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Impact of diabetes mellitus on ocular pseudo exfoliation syndrome and open angle glaucoma in Iraqi patients

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Abstract---Background: Diabetes mellitus cause wide spectrum of ophthalmic complications including cataract and glaucoma. Pseudo exfoliation (PEX), although it is an age related, can lead to the development of glaucoma (secondary open angle glaucoma), but the exact mechanism is not well understood, and was described to be associated with different causes like ethnic, genetic, environmental and other organic causes, and a controversy exist about its relation with diabetes mellitus. Aim: To the impact or the association of state of diabetes mellitus with pseudoexfoliation (PEX) and open angle glaucoma (OAG). Methodology: This is an observational descriptive cross sectional, case control study included; 214 type 2 diabetes mellitus patients aged 45–72 years, and 214 as control non diabetic persons attending The Specialized Center for Endocrinology and Diabetes – Baghdad, the capital of Iraq between May 2020– Jan 2021. Results: Of the 214 diabetic patients 66 (30.84%) were having PEX, versus 12(5.6%), in the control group, with p value < 0,001, and of these 66 patients 44(67.5%) were females and 22 (32.5%) males with ratio 2:1, p value non-significant. Mean age for PEX group was 40.36 ± 4.2 SD, versus 52.43±3.2 SD in non-PEX, with significant p value. The mean HbA1c was 9.84 ± 2.39 SD versus 6.6± 1.6 SD respectively,

which also was significant. Other parameters that show significant p value are the mean RBS, duration of diabetes, and cholesterol levels. Glaucoma or increase intraocular pressure (IOP) found in 11.68 % among diabetic with PXS, 80% of them were discovered to have glaucoma at their first visit in this study. Conclusions: Age, the mean HbA1c, the mean RBS, duration of diabetes and total cholesterol, have significant association with PEX syndrome, and high prevalence of glaucoma among these diabetic persons alarms for the awareness about this condition in periodic ophthalmological examination, and close follow up for the development of glaucoma and increase IOP.

Keywords---pseudo exfoliation PEX, open angle glaucoma OAG, pseudo exfoliation open angle glaucoma (XFG), Type 2 diabetes mellitus(T2DM), intraocular pressure (IOP).

Introduction

Exfoliation syndrome (ES) or Pseudo exfoliation syndrome (PEX) is an age related systemic syndrome characterized by deposition of fibrillary white flaky (dandruff-like) material over the time and frequently associated with secondary open angle glaucoma (OAG), called pseudo exfoliation glaucoma (XFG), because of the blockage in the drainage angle between iris and cornea, and increasing intraocular pressure (IOP), and damage to the optic nerve causing with the time deterioration of vision. It was first described in 1917 by Lindberg, and occurred with variable prevalence rate and different risk factor(s) affected by geographical, ethnic and environmental factors [1] The white fibrillary amyloid like material may derived from abnormal extra cellular metabolism in ocular tissue, and deposited in various ocular tissues including lens capsule, ciliary body, zonular fibers, corneal endothelium, iris and pupillary margins. PEX can also be found in many different organs, like liver, heart, kidneys, blood vessels, lungs or meninges. [2]

Risk factors include; age over 50, genetic because the condition occur more in persons who have family members with XFG, ethnic factors where it is common in northern European ancestry, and may be sex factor as it was described more in women. Other factors like long sun exposure, alcohol consumption, and smoking were mentioned in some studies. But it seems that the risk factors blamed in the etiology of PXS are heterogeneous. [3]

Diabetes mellitus cause a wide spectrum of systemic and ophthalmic complications, and although PEX is an age related process, there was a controversy regard the impact of hyperglycemia as a cause or association with it. PXS is associated with an increased prevalence of vascular disorders, like hypertension, angina, myocardial infarction, cerebrovascular and cardiovascular disease, aortic aneurysm, renal artery stenosis, Alzheimer disease (AD) and hearing loss and sometimes with elevated intra ocular pressure. Some population with PEX have a defect in LOXL1 gene polymorphisms, responsible for metabolism of some components of elastic fibers and extracellular matrix, and increased natural exposure to ambient ultraviolet or caffeine consumption[4]. The most common presentation is asymmetrical and bilateral with variable degree of

mild to severe visual impairment and blindness than in general population due to glaucoma and cataract, and XFG represents the main cause of identifiable glaucoma worldwide and the visual field deterioration is more rapid than that observed in primary open angle glaucoma [5]

Aim of the study

To determine the patient characteristics, and the impact or the association of diabetes mellitus with pseudoexfoliation syndrome (PEX) and open angle glaucoma (OAG).

Patients and Methods

In an observational descriptive cross sectional, case control study, 428

Persons were enrolled, divided into two groups: group A, include 214 persons with type 2 diabetes mellitus, aged 45–72 years, and group B, 214 as control non diabetic, attending The Specialized Center for Endocrinology and Diabetes, in Baghdad, the capital of Iraq between May 2020– Jan 2021.

Participants who fit the criteria were involved in the study after taken a verbal consent. The exclusion criteria were any patient having any other ocular pathology or previous ocular surgery. A special questionnaire form and thorough physical examination and laboratory tests were done, and a comprehensive ophthalmological examination that include:

1. Slit lamp anterior segment, Posterior segment examination
2. Three mirror lens: Gonioscopy, looking for a- heavily pigmented angle and irregular band of pigment running anterior to the Schwalbe line, b- Dandruff – Like PXF, angle deposits may be seen.
3. Intra ocular pressure (I.O.P) estimation Tonometer appln, and optical coherence tomography if indicated (OCT)
4. Visual field assessment.
5. VA by Snellen chart.
6. Full dilated eye examination.
7. Color test Ashihara book.

The definition of T2DM and the reference ranges of blood glucose and HbA1c were depended on the guidelines from American Diabetes Association (ADA) 2021. [6]

Statistical analysis

Data statistical analysis was by using IBM SPSS Statistic for Windows, version 23.0 (IBM Corp. Armonk, NY, USA). Data were presented as number and percent or mean and standard deviation (SD). A *p*-value of less than 0.05 was considered as significant.

Results

Of the 214 diabetic patients 66 (30.84%) were having PEX, and 148 (69.15%) not having PEX, *p* - value < 0.001, and of these 66 patients 44 (67.5%) were females and 22 (32.5%) were males, the *p* - value was non-Significant. Mean age PEX group was 40.36 ± 4.2 SD, versus 52.43 in non- PEX, with significant *p* value < 0,

01. There was significant correlation with increasing age of diabetic patients with PEX; age > 45y =4 (5.97%), 45-55y=17 (25.37%), and $\geq 55y$ =46 (68.65%) with p value < 0, 01. The mean HbA1c was 9.84 ± 2.39 SD, versus 6.6 ± 1.6 SD, and the mean RBS 14.41 ± 6.96 SD versus 9.3 ± 1.78 SD, and the total cholesterol was 4.26 ± 1.39 SD versus 3.05 ± 1.36 SD respectively, and all have significant p value. According to the duration of DM and PEX syndrome was; < 5 years (8), 5-10 years (18), ≥ 10 years (40), which was also statically significant. Patients discovered with PEX having glaucoma were 25 (11. 68%).while those having PEX without evidence of increased intraocular pressure and glaucoma are 189 (88. 3%).See tables 1 and table 2.

Discussion

Pseudoexfoliation syndrome (PEX) is a leading cause of loss of vision. It is a well-known clinical condition worldwide and Iraq, and it has associated with significant problems in the vision that may be overlooked or underestimated. We estimated 214 of persons with diabetes mellitus, both male and female, 66 (30.84 %) having PEX in both eyes, while in the control group only 12 (5.6%), which was statically significant and indicate that glycemic state is important factor, and this was consistent with other study that concluded high incidence of uveal PEX in diabetic patients with or without diabetic retinopathy, due to collagen metabolic alteration[7],but in other researches the effect of glycemic state using multivariate analysis seem to be dependent on other factor like the age , and conclude no contributory effect of diabetes mellitus, arterial hypertension or ischemic heart disease on PEX after controlling the age factor , and diabetes mellitus and hypertension may not be positively associated with primary or secondary open angle glaucoma .[8,9] In addition, a study from Russia concluded that PEX was independent of any systemic parameters like DM, hypertension, previous cardiovascular or cerebrovascular disease and dementia,[10] and less frequently in patients with diabetic background nor proliferative retinopathy , sex,dyslipidemia and body mass index [11,12,13]

Other glycemic parameters like the mean glucose levels, the level of glycated hemoglobin in addition to the duration of diabetes also showed statically significant correlation, that strengthen the theory of presence of causal association of diabetes mellitus with PEX and glaucoma, but this was not proven in a study from Greece, where the PEX was present in 11% among diabetic versus 32.7 non diabetic, with even less among the subgroup with proliferative diabetic retinopathy. [14]

High percentage (80%) of those patients who involved in this study were examined and discovered to have glaucoma for the first time, a fact that alarm about the responsibility of health care system for patient education and screen for the condition in a periodic follow up.

Twenty-five patients of those with PEX have glaucoma of different degree after examination of the visual field and optical coherence tomography (OCT) of the optic nerves and only small number (4) of patients were diagnosed having glaucoma previously.

In this study the prevalence of PEX was 18.2% done in Baghdad, middle of Iraq, and in comparison with two other studies in Iraq; from Sulaimaniya in the north, and from Basra in the south, the prevalence of PXS ranged (29%, 4.45% respectively [15, 16]. In addition, in a big epidemiological review of studies or articles [17] from different part of the world, the prevalence rate range 0.3-22.1%. The prevalence of PEX syndrome in Pakistan was 6.45%, in Saudi Arabia 9.3, in Iran 13.1, while the prevalence in Japanese population in two different studies was 1.2 - 3.4% aged 50 years or more. [18] Ethiopian study show the prevalence of 39.3%, and the mean I.O.P. was higher in these patients (18.4 ± 3.2) mm Hg, versus (15 ± 3.6) mm Hg in those without PEX. [19] A studies from different parts in Greek population revealed over all prevalence of 16.1-27.9% among patients with glaucoma, [20] and high prevalence in Scandinavia population. [21] In all of the previous studies, the age was an important factor, as was in our study, and regarded as independent factor in the pathogenesis and prevalence of PEX, and development of glaucoma (XFG).

In this study, female – male ratio 2:1 among diabetic, and approximate ratio in non-diabetic, and this in agreement with many epidemiological studies, and differ from the previous two studies from Iraq. Yet many other studies concluded that sex is not an independent risk factor for both PXS and XFG, although the diseases are common in female. [22,23]

PEX is now established as a significant risk factor for XFG, though the etiology of later is still unclear. Moreover, it is not well known why only about 30% of PEX eyes develop XFG within their lifetime and why in some literatures there was predominant male affection by XFG. PEX occurs first, followed by the development of ocular hypertension and XFG in a significant proportion of patients, which means that the presence of XFS may serve as a marker for the future development of XFG. New insights have increased the importance of accurate diagnosis. Ritch has calculated that cumulative epidemiological evidence implicates PEX as the cause of about 20% to 25% of cases of open-angle glaucoma, making it the most common identifiable cause worldwide [24,25,26].

Conclusion and recommendation(s).

Age is the only independent factor worldwide of proven effect, as proved in our study also. The pseudoexfoliation syndrome and glaucoma need to look for them during routine ophthalmological assessment, because of the associated risk of visual impairment and blindness, and to be further investigated because of its diversity of the underlying etiological factors, and its association with diabetes mellitus that shown in this study, need to be proved more in a big cohort study.

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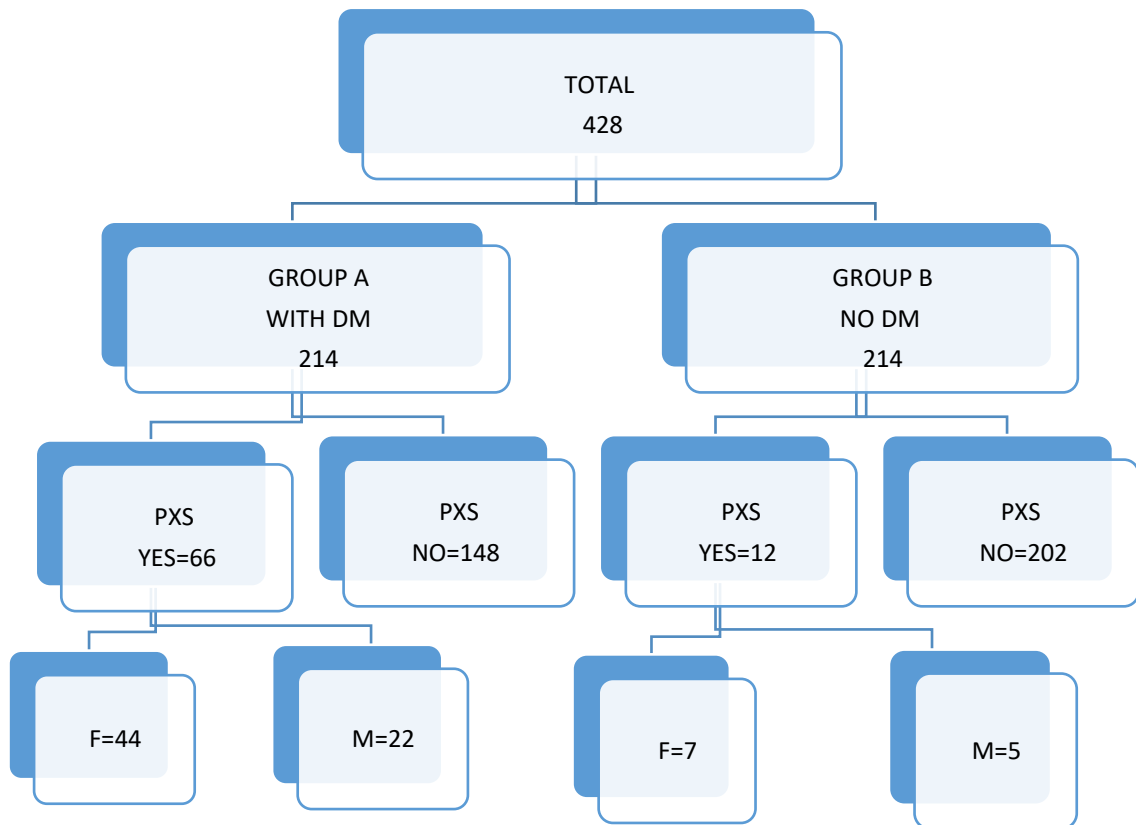


Figure 1 Study design

Table 1 patient's characteristics with PXS and type 2 DM

Parameters		No and %
PXS	Yes	66 (30.84%)
	No	148(69.15%)
Age	≤ 45	4 (5.97%)
	45-55	17 (25.37%)
	≥ 55	46 (68.65%).
Gender	female	44 (20.5%)
	Male	22 (10.2%)
Duration of DM	≤ 5 Y	8 (12.12%)
	5-10 Y	18 (17.27%)
	≥ 10 Y	40 9(60.60%)
Glaucoma or increase IOP	Yes	25 (11.68%)
	No	189 (88.3%).

Table 2 comparison between the two groups of the study

Parameters	Group A=214	Group B=214	P value
PXS Yes No	66 (30.84%)	12(5.6%)	< 0,001
	148(69.15%)	202 (94.4%)	
Age	40.36±4.2 SD	52.43±3.2 SD	< 0,01
Gender female male	44	7	N S
	22	5	
Mean RBS	14.41±6.96 SD	9.3±1.78 SD	< 0,001
HbA1c	9.84±2.39 SD	6.60±1.6 SD	< 0,01
Total cholesterol	4.26±1.39 SD	3.05±1.36 SD	< 0,001