²⁶⁾. Therefore, it is conceivable that the decreased antioxidant levels could further potentiate the deleterious effects of AGE on diabetic retinopathy through the overproduction of VEGF. Moreover, the formation, accumulation, and action of AGE are enhanced under oxidative stress conditions⁽²⁴⁾.

These observations suggest that AGE and oxidative stress generation form a positive feedback loop, thus has an important role in the development and progression of diabetic retinopathy⁽²⁶⁾.

Total antioxidants status in the serum of PDR and diabetic group was inversely correlated to serum levels of sRAGE. It is conceivable that the decreased antioxidant levels could enhance the deleterious effects of AGE on diabetic retinopathy through the overproduction of sRAGE.

Conclusion:

This study suggests that AGE and oxidative stress generation play an

important role in development and progression of proliferative diabetic retinopathy via induction of VEGF. So inhibition of AGE formation or oxidative stress generation could be a potential target for therapeutic intervention of diabetic retinopathy. Also down-regulation of RAGE expression or blockade of the RAGE downstream signaling may be a promising target for therapeutic intervention in diabetic vascular complication.

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دور النواتج النهائية للسكر و عامل النمو للطبقة المبطنة الوعائية فى اعتلال شبكية العين المصاحب لمرض البول السكرى

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يعد مرض اعتلال شبكية العين المصاحب لمرض البول السكرى من الأمراض الخطيرة التى تؤدى إلى فقد البصر.

ويهدف البحث إلى دراسة مستويات النواتج النهائية للسكر ومستقبلاتها و عامل النمو للطبقة المبطنة للأوعية و مضادات الأكسدة الكلية فى السائل الزجاجى و الدم لمرضى البول السكرى المصاحب باعتلال شبكية العين والغير المصاحب و دراسة

دورهم كمسببات لمرض اعتلال شبكية العين المصاحب لمرض البول السكرى .

ولقد تم أخذ عينة من السائل الزجاجى و عينة دم من 30 مريضاً البول السكرى ، 15 مصابين باعتلال شبكية العين المصاحب لمرض البول السكرى المتشعب و 15 غير مصابين كما تم أخذ عينات من المجموعة الضابطة و شملت 15 شخص ليس لديهم مرض البول السكرى . وباستخدام طريقة إمتصاص الإنزيم (الإليزا) تم قياس مستويات النواتج النهائية للسكر ومستقبلاتها و عامل النمو للطبقة المبطنة للأوعية و مضادات الأكسدة الكلية فى جميع العينات .

ولقد أوضحت نتائج هذه الدراسة إن مستويات النواتج النهائية للسكر ومستقبلاتها و عامل النمو للطبقة المبطنة للأوعية فى دم مرضى البول السكرى عالية و ذو دلالة إحصائية عن مستوياتها فى دم المجموعة الضابطة . و أعلى فى مجموعة اعتلال شبكية العين المصاحب لمرض البول السكرى المتشعب عن مستوياتها فى دم مجموعة البول السكرى . وكان هناك علاقات ذات دلالات إحصائية موجبة بين هذه المستويات فى مجموعتى اعتلال شبكية العين المصاحب لمرض البول السكرى المتشعب و مجموعة البول السكرى .

ولقد أوضحت نتائج هذه الدراسة إن مستويات النواتج النهائية للسكر و عامل النمو للطبقة المبطنة للأوعية فى السائل الزجاجى لمرضى البول السكرى عالية و ذو دلالة إحصائية عن مثيلاتها فى المجموعة الضابطة . و أعلى فى مجموعة اعتلال شبكية العين المصاحب لمرض البول السكرى المتشعب عن مستوياتها فى مجموعة البول السكرى . وكان هناك علاقة ذات دلالة إحصائية موجبة بين هذه المستويات فى مجموعتى اعتلال شبكية العين المصاحب لمرض البول السكرى المتشعب و مجموعة البول السكرى .

كما أوضحت أن مستويات مضادات الأكسدة الكلية فى السائل الزجاجى و الدم لمرضى البول السكرى منخفضة و ذو دلالة إحصائية عن مثيلاتها فى المجموعة الضابطة . و أقل فى مجموعة اعتلال شبكية العين المصاحب لمرض البول السكرى المتشعب عن مستوياتها فى مجموعة البول السكرى . كما أن هناك علاقات ذات دلالات إحصائية سالبة بين هذه مستويات مضادات الأكسدة الكلية و مستويات النواتج النهائية للسكر و مستقبلاتها و عامل النمو للطبقة المبطنة للأوعية فى دم مجموعتى اعتلال شبكية العين المصاحب لمرض البول السكرى المتشعب و مجموعة البول السكرى . و هناك علاقات ذات دلالات إحصائية سالبة بين مستويات مضادات الأكسدة الكلية و مستويات النواتج النهائية للسكر و عامل النمو للطبقة المبطنة للأوعية فى السائل الزجاجى لمجموعتى اعتلال شبكية العين المصاحب لمرض البول السكرى المتشعب و مجموعة البول السكرى . ونستنتج من هذه الدراسة أن مستويات النواتج النهائية للسكر ومستقبلاتها و عامل النمو للطبقة المبطنة للأوعية و التوتّر الناتج عن الأكسدة لهم دور كمسببين لمرض اعتلال شبكية العين المتشعب المصاحب لمرض البول السكرى .