Journal of Clinical and Translational Research
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Pigment dispersion syndrome: A brief overview

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Ref.: Ms. No. JCTRes-D-22-00082
Pigment dispersion syndrome (PDS): a brief overview
Journal of Clinical and Translational Research

Dear Dr. Zeppieri,

Reviewers have now commented on your paper. Two reviewers recommended a rejection, one reviewer recommended a major revision, and two reviewers recommended acceptance after minor revisions. We have carefully studied the comments of reviewers 4 and 5, who advised against the publication of the manuscript, to determine whether extending an opportunity to resubmit is warranted. In this case, the editorial board feels that the comments can be addressed of these most critical reviewers through a substantial overhaul of the text. Please note that we are siding with the assessment of reviewers 4 and 5, and therefore require you to make the changes accordingly in order for us to proceed with the handling of your manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

For your guidance, reviewers' comments are appended below.

If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript. Also, please ensure that the track changes function is switched on when implementing the revisions. This enables the reviewers to rapidly verify all changes made.

Your revision is due by Sep 01, 2022.

To submit a revision, go to https://www.editorialmanager.com/jctres/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #1: The manuscript entitled "Pigment dispersion syndrome (PDS): a brief overview" reports a quite interesting review concerning pigment dispersion syndrome and pigmentary glaucoma.
The paper is well written and could be useful for students and general ophthalmologists. Several points, hoiwever, should addressed to improve the manuscript, which include the following:
1) Page 3, line 21 change "when elevated IOP occurs" to "when elevated IOP causes".
2) Page 3, line 24: delete "peripheral".
3) Page 3, line 43: the Authors state that "PDS develops into PG in about 1%". This data appears to be underestimated. Other Authors (Siddiqui Y, et al; Niyadurupola N and Broadway DC; Mastropasqua L. et al: Early stadiation of pigmentary dispersion syndrome and long-term analysis of progression to pigmentary glaucoma. Ann Ophthalmol Glaucoma. 1996;28(5):301e7) report a risk ranging between 10% and 50%.
4) Page 4, line 9: change "anatomical" to "structural".
5) Page 4, line 19: "spindles" should read "spindle".
6) Page 5: some information regarding genetics of the disease should be added (for ex: Lascaratos G, Shah A, Garway-Heath DF: The genetics of pigment dispersion syndrome and pigmentary glaucoma. Surv Ophthalmol. 2013 Mar-Apr;58(2):164-75).
7) Page 5, line 51: change "with a rate of lifetime conversion rate of…" to "with a lifetime conversion rate of..)
8) Page 6, line 26: change "in the presence of" to "with".
9) Page 6, line 48: this phrase is identical to line 21 in the same page. Please check.
10) Page 7, line 7: a new simple method to detect iris spoke-like patterns using an automatic refractometer has been recently introduces and should be cited here (Brusini P, Papa V: Use of Infrared Images of Automatic Refractometer to Screen Pigment Dispersion Syndrome: a Cross-Sectional Observational Study From a Preliminary Hypothesis. Medical Hypothesis, Discovery & Innovation in Optometry. 2020 Summer:1(1);25-28).
11) Page 8, line 29: change "in the presence of" to "with"
12) Page 11, line 16: some other publications should be added here: 1) Buffault J, Leray B, Bouillot A, Baudouin C, Labbé A: Role of laser peripheral iridotomy in pigmentary glaucoma and pigment dispersion syndrome: A review of the literature. J Fr Ophtalmol. 2017 Nov;40(9):e315-e321; 29
13) Page 9, line 48: considering this is a review, some recent publications concerning surgery in pigmentary glaucoma should be added here: 1) Akil H, Chopra V, Huang A, et al. Clinical results of ab interno trabeculotomy using the Trabectome in patients with pigmentary glaucoma compared to primary open angle glaucoma. Clin Exp Ophthalmol. 2016;44(7):563e9; 2) Wang C, Dang Y, Shah P, et al: . Intraocular pressure reduction in a

pigmentary glaucoma model by Goniotome Ab interno trabeculectomy. PLoS One. 2020 Apr 16;15(4):e0231360; 3) Dorairaj SK, Seibold LK, Radcliffe NM, et al. 12-Month outcomes of goniotomy performed using the Kahook dual blade combined with cataract surgery in eyes with medically treated glaucoma. Adv Ther. 2018;35(9):1460e9; 4) Brusini P, Papa V: Canaloplasty in pigmentary glaucoma: long-term outcomes and proposal of a new hypothesis on its intraocular pressure lowering mechanism. J Clin Med, 2020,9,4024)
14) Page 13, line 7: "entità" should read "entity"

Reviewer #2: July, 29, 2022

Manuscript review JCTRes-D-22-00082

The manuscript entitled "Pigment dispersion syndrome (PDS): a brief review" represents a short overview of the Pigment dispersion syndrome (PDS) and the Pigmentary glaucoma (PG), that share the same clinical features and represent different degree of severity of the same clinical condition.

The topic is interesting considering that the PG represent the 1-1.5% of all glaucomatous cases, and that the PDS and PG enter in the differential diagnosis with several other diseases, including the pseudoesfoliatio syndrome (PEX), other causes of pigment deposition in the anterior chamber, and normal tension glaucoma after the burnout phase of the PDS.

The study is nicely presented.

Anyway, some minor issues need to be addressed, which include:

1. Introduction, page 3 line 14: the term "trabecular meshwork" should be changed into the term "iridocorneal angle";
2. Introduction, page 3, line 53: At this point, the possibility of a burnout phase of the PDS, in which a stabilization of the IOP and a reduction or disappearance of the pigment is seen, should be cited;
3. Management, page 9, line 58: at this point, a better explanation of the mechanism of the laser peripheral iridotomy in the management of the PDS is required.

Reviewer #3: The authors present a brief overview of the clinical spectrum of pigment dispersion syndrome and pigmentary glaucoma.
1. There is a need for an English language revision of the entire text. For example, the shorthand for PDS is misspelled several times as "PSD" and "visual field déficits" instead of defects.
2. In the introduction section, authors should be more explicit about the purpose of their work.

They should focus on a particular aspect of the disease since this is not an exhaustive review of the subject.
3. In the introduction, etiology, and discusión sections, the authors only discuss one pathogenic mechanism of OHT and PG in patients with PDS: pigment particles blocking the aqueous outflow through the trabecular meshwork. They should discuss other proposed mechanisms of IOP rise and glaucomatous damage observed in some patients with PDS.
4. The authors should include a more detailed discusión of the potential risk factors for the conversion from PDS to PG because not all PDS cases become PG after all. There are patients¨ demographic and pathologic features, the IOP rise at the beginning of the pigment dispersion episode, and long-term behavior. The authors should revise the following article: Mastropasqua L, et al. Early stadiation of pigmentary dispersion syndrome and long-term análisis of progression to pigmentary glaucoma. Ann Ophthalmol Glaucoma. 1996;28(5):301-7
5. Discuss how frequently PDS converts to PG. Conversion rate 35% in 17 yr to 50% in 4 yr for example. Analyze related references, like Siddiqui Y et al. What is the risk of developing pigmentary glaucoma from pigment dispersion syndrome? Am J Ophthalmol 2003; 135(6), 794-799. Guerrero-de Ferran C, et al. Intraocular pressure variation during episodes of pigment dispersion and its relationship with the development of pigmentary glaucoma. Rev Mex Oftalmol. 2018;92(1):8-13.
6. In the introduction section, the sentence: "There are different forms of glaucoma, the most prominent being primary open-angle glaucoma (POAG). PG is considered a secondary form of open-angle glaucoma." has no backup references. In the same manner, at the end of the discussion section, there is a whole paragraph about surgical methods for PG with no references.
7. The authors should include a brief Diagnosis (diagnostic methods, imaging technologies) section in their manuscript.
8. Clinical images could be helpful to explain clinical findings and diagnosis of PDS-OHT-PG.

Reviewer #4: The Authors wrote a manuscript regarding an interesting and relatively rare clinical entity called pigment dispersion syndrome. I will give a few general statements regarding this manuscript. I hope the authors find the following comments helpful.
The manuscript is for the most part well written. The manuscript however has to be more robust. The issue when reading was that information repeats itself too often. Pathophysiology is written in the abstract, the introduction, etiology, histopathology and conclusion sections. I would therefore urge the authors to delete some sections of the manuscript and perhaps include some newer information regarding PDS which is not included (see literature).

Abstract
Background: Give few brief facts in the abstract section and don't go into patophysiology of the disease. Examples:
- PDS is characterized by dispersion of pigment in the anterior chamber structures and can present with ...
- It is more common in myopic patients in age groups... what percentage of the population it affects.
- State that PDS can lead to a rise in IOP and secondary glaucoma
Relevance for patients: Simplify. Early diagnosis, appropriate management and follow-up of patients with PDS is important to prevent vision deterioration or blindness due to

glaucomatous optic neuropathy. Including treatment in this section is not relevant.

Introduction
Compress the three sections into one robust section; most of the information you give here is then written again in the History, Etiology, Epidemiology, Histopathology, Conclusion...
Write what PDS is, that it can lead to secondary IOP rise and that it can damage the optic nerve in terms of pigmentary glaucoma development, which is a secondary type of glaucoma and aims for this brief overview. You do not need to write about POAG, complete clinical picture etc.
It is not true that PDS presents with a triad of signs and symptoms. It presents with a variety of signs and symptoms (more about this in clinical features).

History
Please include a few sentences what the big study discovered: most common features and/or effect of medical therapy etc.
Etiology
I would rather see a combined section of etiology and clinical features than two stand alone sections of the manuscript because they are very similar.

Epidemiology
Move the epidemiology of worldwide glaucoma to the first statement of this section then write what percentage of patients have PDS and PG. Latter write that PDS and PG are more common in caucasian patients with myopia between 20-40 years of age with an even distribution between males and females. PG is more common in males, not PDS. Then the risk of conversion from PDS to PG. Please include some longitudinal studies.

Pathophysiology and Clinical features
Move etiology to this section. Also make it more robust stating only relevant information in as few sentences as possible. Do not repeat statements like backward bowing of the iris and reverse pupillary block mechanisms - write it only once.
The diagnosis is clinical and may be challenging due to a wide variety of clinical features. PDS may present with any of the following signs: Krukenberg spindle (pigment deposition on the endothelium), pigment granules on the iris, concave configuration of the peripheral iris, spoke-like transilumination defects of the iris, pigment deposition on the anterior lens capsule, pigment deposition on the posterior lens capsule (Scheie stripe or Zentmeyr line, recent observations also include deposition on the more central part of the posterior lens capsule), pigmentation of trabecular meshwork using gonioscopy (also line similar to Sampaolesi's line). Literature (doi):
- 10.2147/EB.S160999
- 10.4103/0301-4738.64135
- 10.5693/djo.02.2011.10.003
- 10.1186/s12886-020-01728-y
- 10.1007/s10792-007-9158-2
- 10.1097/00061198-200312000-00009
When writing about glaucomatous visual field defects, do not write peripheral.

Differential diagnosis
Delete the first sentence in this section. Include UGH syndrome.

Management (treatment and management are all the same, do not separate these two sections)
Currently management includes IOP lowering strategies which is initialized in PDS patients with increased risk of developing PG (high IOP) and patients with developed PG. The stages written in the manuscript are advocated by some authors as useful but are in my opinion redundant because they are not relevant for the management (they are for the most part also not advocated by most authors and glaucoma practices). Also if this is a BRIEF overview, stages are irrelevant.
The phrase »burnout phase« is a phrase conjured by one author and has been used freely afterwards with no real evidence basis. I would rather write that some authors theorize that some patients develop a burn-out phase in which signs of PDS or PG aren't evident. Some call it also pigment reversal sign. This is why some patients are misdiagnosed as having POAG or NTG (as written by the authors). That this occurs after 10 years is errorous but rather later in life.

Conclusions
The conclusion section is meant to shortly summarize the most important points of the manuscript. That PDS is actually a relatively common entitiy with a wide variety of clinical features. Early diagnosis, patient education and treatment of patients at risk is of great socioeconomical and individual importance. Write that it is usually identified on routine ophthalmologic visits and that patients are usially asymptomatic. Therefore preventive ophthalmic visits are of utmost importance...
Do not repeat the sentence release of pigment in the AC caused by the constant friction. The point of this brief overview is (as I see it) to educate clinicians and patients about the relevance of identifying PDS and PG and not understanding its pathophysiology (which is still somewhat unclear).

Reviewer #5: The manuscript entitled "Pigment dispersion syndrome (PDS): a brief overview" has provided limited horizon for the knowledge of PDS, which manifests differently among different races. Triad of a Krukenberg spindle, spoke-like iris transillumination defects, and homogeneous TM pigmentation is typical and classic findings in white patient. However, in the pigmented races, iris transillumination defects are usually absent. Nevertheless, PDS in pigmented races like Asian and black people is highly sight threatening because the volume of pigment granules in IPE layer is huge and may cause very serious TM pigmentation and rapid AH outflow blockage, resulting in constant high IOP and glaucomatous neuropathy and blindness. In clinical practise, the burnout phase is scarcely seen in pigmented PDS patients.
Several linguistic errors need to be corrected:
1.Uncorrect spelling, the third and six line of second paragraph, 2nd page, "PSD" should be "PDS". The expression of "Relevance for patients", 2nd page need linguistic correction.
2.Management section, the first line "PD" should be "PG".
3.The forth line in Management section "If PDS does not show elevated levels of IOP, therapy is normally not required, however, periodical ophthalmologic examinations with instrumental testing, if needed, is important." is not correct. In pigmented races, like Asian or the black people, pigment dispersion is highly dangerous for visual function due to high volume of pigment in the IPE layer of the iris. Reverse pupillary block and pigment dispersion warrant more active and aggressive interference in the pigmented races.

There is additional documentation related to this decision letter. To access the file(s), please click the link below. You may also login to the system and click the 'View Attachments' link in the Action column.

Author's response

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Udine, August22, 2022

Ref.: Ms. No. JCTRes-D-22-00082
Pigment dispersion syndrome (PDS): a brief overview
Invited paper to Journal of Clinical and Translational Research
CC: m.heger@jctres.com

Dear Dr. Michal Heger, Editor-in-Chief of Journal of Clinical and Translational Research**,**

I would like to extend my gratitude for the efforts and time spent reviewing my manuscript entitled "Pigment dispersion syndrome (PDS): a brief overview". The Reviewers make excellent points and offer valuable suggestions to improve the manuscript. I have addressed all comments of the reviewers using the track changes function in Word (attached as supplementary material not for publication). Moreover, every modification or rebuttal of the reviewer's comments is detailed per comment below in red italics.

I am grateful for the useful comments of the reviewers, as a result of which the paper has been considerably improved. I look forward to your final decision regarding the modifications, and am ready to address further issues if necessary.

Kindest regards,
Marco Zeppieri

REVIEWER COMMENTS

Editor-in-Chief

Reviewers have now commented on your paper. Two reviewers recommended a rejection, one reviewer recommended a major revision, and two reviewers recommended acceptance after minor revisions. We have carefully studied the comments of reviewers 4 and 5, who advised against the publication of the manuscript, to determine whether extending an opportunity to resubmit is warranted. In this case, the editorial board feels that the comments can be addressed of these most critical reviewers through a substantial overhaul of the text. Please note that we are siding with the assessment of reviewers 4 and 5, and therefore require you to make the changes accordingly in order for us to proceed with the handling of your manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

I am grateful for the opportunity to modify the manuscript with hopes that I can address all the issues raised. Just a small remark about the aim of the paper. With regards to how the paper was planned, once I received the invitation from your journal to submit a paper, I sent the preliminary abstract. The paper was designed as a brief summary and as a brief reminder of key points regarding this condition for clinicians and not a thorough overview of pigment dispersion syndrome. This idea was approved by the journal prior to commencing the paper. I kept this in mind when preparing it.

The Reviewers all make excellent points, which will surely enhance the quality of the manuscript. The modified paper has been completely changed in accordance to the suggestion made by each Reviewer. A total of 16 references have been added and several key points have been incorporated and enhanced to make the paper more thorough and robust. Several subheadings have been removed to avoid repetition and improve the flow of the paper.

Reviewer 1

The manuscript entitled "Pigment dispersion syndrome (PDS): a brief overview" reports a quite interesting review concerning pigment dispersion syndrome and pigmentary glaucoma. The paper is well written and could be useful for students and general ophthalmologists.

Many thanks for the positive comments regarding our manuscript.

Several points, however, should addressed to improve the manuscript, which include the following:
1) Page 3, line 21 change "when elevated IOP occurs" to "when elevated IOP causes".
2) Page 3, line 24: delete "peripheral".
4) Page 4, line 9: change "anatomical" to "structural".
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8) Page 6, line 26: change "in the presence of" to "with".
9) Page 6, line 48: this phrase is identical to line 21 in the same page. Please check.
11) Page 8, line 29: change "in the presence of" to "with".
14) Page 13, line 7: "entità" should read "entity"

The minor correction have been made accordingly.

3) Page 3, line 43: the Authors state that "PDS develops into PG in about 1%". This data appears to be underestimated. Other Authors (Siddiqui Y, et al; Niyadurupola N and Broadway DC; Mastropasqua L. et al: Early stadiation of pigmentary dispersion syndrome and long-term analysis of progression to pigmentary glaucoma. Ann Ophthalmol Glaucoma. 1996;28(5):301e7) report a risk ranging between 10% and 50%.

Mention regarding 1% conversion rate has been deleted. A new sentence with the 3 appropriate references have been added in this section to read:

"PDS is a risk factor to develop PG, especially in the presence of OHT and an anatomic myopic predisposition, with a lifetime conversion rate of 10-50% (1,13,14)."

6) Page 5: some information regarding genetics of the disease should be added (for ex: Lascaratos G, Shah A, Garway-Heath DF: The genetics of pigment dispersion syndrome and pigmentary glaucoma. Surv Ophthalmol. 2013 Mar-Apr;58(2):164-75).

Additional information with the suggested reference regarding the genetics of PDS has been added in this section to read:

"Studies have reported several genetic locus associated with PDS, which include Glycoprotein nmb (GpnmbR150x), Gene GPDS1 (glaucoma-related pigment dispersion syndrome 1) and (OMIM ID 600510) (22)".

10) Page 7, line 7: a new simple method to detect iris spoke-like patterns using an automatic refractometer has been recently introduces and should be cited here (Brusini P, Papa V: Use of Infrared Images of Automatic Refractometer to Screen Pigment Dispersion Syndrome: a Cross-Sectional Observational Study From a Preliminary Hypothesis. Medical Hypothesis, Discovery & Innovation in Optometry. 2020 Summer:1(1);25-28).

The detection of PDS with a refractometer with the appropriate citation have been added in this section to read:

"A new simple method to detect iris spoke-like patterns using an automatic refractometer has been recently been proposed, which is simple and can be useful in a routine clinical setting (52)."

12) Page 11, line 16: some other publications should be added here: 1) Buffault J, Leray B, Bouillot A, Baudouin C, Labbé A: Role of laser peripheral iridotomy in pigmentary glaucoma and pigment dispersion syndrome: A review of the literature. J Fr Ophtalmol. 2017 Nov;40(9):e315-e321; 29

The reference has been cited in this section as recommended.

13) Page 9, line 48: considering this is a review, some recent publications concerning surgery in pigmentary glaucoma should be added here: 1) Akil H, Chopra V, Huang A, et al. Clinical results of ab interno trabeculotomy using the Trabectome in patients with pigmentary glaucoma compared to primary open angle glaucoma. Clin Exp Ophthalmol. 2016;44(7):563e9; 2) Wang C, Dang Y, Shah P, et al: . Intraocular pressure reduction in a pigmentary glaucoma model by Goniotome Ab interno trabeculectomy. PLoS One. 2020 Apr 16;15(4):e0231360; 3) Dorairaj SK, Seibold LK, Radcliffe NM, et al. 12-Month outcomes of goniotomy performed using the Kahook dual blade combined with cataract surgery in eyes with medically treated glaucoma. Adv Ther. 2018;35(9):1460e9; 4) Brusini P, Papa V: Canaloplasty in pigmentary glaucoma: long-term outcomes and proposal of a new hypothesis on its intraocular pressure lowering mechanism. J Clin Med, 2020,9,4024).

The recent references listed by the Reviewer regarding surgical treatment have been added in this section to read:

"Alternative surgical methods (59-63) like canaloplasty, goniotomy, Ab interno trabeculectomy, trabectome…"

Reviewer 2

The manuscript entitled "Pigment dispersion syndrome (PDS): a brief review" represents a short overview of the Pigment dispersion syndrome (PDS) and the Pigmentary glaucoma (PG), that share the same clinical features and represent different degree of severity of the same clinical condition.
The topic is interesting considering that the PG represent the 1-1.5% of all glaucomatous cases, and that the PDS and PG enter in the differential diagnosis with several other diseases, including the pseudoesfoliatio syndrome (PEX), other causes of pigment deposition in the anterior chamber, and normal tension glaucoma after the burnout phase of the PDS. The study is nicely presented.

Many thanks for the positive comments regarding our manuscript.

Anyway, some minor issues need to be addressed, which include:
1. Introduction, page 3 line 14: the term "trabecular meshwork" should be changed into the term "iridocorneal angle"

The term "iridocorneal angle" has been added.

2. Introduction, page 3, line 53: At this point, the possibility of a burnout phase of the PDS, in which a stabilization of the IOP and a reduction or disappearance of the pigment is seen, should be cited;

The following sentence have been added in the Introduction section as suggested:

"Some studies have theorized a burn-out phase or pigment reversal later in life in some patients, in which signs of PDS or PG are less evident."

3. Management, page 9, line 58: at this point, a better explanation of the mechanism of the laser peripheral iridotomy in the management of the PDS is required.

Brief mention regarding effects of laser has been added here. Detailed information regarding laser treatment is explained further in successive paragraphs:

"…can benefit in preventative laser peripheral iridotomy (LPI), mainly by inducing iris flattening to reduce concavity, posterior iris bowing, and reverse pupillary block."

Reviewer 3

The authors present a brief overview of the clinical spectrum of pigment dispersion syndrome and pigmentary glaucoma. 1. There is a need for an English language revision of the entire text. For example, the shorthand for PDS is misspelled several times as "PSD" and "visual field deficits" instead of defects.

The English has been checked and corrected throughout the paper. "PDS" and "deficits" have been modified accordingly.

2. In the introduction section, authors should be more explicit about the purpose of their work. They should focus on a particular aspect of the disease since this is not an exhaustive review of the subject. 3. In the introduction, etiology, and discussion sections, the authors only discuss one pathogenic mechanism of OHT and PG in patients with PDS: pigment particles blocking the aqueous outflow through the trabecular meshwork. They should discuss other proposed mechanisms of IOP rise and glaucomatous damage observed in some patients with PDS.

The Reviewer raises important points here, which have also been brought up by other Reviewers. Major modifications have been done throughout the paper. The sections have been reorganized, modified and synthesized. Several subheading have been removed and sections have been merged.

With regards to the purpose of the study, the following has been added to read:

"The aim of this brief overview is to provide a quick review for clinician regarding important points and brief take home messages to remember when diagnosing, treating and managing patients with PDS. A better understanding of PDS is of utmost importance in the differential diagnosis, treatment, and management of patients with PDS and PG to avoid the onset and/or progression of irreversible glaucomatous structural and functional damage."

With regards to the other proposed mechanisms of IOP rise, mention with appropriate references have been made in various sections regarding the mechanical, genetic, and possible anomalies in ocular structures that can play a role in IOP rises.

4. The authors should include a more detailed discussion of the potential risk factors for the conversion from PDS to PG because not all PDS cases become PG after all. There are patients¨ demographic and pathologic features, the IOP rise at the beginning of the pigment dispersion episode, and long-term behavior. The authors should revise the following article: Mastropasqua L, et al. Early stadiation of pigmentary dispersion syndrome and long-term analysis of progression to pigmentary glaucoma. Ann Ophthalmol Glaucoma. 1996;28(5):301-7.

5. Discuss how frequently PDS converts to PG. Conversion rate 35% in 17 yr to 50% in 4 yr for example. Analyze related references, like Siddiqui Y et al. What is the risk of developing pigmentary glaucoma from pigment dispersion syndrome? Am J Ophthalmol 2003; 135(6), 794-799. Guerrero-de Ferran C, et al. Intraocular pressure variation during episodes of pigment dispersion and its relationship with the development of pigmentary glaucoma. Rev Mex Oftalmol. 2018;92(1):8-13.

The article has been cited in the text as reference 14. Additional information regarding conversion has been added. Data regarding conversion rates vary in literature. Several authors show very low conversion rates, while others show a relatively high risk factor for conversion to PG from PDS.

The following sentences and suggested reference have been added to read:

"PDS usually does not express itself until adulthood, and does not convert to PG. PDS is a risk factor, however, several longitudinal studies suggest that most PDS eyes never develop PG (14). The difference could partially be due to the ability of the TM to tolerate or remove pigment particles and control AH outflow mechanisms. Other studies, however, have reported conversion rates that vary, which can be as high as 50% in some cases. Siddiqui et al reported that that 10% of PDS eyes developed PG after five years, and 15% developed PG after 15 years (13)."

6. In the introduction section, the sentence: "There are different forms of glaucoma, the most prominent being primary open-angle glaucoma (POAG). PG is considered a secondary form of open-angle glaucoma." has no backup references. In the same manner, at the end of the discussion section, there is a whole paragraph about surgical methods for PG with no references.

I apologize for overlooking this point. Three pertinent references (references 1-3) have been added to the Introduction section regarding PG as a secondary form and 5 (references 59-63) have been added to the section about surgical methods.

7. The authors should include a brief Diagnosis (diagnostic methods, imaging technologies) section in their manuscript.

Additional information regarding Diagnosis has been added to read:

"With regards to diagnosis, PDS tends to be first seen during a routine eye examination. The patients are usually asymptomatic and seek the clinician for an eye examination or prescription glasses. The clinical signs regarding pigment deposits in in the AC structures and cornea are evident with examination at the slit-lamp, in addition to the spoke-like iris transillumination defects. Pigment accumulation can be seen with gonioscopy. PDS conversion to PG is diagnosed and managed with the same methods used in managing glaucoma, which include tonometry, visual field examination, optical coherence tomography, etc."

8. Clinical images could be helpful to explain clinical findings and diagnosis of PDS-OHT-PG.

Unfortunately, I do not have access to clinical images at this moment.

Reviewer 4

The Authors wrote a manuscript regarding an interesting and relatively rare clinical entity called pigment dispersion syndrome. I will give a few general statements regarding this manuscript. I hope the authors find the following comments helpful. The manuscript is for the most part well written. The manuscript however has to be more robust. The issue when reading was that information repeats itself too often. Pathophysiology is written in the abstract, the introduction, etiology, histopathology and conclusion sections. I would therefore urge the

authors to delete some sections of the manuscript and perhaps include some newer information regarding PDS which is not included (see literature).

I am grateful to the Reviewer for providing a thorough review of my paper. It is important to note how the manuscript was planned from the start. I received an invitation from the journal to submit a minireview, thus the aim of this paper was to provide a brief overview of pigment dispersion syndrome and not an extensive robust overview of the PDS literature. I wanted to provide a simple and quick review for clinician with a brief description, important points and a few take home messages to remember when managing these patients.

The Reviewer makes excellent comments that will surely enhance the quality of the paper. The formatting of the sections and specific points raised have been modified in accordance to the suggestions. I hope I have managed to address all these points in an adequate manner.

Abstract Background: Give few brief facts in the abstract section and don't go into pathophysiology of the disease. Examples:- PDS is characterized by dispersion of pigment in the anterior chamber structures and can present with ...
- It is more common in myopic patients in age groups... what percentage of the population it affects.
- State that PDS can lead to a rise in IOP and secondary glaucoma
Relevance for patients: Simplify. Early diagnosis, appropriate management and follow-up of patients with PDS is important to prevent vision deterioration or blindness due to glaucomatous optic neuropathy. Including treatment in this section is not relevant.

The Abstract has been greatly improved thanks to the suggestions made by the Reviewer. The modified Abstract has been changed to read:

*"**Background**. Pigment dispersion syndrome (PDS) is characterized by dispersion of pigment in the anterior chamber structures and can present with deposits on the central corneal endothelium or Krukenberg spindle, iris trans-illumination spoke-like defects, and increased pigmentation in the iridocorneal angle. It is more common in myopic patients with a predominance in young males in the third to fifth decade of life that affects about 1-2% of the population. PDS is a risk factor and can give lead to a rise in intraocular pressure (IOP) and secondary glaucoma. Pigmentary glaucoma (PG) can develop from PDS in the presence of elevated IOP coupled with glaucomatous optic neuropathy, retinal nerve fiber thinning, and/or visual field defects. PDS and PG have the same clinical features, representing different levels of severity on the same clinical spectrum.*
***Relevance for patients.** Early diagnosis, appropriate management and follow-up of patients with PDS is important to prevent vision deterioration or blindness due to glaucomatous optic neuropathy."*

Introduction: Compress the three sections into one robust section; most of the information you give here is then written again in the History, Etiology, Epidemiology, Histopathology, Conclusion... Write what PDS is, that it can lead to secondary IOP rise and that it can damage the optic nerve in terms of pigmentary glaucoma development, which is a secondary type of glaucoma and aims for this brief overview. You do not need to write about POAG, complete clinical picture etc.
It is not true that PDS presents with a triad of signs and symptoms. It presents with a variety of signs and symptoms (more about this in clinical features).
History: Please include a few sentences what the big study discovered: most common features and/or effect of medical therapy etc.
Etiology: I would rather see a combined section of etiology and clinical features than two stand-alone sections of the manuscript because they are very similar.
Epidemiology: Move the epidemiology of worldwide glaucoma to the first statement of this section then write what percentage of patients have PDS and PG. Latter write that PDS and PG are more common in Caucasian patients with myopia between 20-40 years of age with an even distribution between males and females. PG is

more common in males, not PDS. Then the risk of conversion from PDS to PG. Please include some longitudinal studies.

The section subheadings have been removed and compressed in the Introduction section.

The important points regarding PDS, secondary IOP rise, secondary glaucoma, PG development and aims of the paper have been modified accordingly. Sections regarding POAG have been deleted.

The word "triad" has been deleted throughout the paper and replaced with "variety" as suggested.

The paragraph in the Epidemiology section has been reworded and formatted in accordance to the suggestions by the Reviewer.

Information and citations regarding important longitudinal studies have been added.

Pathophysiology and Clinical features
Move etiology to this section. Also make it more robust stating only relevant information in as few sentences as possible. Do not repeat statements like backward bowing of the iris and reverse pupillary block mechanisms - write it only once. When writing about glaucomatous visual field defects, do not write peripheral.
The diagnosis is clinical and may be challenging due to a wide variety of clinical features. PDS may present with any of the following signs: Krukenberg spindle (pigment deposition on the endothelium), pigment granules on the iris, concave configuration of the peripheral iris, spoke-like transillumination defects of the iris, pigment deposition on the anterior lens capsule, pigment deposition on the posterior lens capsule (Scheie stripe or Zentmeyr line, recent observations also include deposition on the more central part of the posterior lens capsule), pigmentation of trabecular meshwork using gonioscopy (also line similar to Sampaolesi's line). Literature (doi):
- 10.2147/EB.S160999
- 10.4103/0301-4738.64135
- 10.5693/djo.02.2011.10.003
- 10.1186/s12886-020-01728-y
- 10.1007/s10792-007-9158-2
- 10.1097/00061198-200312000-00009

The sections have been reorganized in accordance to the suggestions.

Repeated concepts have been removed in the text to render it more robust.

The word "peripheral" has been deleted throughout the text when describing visual field defects.

The section regarding the importance of clinical diagnosis has been added to the end of this section.

I apologize for missing the important clinical feature mentioned here regarding the interesting case reports and studies. A paragraph regarding the presence of pigment deposition on the posterior lens capsule in PDS has been included, along with the 6 suggested references. The following has been added in this section:

"Various case reports have also reported a less common feature that is sometimes overlooked in PDS and PG eyes. Central profound pigment deposits near the equator can also be found on the posterior lens capsule, probably due to a communication between posterior chamber and the posterior lens capsule and anatomic anomalies in Wiegers ligament (33-38)."

Differential diagnosis
Delete the first sentence in this section. Include UGH syndrome.
Management (treatment and management are all the same, do not separate these two sections)
Currently management includes IOP lowering strategies which is initialized in PDS patients with increased risk of developing PG (high IOP) and patients with developed PG. The stages written in the manuscript are advocated by some authors as useful but are in my opinion redundant because they are not relevant for the management (they are for the most part also not advocated by most authors and glaucoma practices). Also, if this is a BRIEF overview, stages are irrelevant.
The phrase »burnout phase« is a phrase conjured by one author and has been used freely afterwards with no real evidence basis. I would rather write that some authors theorize that some patients develop a burn-out phase in which signs of PDS or PG aren't evident. Some call it also pigment reversal sign. This is why some patients are misdiagnosed as having POAG or NTG (as written by the authors). That this occurs after 10 years is erroneous but rather later in life.

The first sentence has been deleted. Mention about UGH with an appropriate reference has been added in the differential diagnosis section to read:

"Uveitis-Glaucoma-Hyphema (UGH) syndrome, or Ellingson syndrome, which is a rare complication after intraocular lens (IOL) implants that can cause iris transillumination defects, pigmentary dispersion, elevated IOP, and hyphemas and hyphemas must be considered in the differential diagnosis after cataract surgery (46)."

The sections regarding treatment and management have been joined.

With regards the staging method, the Reviewer makes a good point about the use and practicality in a routine clinical setting. This section has been toned down. A sentence regarding the routine use of these methods has been added to read:

"It is important to note that although these methods of staging have been proposed in studies, clinician may not necessarily advocate and use them in a routine clinical setting when managing patients."

The section regarding "the burnout phase" has been toned down and modified according the points raised by the Reviewer to read:

"Some authors theorize that some patients develop a burn-out phase later in life in which signs of PDS or PG are less evident. Some call it also pigment reversal sign.. Some authors have stated that the presence of less pigment in the TM and normal IOP can lead to the misdiagnosis of patients as having POAG or normal-tension glaucoma (40)."

Conclusions
The conclusion section is meant to shortly summarize the most important points of the manuscript. That PDS is actually a relatively common entity with a wide variety of clinical features. Early diagnosis, patient education and treatment of patients at risk is of great socioeconomical and individual importance. Write that it is usually identified on routine ophthalmologic visits and that patients are usually asymptomatic. Therefore, preventive ophthalmic visits are of utmost importance...
Do not repeat the sentence release of pigment in the AC caused by the constant friction. The point of this brief overview is (as I see it) to educate clinicians and patients about the relevance of identifying PDS and PG and not understanding its pathophysiology (which is still somewhat unclear).

The Conclusion section has been shortened to summarize only the important points to read:

"PDS is a relatively common entitiy with a wide variety of clinical features. Early diagnosis, patient education and treatment of patients at risk is of great socioeconomical and individual importance. It is usually identified on routine ophthalmologic visits. Patients are usually asymptomatic. Therefore, preventive ophthalmic visits are of utmost importance."

Reviewer 5

The manuscript entitled "Pigment dispersion syndrome (PDS): a brief overview" has provided limited horizon for the knowledge of PDS, which manifests differently among different races. Triad of a Krukenberg spindle, spoke-like iris transillumination defects, and homogeneous TM pigmentation is typical and classic findings in white patient. However, in the pigmented races, iris transillumination defects are usually absent. Nevertheless, PDS in pigmented races like Asian and black people is highly sight threatening because the volume of pigment granules in IPE layer is huge and may cause very serious TM pigmentation and rapid AH outflow blockage, resulting in constant high IOP and glaucomatous neuropathy and blindness. In clinical practice, the burnout phase is scarcely seen in pigmented PDS patients.

Mention regarding PDS in pigmented races has been included in the text to read:

"With regards the influence of race, is important to note that Krukenberg spindle, spoke-like iris transillumination defects, and homogeneous TM pigmentation is typical and classic findings in white patient. However, in the pigmented races, iris transillumination defects are usually absent. Nevertheless, PDS in pigmented races like Asian and black people is highly sight threatening because the volume of pigment granules in IPE layer is huge and may cause very serious TM pigmentation and rapid AH outflow blockage, resulting in constant high IOP and glaucomatous neuropathy and blindness. In clinical practice, the burnout phase is scarcely seen in pigmented PDS patients."

Several linguistic errors need to be corrected:
1.Uncorrect spelling, the third and six line of second paragraph, 2nd page, "PSD" should be "PDS". The expression of "Relevance for patients", 2nd page need linguistic correction.
2.Management section, the first line "PD" should be "PG".
3.The fourth line in Management section "If PDS does not show elevated levels of IOP, therapy is normally not required, however, periodical ophthalmologic examinations with instrumental testing, if needed, is important." is not correct. In pigmented races, like Asian or the black people, pigment dispersion is highly dangerous for visual function due to high volume of pigment in the IPE layer of the iris. Reverse pupillary block and pigment dispersion warrant more active and aggressive interference in the pigmented races.

The typing "PSD" and PD" typing errors have been corrected.

The expression of "Relevance for patients" is a requirement stated in the journal guidelines.

The Reviewer raised an important point here. The paragraph has been modified to read:

"If PDS does not show elevated levels of IOP, therapy may not necessarily be required... In pigmented races, like Asian or the black people, pigment dispersion is highly dangerous for visual function due to high volume of pigment in the IPE layer of the iris. Reverse pupillary block and pigment dispersion warrant more active and aggressive interference in the pigmented races."

2nd Editorial decision
23-Aug-2022

Ref.: Ms. No. JCTRes-D-22-00082R1
Pigment dispersion syndrome (PDS): a brief overview
Journal of Clinical and Translational Research

Dear authors,

I am pleased to inform you that your manuscript has been accepted for publication in the Journal of Clinical and Translational Research.

You will receive the proofs of your article shortly, which we kindly ask you to thoroughly review for any errors.

Thank you for submitting your work to JCTR.

Kindest regards,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Comments from the editors and reviewers: