Diabetes & Metabolic Syndrome: Clinical Research & Reviews 13 (2019) 2361–2364

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Original Article

Serum Pentraxin 3 level as a recent biomarker of diabetic retinopathy in Egyptian patients with diabetes

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ARTICLE INFO

Article history:
Received 7 May 2019
Accepted 7 June 2019

Keywords:
Serum Pentraxin3
Biomarker and diabetic retinopathy

ABSTRACT

Introduction: Serum Pentraxin3 Level As A recent Biomarker Of Diabetic Retinopathy In Egyptian patients with diabetes.
Objective: To evaluate the association between elevated levels of plasma pentraxin 3 and the development and/or progression of diabetic retinopathy.
Subjects: and methods: This case control study was carried out in internal medicine department, outpatient clinic of internal medicine and outpatient clinic of ophthalmology, at Zagazig university Hospital, 2018. Serum PTX3 level, HsCRP, HbA1c, lipid profile, serum creatinine were determined in 20 normal subjects, 20 patients with prediabetes, 20 patients with diabetes without diabetic retinopathy (DR), 20 patients with non-proliferative diabetic retinopathy (NPDR) and 20 patients with proliferative diabetic retinopathy (PDR).
Results: Serum PTX3 level significantly increased in patients with DR more than patients without DR with cut off point 1150 pg/ml, sensitivity 93.3%and specificity 72%. Serum HsCRP level significantly increased in patients with DR more than patients without DR with cut off point of 7.60 pg/ml has sensitivity 93.3% and specificity 68%.. Combined use of PTX3 and HsCRP decreases sensitivity to 76.7%, but combined use increases specificity to 90%.Significant relation between poor glycemic control and development of DR and its severity as showed by HbA1c.
Conclusion: Serum PTX3 levels mayt have significant role in the development of DR and its severity. Serum HsCRP increased with DR progression. Poor glycemic control significantly associated with high incidence of diabetic retinopathy and its severity. Longer diabetes duration is associated with progression of DR.

1. Introduction

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both [1]. Long-term complications of diabetes include retinopathy with potential loss of vision; nephropathy; peripheral neuropathy, atherosclerotic cardiovascular, peripheral arterial and cerebrovascular disease [1].Diabetic retinopathy (DR) is one of the most prominent pathologic vascular complications of diabetes and is the most common cause of blindness in the working-age group [2]. Diabetic retinopathy can be classified into two categories: non-proliferative (NPDR) and proliferative (PDR) [3]. PDR occurs with severe retinal ischemia and is characterized by the growth of new blood vessels on the optic disc or elsewhere in the retina [3]. Diabetic macular edema (DME) can occur at any stage of DR and is regarded as the principal cause of vision loss in patients with diabetes [3].Common risk factors for the development of DR include duration of diabetes, poor glycemic control, elevated blood pressure, presence of diabetic nephropathy and dyslipidemia [4].Pentraxin 3 (PTX3) is an acute-phase reactant characterized by a cyclic multimeric structure. Pentraxin 3, in the form of a long pentraxin, is produced by peripheral tissues and reflects impaired vascular endothelial function [5].

Pentraxin 3 inhibits angiogenesis, promotes restenosis, and increases formation of advanced atherosclerotic lesions, typically by inhibiting the Fibroblast growth factor (FGF2) reaction of

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https://doi.org/10.1016/j.dsx.2019.06.007
1871-4021/

angiogenesis [6]. Recently, PTX3 has been shown to be a sensitive biomarker of localized inflammatory reactions and innate immunity in cardiovascular and renal diseases [7]. PTX3 levels were independently associated with endothelial dysfunction in an end-stage kidney disease population, and suggested the possibility of using PTX3 as a biomarker of peripheral vascular damage [8].

2. Subjects and methods

This case control study was conducted in internal medicine department, outpatient clinic of internal medicine and outpatient clinic of ophthalmology, at Zagazig University Hospital at 2018 and included 100 individuals divided into 5 groups as following:

Group A: contains 20 normal subjects as a control group.
Group B: contains 20 patients with prediabetes based on fasting and post prandial blood glucose level.
Group C: contains 20 patients with diabetes without diabetic changes of their retina.
Group D: contains 20 patients with non-proliferative diabetic retinopathy.
Group E: contains 20 patients with proliferative diabetic retinopathy.

We selected 60 diabetic patients, their disease duration more than 5 years and another 20 prediabetic patients for our study. Patients with history of (cardiac disease, stroke, malignancies, end stage renal disease, current or past history of immune-modulating drugs, IV drug users and severe eye disease or retinal detachement) have been excluded.

All patients were submitted to the following:

1 Full history taking. clinical examination including the following items:, Assessment of anthropometric measures (BMI and waist circumference), assessment of blood pressure.
2 Fundus examination.

All patients were informed about the study and consents were taken from all patients before taking the blood samples and fundus examination.

2.1. Ophthalmological examination

A complete ophthalmological examination was performed including fundus examination with slit lamp biomicroscope and indirect ophthalmoscopy, fundus colour photograph centered on the macula and fundus fluorescein angiography wherever indicated, subjects of the study were classified into group A (normal persons with normal fundus examination), group B (prediabetic persons with normal fundus examination), group C (patients with diabetes without diabetic changes of their retina), group D (patients with NPDR) and group E (patients with PDR).

2.2. Laboratory evaluation

1 HbA1C, Serum SGOT, SGPT, Blood urea and serum creatinine.-Serum lipid profile including serum triglycerides, high density lipoprotein, low density lipoprotein and total cholesterol level.
2 Serum pentraxin3.
3 hsCRP.

2.3. Statistical analysis

The SPSS software was used for all statistical analyses. Correlations between PTX3 and various parameters were analyzed using Pearson's correlations. Linear regression analysis was done for each independent parameter with PTX3. To evaluate the diagnostic performance of PTX3, receiver operating characteristic (ROC) curve was conducted. The P-value of <0.05 was considered significant.

3. Results

Patients with diabetic retinopathy (group D and E) have poor glycemic control more than those without retinopathy (group C), prediabetics (group B) and normal subjects (group A). This elevation in HbA1c is associated with elevation in the serum level of HsCRP and PTX3 in the same groups.

HbA1c, HsCRP and PTX3 have a significant predictive value in development of diabetic retinopathy.

Positive correlation and significance between PTX3 with HbA1c and total cholesterol.

Positive correlation and significance between PTX3 with creatinine and HsCRP, while it has significantly negative correlation with HDL.

HbA1c, Creatinine and HsCRP were independent predictors for increased PTX3.

No significant difference between studied groups as regard to gender, age, BMI, serum level of LDL, HDL and TG.

No significant difference between studied groups containing diabetic patients (group C,D&E), as regard the mean duration of diabetes, while there is increased incidence of diabetic retinopathy in patients with longer duration of diabetes in each group.

4. Discussion

Diabetic retinopathy represents a major cause of loss of vision in the working age in the developed countries. Thus, there is a need to implement effective strategies being able to prevent DR and to identify specific and early predictors. The etiology of DR is multifactorial, but reported risk factors include increased duration of diabetes mellitus, as well as severity of hypertension and hyperglycemia [9].

Hyperlipidemia is a powerful risk factor for atherosclerosis and related disorders such as ischemic heart disease, cerebrovascular diseases and retinal atherosclerosis [10].

Endothelial dysfunction is a well-known finding in hypercholesterolemic patients and it was proposed that hyperlipidemia might contribute to DR and macular edema by endothelial dysfunction and breakdown of the blood retinal barrier leading to exudation of serum lipids and lipoproteins [11].

Our study showed that no significant age difference between groups, Similar to hyun et al. study [12].

Our study showed that there was no sex effect on the development of diabetic retinopathy in diabetic patients. Similarly, in (hyun et al. [12]) and (zhou [13]) studies.

In our study, no role for smoking in the development of DR. likely in The Hoorn study demonstrated non-significant association between diabetic retinopathy incidences in cigarette smokers [14].

In our study, there is no BMI difference in retinopathy group than control group, prediabetes group and diabetes with normal fundus group, this agreed with hyun et al., study [12]. While in contrast to price et al. study which showed that obesity with a BMI of >30 kg/m^2 is a major risk factor for DR [15].

Our study showed that patients with DR had longer disease duration than those without DR inspite of no significant difference in the disease duration between various groups, similarly the incidence of DR is related primarily to duration and control of diabetes (Table 1) [16].

Table 1
P value of the different studied parameters.

	Group A	Group B	Group C	Group D	Group E	Total	P value
Gender (M/F)	8/12	11/9	8/12	10/10	12/8	49/51	0.634
Age(y)	54 ± 6.18	55 ± 2.6	58.3 ± 2	55.6 ± 3	56 ± 4.5	55 ± 4.87	**0.105**
BMI(Kg/m2)	31.8 ± 3	31.7 ± 3	32 ± 2.3	31 ± 4	30.5 ± 2.7	31.4 ± 3	0.546
Duration of DM (y)	–	–	14 ± 5	14.7 ± 5.6	15.5 ± 4.8	14.73 ± 5.13	**0.550**
HbA1c	5.1 ± 0.7	5.3 ± 0.7	8.2 ± 0.8	11.8 ± 1.2	12 ± 0.8	8.6 ± 3	**0.0001***
Creatinine(mg/dl)	0.5 ± 0.1	0.5 ± 0.1	0.8 ± 0.1	1.7 ± 0.1	1.7 ± 0.1	1.1 ± 0.6	**0.0001***
LDL(mg/dl)	140 ± 21	148 ± 20	148 ± 33	142 ± 35	160 ± 28.6	148 ± 28.6	0.235
TG (mg/d)l	209 ± 53	193 ± 45	265 ± 160	227 ± 68	233 ± 71	225 ± 91	0.134
HDL (mg/dl)	40 ± 6.6	41 ± 8	40 ± 7	37 ± 6	37 ± 5	39 ± 6.7	0.311
Total cholesterol(mg/dl)	127 ± 55	161 ± 50	172 ± 64	255 ± 43	248 ± 39	192 ± 71	**0.0001***
HsCRP(pg/ml)	4.27 ± 0.14	4.29 ± 0.18	9.53 ± 0.29	7.29 ± 4.2	10.1 ± 2.4	7.00 ± 0.97	**0.0001**
PTX3(pg/ml)	795 ± 27	788 ± 24	930 ± 16	1465 ± 179	1507 ± 145	1097 ± 339	**0.0001***

*significant $P < 0.05$.
BMI; body mass index, HbA1c; hemoglobin A1c, LDL; low density lipoprotein cholesterol, TG; triglyceride, HDL; high density lipoprotein cholesterol, HsCRP; high sensitivity CRP, PTX3; pentraxin3.

Similar to our study, according to reports published by Wisconsin epidemiologic study of diabetic retinopathy (WESDR), the general 10-year incidence of DR was 74%. However, the same study showed that 64% of people with baseline DR developed more severe DR and 17% of those advanced to proliferative DR [16].

Sjølie et al.(2008), showed that duration of DM and coexisting hypertension remain the most significant risk factors for PDR and DME. Moreover, control of hypertension significantly reduced the development and progression of DR and DME [17].

Another review reaches a quite different conclusion, reporting that the control of blood pressure has an impact on the prevention of DR only for patients with diabetes up to 4–5 years [18].

We have found a significant correlation between glycemic control (HbA1c) and development of DR in diseased groups more than control. A higher HbA1c is associated with both increased incidence as well as progression of diabetic retinopathy (Table 2) [19].

High blood glucose affects morphology and physiology of retinal vascular cells including endothelial cells, pericytes, and astrocytes leading to dysfunction of retinal vasculature [20].

In contrast to our study, Agroiya, et al. found that there was no association between HbA1c and DR [21].In our study, we have found non-significant correlation between DR with triglycerides and HDL, as in Tomić et al. study [22]. Zhou et al. study and the Multi–Ethnic Study of Atherosclerosis (MESA) that showed no association of serum lipids with diabetic retinopathy [10].

In our study, we have found significant correlation between DR and serum total cholesterol, similar to Yau et al. study that reported a higher prevalence of diabetic macular edema and diabetic retinopathy with elevated total serum cholesterol. Also, Gnaneswaran et al. observed significant differences between the levels of total cholesterol and LDL-C in diabetic patients with DR [10].

As regard PTX3, there's significant increase in its level with development and progression of DR. With cutoff point of 1150 pg/ml has sensitivity 93.3% and specificity 72%. PTX 3 is higher in retinopathy group more than control, prediabetes and diabetes with normal fundus group (Table 3). This agreed with hyun et al. and Zhou et al., PTX3 level increase with DR development and progression [12,13].As regard HsCRP, there's significant increase in its level with development and progression of DR. With cutoff point of 7.60 pg/ml has sensitivity 93.3% and specificity 68% higher in retinopathy group more than control, prediabetes and diabetes with normal fundus group (Fig. 1). Also, agreed with hyun et al. and Zhou et al. studies [12,13].Combined use of PTX3 and HsCRP decrease sensitivity to 76.7%, but combined use increase specificity to 90%.In our study, increased in serum PTX3 levels are associated with impaired renal function.. Unlike (Abu Seman et al. [23]) where there is a decreased plasma PTX3 levels in patients with type 2 DM and diabetic nephropathy more than patients with type 2 DM without nephropathy.

5. Conclusion

From our study, we concluded that: Serum PTX3 levels may have significant role in the development of DR and its severity. Serum HsCRP increased with DR progression. Poor glycemic control significantly associated with high incidence of diabetic retinopathy and its severity. Longer diabetes duration is associated with progression of DR.

We recommended that: Larger studies using more defined populations are required to better understand the relationship between PTX 3 concentrations and retinopathy in patients with diabetes mellitus..

Table 2
Correlation between PTX3 with various parameters.

	PTX3 (pg/ml)	
	r	P-value
Age (years)	0.114	0.257
Duration of DM (yr)	0.109	0.407
BMI (kg/m2)	0.085	0.398
Total cholesterol (mg/dl)	0.678	<0.001
LDL (mg/dl)	0.077	0.444
TG (mg/dl)	0.108	0.287
HDL (mg/dl)	0.199	0.047
Creatinine (mg/dl)	0.949	<0.001
HbA1c	0.931	<0.001
HsCRP (mg/L)	0.412	<0.001

Table 3
Logistic regression of significant factors in development of DR.

	B	Sig.	Exp(B)	95% C.I. for Exp(B)	
				Lower	Upper
HbA1c	0.269	0.021	1.269	0.010	3.005
HsCRP	0.737	0.048	1.739	0.396	4.007
PTX3	0.820	0.039	2.270	0.268	5.323

This table shows that HbA1c, HsCRP and PTX3 have a significant predictive value in development of diabetic retinopathy.

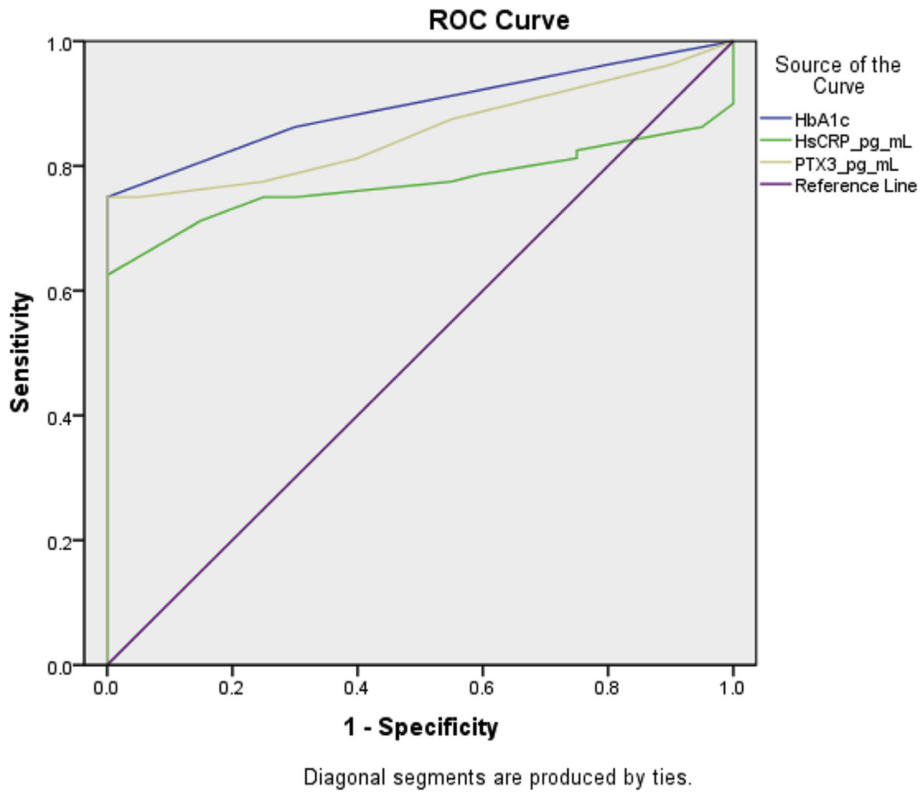

Fig. 1. ROC curve showing the sensitivity and specificity of PTX3, hsCRP and HbA1c.

Conflicts of interest

There is no conflict of interest.

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