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Research Article

Advanced End Glycation Products, Advanced Oxidation Protein Products and Ferritin Reducing Ability of Plasma as Markers of Diabetic Retinopathy

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Abstract

Background: Advanced Glycation End-products (AGEs) and Advanced Oxidation Protein Products (AOPP) are able to trigger inflammation, oxidative stress and neovascularization in diabetic retinopathy. The aim of this research was to study AGEs, AOPP and Ferric Reducing Ability of Plasma (FRAP) in different stages of diabetic retinopathy.

Methods: A total of 88 patients with T2DM, 29 with Proliferative Diabetic Retinopathy (PDR), 30 with Non-Proliferative Diabetic Retinopathy (NPDR), 29 without Retinopathy (NDR) and 43 healthy control groups were enrolled in this study.

Results: AGEs and AOPP levels were significantly higher in patients with retinopathy, PDR (87.08±14.80%, 156.75±30.36µmol/L respectively) and NPDR (88.55±9.41%, 161.84±20.29µmol/L respectively), compared to patients without retinopathy (57.90±16.3%, 122.39±34.97µmol/L respectively) and control group (44.62±7.08 %, 135.17±13.94µmol/L respectively) *(p<0.001)* but the difference was not significant between the PDR and NPDR group. FRAP level was significantly lower in PDR (768.68±297.93µmol/L) and NPDR (756.68±266.40µmol/L) group compared to NDR (1317.14±357.8µmol/L) and control group (1000.09±213.94µmol/L) *(p=0.001)*. FRAP level in control group was lower than NDR group. There was a strongly significant negative correlation between AGEs and FRAP levels in NDR (P=0.001, r=-0.7), NPDR (P=0.001, r=-0.6), PDR group (P=0.004, r=-0.5) and control group (p=0.001, r=-0.8), but there was no correlation between AOPP and FRAP. The Area Under the Curve (AUC) of AGEs, AOPP and FRAP for predicting NPDR and PDR were0.6, 0.6 and 0.3 respectively (p=0.01).

Conclusion: Increased levels of AGES and AOPP and decreased levels of FRAP had predictive value in early stages of diabetic retinopathy, suggests that these serum markers can be used to detect and monitor early stages of retinopathy in diabetic patients.

Keywords: Oxidative stress; Advancedglycation end-products; Advanced oxidation protein products; Ferric reducing ability of plasma; Diabetic retinopathy

Abbreviations

AGEs: Advanced Glycation End-products; AOPP: Advanced Oxidation Protein Products; FRAP: Ferric Reducing Ability of Plasma; T2DM: Type 2 Diabetes Mellitus; NDR: No Diabetic Retinopathy; NPDR: Non Proliferative Diabetic Retinopathy; PDR: Proliferative Diabetic Retinopathy; PBS: Phosphate Buffered Saline; RAGEs: Receptor of AGEs; ROS: Reactive Oxygen Species; NIDDM: Non Insulin Dependent Diabetes Mellitus; FBS: Fasting Blood Sugar; BMI: Body Mass Index; SBP: Systolic Blood Pressure; TG: Triglyceride; LDL-C: Low Density Lipoprotein; HDL-C: High Density Lipoprotein; Cr: Creatinine; HbA1c: Hemoglobin A1C

Introduction

By increasing the prevalence of diabetes, diabetic retinopathy will become epidemic. Nearly all patients with Type 1 diabetes and > 60% of patients with type 2 diabetes expected to progress to retinopathy by the first decade of disease [1]. Diabetic retinopathy is a common and specific micro vascular complication of diabetes and one of the leading causes of visual impairment and preventable blindness among persons of working age in the developed world [2-5]. Blindness is approximately 25 times more common in persons with diabetes than in those without the disease [6,7]. The pathogenesis of diabetic retinopathy is multifactorial, and a range of hyperglycemia-linked pathways have been implicated in the initiation and progression of this condition [8].

Oxidative stress is a state in which the balance between oxidants and antioxidants is shifted in the favor of the former. During oxidation, Reactive Oxygen Species (ROS) are produced [9]. ROS are normally scavenged by endogenous anti-oxidative systems. However, if antioxidant defenses are insufficient, then damage of

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Table 1: Baseline characteristics of patients with type 2 diabetes, without retinopathy (NDR), Non Proliferative Retinopathy (NPDR) and Proliferative Retinopathy (PDR).

	Healthy Control	NDR	NPDR	PDR	P-value
	n=43	n=29	n=30	n=29	
Gender(female/male)	23/20	19/10	21/9	16/13	NS
Age (yrs)	52.73±1.72	57.89±8.9	59.96±7.4	58.34±9.2	NS
BMI (kg/m2)	26.8±0.5	27.95±3.3	25.80±2.3#	25.36±3.5#	0.005
Duration of DM(years)	–	7.07±1.01*	9.2±1.2	12.48±4.9	<0.01
SBP(mm Hg)	125.22±1.55	121.37±17.6	134.16±18.00#	142.24±26.44#	0.001
Creatinin(mg/dl)	0.93±0.024	0.1±0.84	0.1±0.90	0.1±0.91	NS
FBS(mg/dl)	85.92±1.26	172.65±53.42*	210.30±68.58#*	212.17±53.87#*	0.019
HbA1C(%)	4.88±0.06	8.3±1.8*	8.02±1.38*	9.1±2.08*∞	0.05
Triglycerides(mg/dl)	135.00±9.85	198.7±103.1*	165.46±84.45*	202.93±93.10*	NS
Cholestrol(mg/dl)	183.14±5	205.6±54.56	206.13±53.00	210.10±45.59	NS
LDL-C(mg/dl)	92.78±2.73	116.0±35.88*	132.53±35.95*	127.82±31.12*	NS
HDL-C(mg/dl)	43.24±2.22	42.6±7.0	41.73±11.69	43.10±8.60	NS
AGES (%)	44.62±7.08	57.90±16.3	88.55±9.41#	87.08±14.80#	0.001
AOPP(µmol/L)	135.17±13.94	122.39±34.97	161.84±20.29#	156.75±30.36#	0.001
FRAP (µmol/L)	1000.09±213.94Ø	1317.14±357.8	756.75±266.40#	768.68±297.93#	0.001

Normally distributed variables are expressed as mean±standard deviation. NDR: No Diabetic Retinopathy; NPDR: Non-Prolifrative Diabetic Retinopathy; PDR: Prolifrative Diabetic Retinopathy; BMI: Body Mass Index; SBP: Systolic Blood Pressure; FBS: Fasting Blood Sugar; HbA1C: Hemoglubin A1C; LDL-C: Low-Density Lipoprotein Cholestrol; HDL-C: High –Density Lipoprotein; CRP: C-Reactive Protein; AGES: Advanced Glycation End Products; AOPP: Advanced Oxidation Protein Products; FRAP: Ferric Reducing Abillity of Plasma; NS: Non Significant

ØSignificant difference between Control versus NDR.

*Significant difference between NDR-NPDR-PDR versus Control.

#Significant difference between NPDR-PDR versus NDR.

∞Significant difference between PDR versus NPDR.

protein, lipids, and DNA can occur [10]. In DM, free radical load is disproportionately high and markers for oxidative stress are markedly increased [11]. Research has shown that DM results in marked biochemical perturbations and the production of ROS in the retina [12]. In animal models of DM reduced levels of retinal antioxidants have been observed [13]. The retina is particularly susceptible to oxidative stress of intracellular hyperglycemia because retinal vascular endothelial cells do not alter the rate of glucose transport across the plasma membrane in conditions of high glucose [14].

Oxidative stress is a state in which, apoptosis of retinal pericytes, endothelial and neural cells leads to capillary closure and retinal ischemia [13-15].

In the diabetic state and chronic hyperglycemia we have an increased tendency for oxidative stress and accumulation of oxidized proteins or lipids and also biochemical process of advanced glycation [16,17]. The oxidative stress and oxidative markers such as AGES and AOPP have important role in these mechanisms [3,18-21]. Sustained hyperglycemia leads to a series of non-enzymatic reactions between reducing sugar or other carbohydrates with amino acids, lipids and nucleic acids. These irreversible formed products collectively called Advanced Glycation End products (AGEs) [22]. The cross-link of AGEs with lipid and protein molecules can disrupt their functional structure. Moreover, binding to their receptors (RAGES) diminished the intracellular antioxidant capacity and activate a cascade of cytokines, growth factors and pro-inflammatory compounds which promote oxidative stress, inflammation and tissue damage [23]. Because of the central role of AGES in oxidative stress, they have repeatedly been linked to diabetes related complications including retinopathy [16,20,24]. AOPP defined as dityrosine containing cross-linked protein products that formed during oxidative stress and are considered to be a reliable marker of protein oxidation. Diabetic patients have lower antioxidant capacity than healthy individuals [25].

Ferric Reducing Ability of Plasma, FRAP assay is an index of antioxidant capacity that is decreased in diabetic patients [26]. FRAP assay is a novel method for assessing antioxidant power. FRAP include the total activity of antioxidant vitamins and enzymes which separately estimation of each component is difficult [27].

Pathophysiology of diabetic retinopathy is not fully understood and the role of oxidative markers, AGEs and AOPP and antioxidant marker FRAP in progression of retinopathy in diabetic patients and their correlations are not clearly studied in researches. In current study we evaluated the level of AGES, AOPP and FRAP in T2DM patients without retinopathy, non-proliferative and proliferative retinopathy, and also studied their correlation with severity of condition as well as utility for prediction of diabetic retinopathy.

Materials and Methods

We performed a cross sectional study in a group of 88 patients with type 2 diabetes, 29 patients with Proliferative Diabetic Retinopathy (PDR), 30 with Non-Proliferative Diabetic Retinopathy (NPDR), 29 patients without Retinopathy (NDR) and 43 healthy control group.

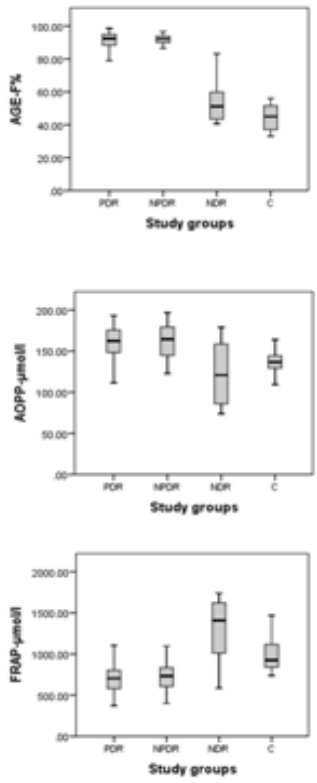

Figure 1: Box plot of AGEs, AOPP and FRAPP in studied groups. Distribution of AGEs, AOPP and FRAP in diabetic patients and control group. C: Control; NDR: No Diabetic Retinopathy; NPDR: Non-Proliferative Diabetic Retinopathy: PDR: Prolifrative Diabetic Retinopathy.

T2DM was diagnosed according to American Diabetic Association criteria (2014). Diabetic retinopathy was diagnosed by an expert ophthalmologist based on chart review results and ophthalmologic fundoscopic examination. Patients with diabetic foot, chronic inflammatory disease, acute or chronic infectious disease, neoplasm, renal failure (creatinine >2 mg/dl or GFR<30 ml/min) were excluded. None of patients were taken glucocorticoid and thiazolodindiones and Immunosuppressive or cytotoxic drugs.

Demographic and anthropometric data are illustrated in Table 1. Body mass index was calculated by the formula: weight/height in kilogram per square meter, blood pressure was measured in sitting position after 5 minutes rest and repeated twice after 10 minutes and averaged.

Blood samples were drawn after 12 hours of overnight fasting in the hospital laboratory, and plasma glucose, creatinine, total cholesterol, triglycerids, HDL-C, LDL-C, HbA1c, AGEs, AOPP and FRAP were measured. Glucose measurements were performed by glucose oxidase method, (intra-assay coefficient of variantion: 2.1%, inter-assay CV: 2.6%). Cholesterol, HDL-C and LDL-C were determined using enzymatic methods.HbA1c was measured by high-pressure liquid chromatography method. AOPP concentrations was measured using spectrophotometric methods (FLUO star OPTIMA, BMG, Germany) as described by Kalousova et al. at 2002 [3]. In this method, 200 mL of serum is diluted by a factor of 5, in Phosphate Buffered Saline (PBS). In addition, 200 mL of chloramines T (0 -100 µmol/l) for calibration, and 200 µg of PBS as blank is also added to different micro plates finally 10µg of acetic acid, and 20µL of 1.16 M potassium Iodide is added to preparations. Measurements are done at absorbance of 340nm and are expressed in chloramine units (µmol/L). FRAP was assessed by spectrophotometry as described Benzie and Strain (1996) [28]. Based on this method, FRAP reagent was prepared with mixing 300 mmol/L of acetate buffer (PH: 3.6), 10mmol/l of tripyridyltriazine in 40 mmol/l HCL, and 20 mmol/l Fecl3.6H2O. Twenty five µl of serum is then added to 750µl FRAP reagent and absorbance is recorded at 593 nm. Readings were expressed in µmol/l. AGEs were measured by the spectrophotometric method of Kalousova et al. (2002) [3]. Blood serum was diluted 1:50 with PBS pH 7.4 and fluorescence intensity was recorded at the emission maximum (~440nm) upon excitation at 350. It was expressed as percentage of fluorescent emission.

Statistical package for social science (SPSS for windows, version 19; Chicago, IL) program was used for analyzing of data. Data was presented as Mean ± Standard Deviation of Mean (SDM) or number (percent). For variable with non-Gaussian distributions, log-transformed values were used in analysis. One way analysis of variance (ANOVA) and chi-squared test were used for group comparisons, as appropriate. Receiver Operating Characteristics (ROC) curve analysis was used for sensitivity and specify analysis. Linear regression was recruited for data modeling. Two sided P-values <0.05 were considered statistically significant.

This study complied with the principles of the Declaration of Helsinki. Local ethics committee approved the study protocol. Written informed consent obtained from all patients.

Results

Baseline demographic and biochemical characteristics of the case and control groups is shown in Table 1. No significant difference was observed regarding age, gender, total cholesterol, HDL-C, LDL-C, Cr and TG between diabetic groups.

Systolic blood pressure in NPDR was 134.16±18.00 mmHg, and in PDR group was 142.24±26.44 mmHg which were significantly higher compared to NDR group 121.37±17.6 mmHg (P=0.02 and P=0.001,respectively) and control healthy group (p=0.03 and p=0.005). Patients in NDR group had higher BMI compared to PDR and NPDR group (27.95±3.3 kg/m^2 versus 25.36±3.5kg/m^2, p=0.002 and p=0.011 respectively). Duration of diabetes in PDR group (12.48±4.9 years) and in NPDR group (9.2±1.2 years), were longer compared to NDR group (7.07±1.01 years, p<0.01). The patients in PDR and NPDR group had higher FBS (212.17±53.78 mg/dl, p=0.013 and 210.30±68.58 mg/dl, p=0.017 respectively) compared to NDR group (172.65±53.42 mg/dl). HbA1C was significantly higher in PDR group (9.1±2.08%) compared to NPDR group (8.02±1.38%) (p=0.021). AGEs in patients with PDR and NPDR were 87.08±14.80 % and 88.55±9.41% respectively which were significantly higher compared to NDR groups (57.905±16.35%, p=0.001) and control group (44.627±7.08%,p=0.001). In PDR group AOPP level was 156.75±30.36µmol/Land in NPDR group was 161.84±20.29 µmol/L which both of them were significantly higher compared to NDR group (122.39±34.97µmol/L, p=0.001) and control group (136.172±13.949µmol/L, p=0.001). Both AGEs and AOPP had

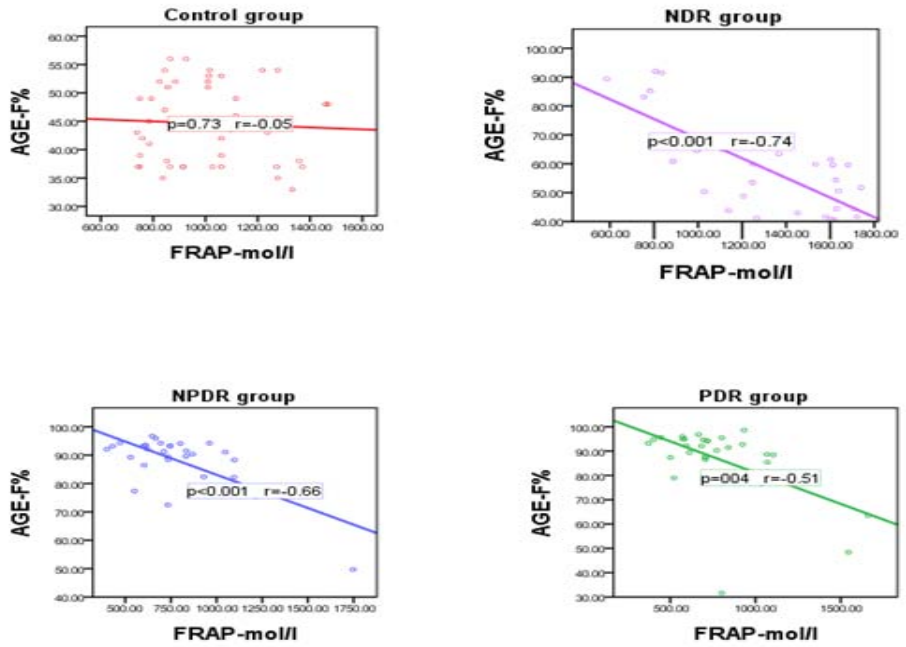

Figure 2: Scatter plots of AGE and FRAP in all study groups.

not significant difference between PDR and NPDR group. AOPP level was higher in control group compared to NDR group. Antioxidant marker FRAP level was significantly lower in PDR and NPDR group (768.68±297.93µmol/L and 756.75±266.40µmol/L respectively) compared to NDR group (1317±357.8µmol/L, p=0.001) and control group (1000.093±213.94µmol/L) but there was no significant difference between PDR and NPDR group. AGEs levels were significantly lower in control group compared to NDR group (p=0.001). FRAP level was significantly higher in NDR group compared to control group (p=0.001).

There was significant negative correlation between AGEs and FRAP in control (p=0.001, r=-0.8) NDR (P=0.001, r=-0.7), NPDR (P=0.001, r=-0.6) and PDR group (P=0.004, r=-0.5) but there was not any correlation between AOPP and FRAP.

The AUC of AGES, AOPP and FRAP were not significantly different between the non- proliferative and proliferative groups. The AUC of AGEs for predicting NPDR and PDR were 0.6(p=0.01) and 0.7(p=0.01) respectively. The sensitivity and specificity of AGEs after balancing was 96% and 83% respectively. The AUC of AOPP for predicting NPDR and PDR were 0.6(p=0.01) and 0.7(p=0.05) respectively. The sensitivity and specificity of AOPP after balancing was 82% and 68% respectively. The AUC of FRAP for predicting NPDR and PDR were 0.3(p=0.01) and 0.7(p=0.01) respectively. The sensitivity and specificity of FRAP after balancing were 85% and 15% respectively.

Discussion

In this study advanced glycation end products and advanced oxidation protein products were significantly higher in PDR and NPDR groups compared to NDR and control group. AGEs were increased in patients without retinopathy and remained significantly elevated in PDR and NPDR group. There was no significant difference between AGES and AOPP levels in the patients with established retinopathy (Figure 1). Yuri Ono et al determined serum AGEs levels in 125 patients with NIDDM in 1996 and they found serum AGEs were significantly higher in patients with retinopathy with creatinine 2-3.9 compared to patients without proliferative retinopathy. We did not find significant difference between AGEs levels in the PDR and NPDR group with normal creatinine [29]. Francesco Chiarelli et al. found elevated AGEs levels in diabetic children without micro-vascular complication and adolescents with retinopathy that means the risk of micro-vascular complications may be present from early age [30]. In accordance to our observations M. Kalousova et al. studied the AGES and AOPP levels in 52 patients with diabetes mellitus, 18 with Type 1 and 34 Type 2 DM and found the slight elevation of AGEs and AOPP in both types of diabetic patients in comparison to healthy subjects, but this finding finally was significant only in the patients with Type 2 diabetes mellitus. They didn't find any statistically significant difference in elevation of AGES and AOPP level between their patients with and without diabetic complications [3]. Pan HZ et al and G. Baskol et al. measured serum level of AOPP in diabetic patients with and without diabetic retinopathy and a healthy control group. AOPP was higher in diabetic group compared to healthy group and also it was higher in Diabetic Retinopathy group compared to NDR group [31].

In our study AOPP were not significantly different between control and NDR group but was significantly elevated in patients with retinopathy. This finding is in contrary to AGEs which were elevated in diabetic patients without retinopathy. This shows that AGEs reflect oxidative stress earlier. In our study FRAP values were significantly lower in PDR and NPDR group compared to NDR and control group while there were no significant difference between the PDR and NPDR group in FRAP levels. We found that FRAP levels were higher in NDR group compared to control group, this may reflect as a defense mechanism in a phase of diabetes without retinopathy.

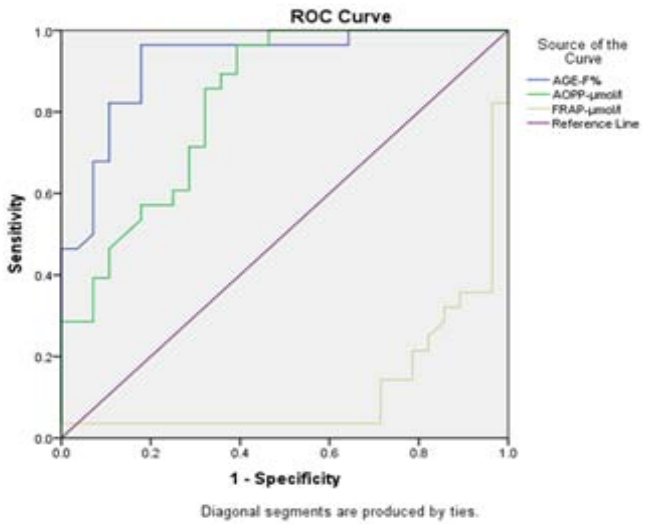

Figure 3: The ROC curve for AGEs, AOPP, FRAP in predicting proliferative and non proliferative diabetic retinopathy.

Pj Hisalkar and B. SaiRavikir et al. reported that FRAP levels in poorly controlled diabetic patients were significantly lower compared to healthy group [32,33]. Maura Lodovici et al. recruited 39 diabetic patients and 18 healthy subjects as control group and measured their plasma FRAP. They observed that FRAP level was significantly lower in diabetic subjects with poor glycemic control than healthy subjects. They found a negative correlation with glycemic level and HbA1c but patients with good glycemic control had FRAP values similar to controls [25]. In our study Levels of HbA1c were not different in patients with retinopathy versus patients without retinopathy so this finding of decreasing level of FRAP may not reflect the glycemic control.

As illustrated in Figure 2, there was no correlation between AGEs and FRAP in control group but we observed a significant negative correlation between AGEs and FRAP in patients without retinopathy. This correlation was attenuated in NPDR and PDR groups. We suggest with progression of complications, the correlation may change. In contrary to AGEs we did not observed any significant correlation between AOPP and FRAP.

Systolic blood pressure was significantly lower in NDR group compared to PDR and NPDR group although the association between AGES and AOPP and retinopathy remained significant after adjustment for BMI and SBP. This shows that AGES and AOPP are independent factors to predict diabetic retinopathy.

We compared the diagnostic accuracies of AGEs, AOPP and FRAP using ROC curve analysis and area under the curve. The predictive value of these markers to predict retinopathy was significantly high, which is the reflection of how good these markers are at distinguishing between patients with and without diabetic retinopathy (Figure 3).

Conclusion

Current study demonstrate that increased levels of AGES and AOPP and decreased levels of FRAP had predictive value in early stages of diabetic retinopathy. It suggests that AGES and AOPP and FRAP can be used as serum markers to detect and possibly control early stages of retinopathy in diabetic patients.

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