

Association between estradiol and idiopathic macular hole in postmenopausal women

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Research

Keywords: idiopathic macular hole; postmenopause; female; estradiol; vitreous

Posted Date: February 11th, 2020

DOI: <https://doi.org/10.21203/rs.2.23249/v1>

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Abstract

Background

Estradiol, a predominant female sex hormone, is not only related to reproductive function but also to the ocular disorders. The purpose of this study was to investigate the association between estradiol and idiopathic macular hole (IMH) in postmenopausal women.

Method

This study included 30 postmenopausal patients with IMH for the study group and 32 postmenopausal patients with uncomplicated primary retinal detachment for the control group. The two groups were compared of serum and vitreous estradiol levels, and clinical variables.

Results

There was no statistically significant difference in age between the two groups ($P = 0.071$). Estradiol in the serum was lower in subjects with idiopathic macular hole than that in control participants (18.9 ± 4.5 vs. 43.7 ± 6.1 pg/mL, $P < 0.001$). Estradiol in the vitreous body was higher in the study group than in the controls (121.2 ± 41.6 vs. 79.8 ± 10.1 pg/mL, $P < 0.001$). There was a significant correlation between serum estradiol and vitreous estradiol ($r = -0.440$, $P < 0.001$).

Conclusion

Lower estradiol levels in the serum and higher estradiol levels in the vitreous body after menopause are associated with the occurrence of idiopathic macular hole in postmenopausal women.

Background

Idiopathic macular hole (IMH), which is widely thought caused by the vitreoretinal contraction (1,2), is a major cause of diminished vision in the elderly. Previous studies have reported that IMH has strong correlations with female sex (the female-to-male ratio is 3.3:1) (3,4) and predominantly occur in postmenopausal women (5). However, the precise reason for the higher risk of IMH development in postmenopausal women is not yet clear.

Estradiol (E2), synthesized mainly in the ovaries and placenta, and acting on various tissues in the body such as bone and cardiovascular system (6), is recognized as a predominant female sex hormone. And also, it can be synthesized in the retina through cholesterol-based pathway and testosterone aromatization (7). E2 is reported to exert a neuroprotective role and influence tissue perfusion by modulating retinal and choroid blood flow in the eyes (8). Evidence exists about the presence of estradiol receptors (ERs) in the retina, which mediates immediate responses to E2 (9). Although some studies have

been carried out on the relationship between E2 and certain retinal disorders such as age-related macular degeneration, diabetic retinopathy or glaucoma (10–13), further studies are still essential owing to limited research on E2 and IMH.

The aim of this paper was to elucidate the association between E2 and IMH in postmenopausal women, and to help with designing potential new strategies for preventing and treating IMH.

Materials And Methods

Study design

This study included 30 postmenopausal IMH patients and 32 controls. All patients were treated at the Department of Ophthalmology, First Affiliated Hospital of Zhengzhou University in China from December 2018 to April 2019. The study protocol and data collection were conducted according to the guidelines in the Declaration of Helsinki. This study was approved by the ethics committee of the First Affiliated Hospital of Zhengzhou University and written informed consent was obtained from all participants.

All subjects required a vitrectomy, and provided a complete history and received a thorough ophthalmic examination. Routine clinical data collected included age, pseudophakia, plasma fibrinogen, BCVA, a history of hypertension, coronary artery disease and hyperlipidemia.

Inclusion and Exclusion Criteria

The study group were female patients diagnosed of full-thickness IMH by clinical and OCT examinations. The control group were female patients with uncomplicated primary retinal detachment (RD). Given that E2 can be affected by a variety of factors, this study only included postmenopausal women to rule out the effects of physiological periods on E2. Any patient with high myopia (> 6 diopters), trauma, age-related macular degeneration, diabetic retinopathy, retinal detachment due to macular hole, a history of previous parsplana vitrectomy as well as gynecological surgery, and oral administration of estrogen or estrogen inhibitors were excluded from both cases and controls.

Samples preparation and biochemical analysis

4 ml of blood sample was collected from the vein in the forearm prior to vitreous surgery. After adequate centrifugation at 1000 x g for 15 min, the serum samples were extracted and stored in – 80 °C deep freezer immediately. Pure vitreous samples (approximately 0.5 mL) were obtained from each eye before initiating intraocular infusion at the time of vitreous surgery. Vitreous samples were immediately frozen at – 80 °C until analysis. The serum and vitreous E2 levels were determined by using Enzyme-linked immunosorbent assay (R&D System, Inc., Minneapolis, MN, USA) according to the manufacturer's protocol.

Statistics

Normal distribution variables were described with the mean \pm standard deviation (SD). Variables with a skewed data distribution were presented as medians with interquartile ranges, and qualitative variables

with absolute (n) and relative (%) frequencies. Visual acuity was converted to LogMAR for data analysis. Statistical analyses were performed using the independent sample t-tests and the Mann-Whitney test for quantitative variables, and the chi-square tests for categorical variables. Pearson correlation analysis was performed to assess the correlation between E2 and quantitative variables. A $P < 0.05$ was considered to indicate statistical significance. All analyses were performed using the SPSS software, version 19.0 (SPSS, Inc, Chicago, IL).

Results

The general characteristics of IMH patients

The general characteristics of IMH patients are shown in Table 1. The mean age of the study group and the control group was 63.0 ± 4.6 years and 60.7 ± 5.2 years, respectively. There was no statistically significant difference in age between the two groups ($P = 0.071$). Plasma fibrinogen in IMH group was 2.9 ± 0.3 g/L, which was lower than that in controls ($P = 0.034$). The analysis of the logMAR BCVA showed a significant difference between the IMH patients and the controls (1.0 ± 0.3 vs. 1.3 ± 0.5 , $P = 0.030$). However, there was no significant difference in hypertension, coronary artery disease, hyperlipidemia, pseudophakia between the two groups ($P \geq 0.05$).

Table 1
Characteristics of the IMH patient cohort

Characteristic	IMH Group (n = 30)	Control Group (n = 32)	P
Age, (years)	63.0 ± 4.6	60.7 ± 5.2	0.071
Hypertension, n (%)	15 (50.0)	14 (43.8)	0.620
Coronary artery disease, n (%)	3 (10.0)	4 (12.5)	0.756
Hyperlipidemia, n (%)	17 (56.7)	12 (37.5)	0.131
Pseudophakia, n (%)	4 (13.3)	4 (12.5)	0.922
Plasma fibrinogen, (g/L)	3.0 ± 0.3	3.2 ± 0.5	0.034
LogMAR BCVA			0.030
Median	1.0	1.1	
Interquartile range	0.7–1.1	0.9–2.0	
Serum estradiol, (pg/mL)	18.9 ± 4.5	43.7 ± 6.1	0.000
Vitreous estradiol, (pg/mL)	121.2 ± 41.6	79.8 ± 10.1	0.000
IMH, idiopathic macular hole			

Correlations between serum and vitreous E2 levels and clinical variables

There was a significant correlation between serum E2 level and vitreous E2 level ($r = -0.440$) (Table 2 and Table 3). Vitreous E2 levels correlated significantly with age ($r = 0.315$) (Table 3). Serum E2 levels were not related to age and plasma fibrinogen ($P = 0.480$, $P = 0.217$, respectively) (Table 2). Vitreous E2 levels were not related to plasma fibrinogen ($P = 0.110$) (Table 3).

Table 2

Correlation of serum estradiol with age, plasma fibrinogen, and vitreous estradiol

Variable	r*	P
Age	-0.091	0.480
Plasma fibrinogen	0.159	0.217
Vitreous estradiol	-0.440	0.000
*Pearson correlation		

Table 3

Correlation of vitreous estradiol with age, plasma fibrinogen, and serum estradiol

Variable	r*	P
Age	0.315	0.013
Plasma fibrinogen	-0.205	0.110
Serum estradiol	-0.440	0.000
*Pearson correlation		

E2 levels in the postmenopausal IMH patients and the control group

The mean E2 in the serum samples obtained from the postmenopausal IMH patients was 18.9 ± 4.5 pg/mL, which was significantly lower than that in the controls (43.7 ± 6.1 pg/mL, $P < 0.001$) (Fig. 1). The mean E2 in the vitreous samples obtained from the postmenopausal IMH patients was 121.2 ± 41.6 pg/mL, which was significantly higher than that in the controls (79.8 ± 10.1 pg/mL, $P < 0.001$). In the two groups, E2 in the vitreous body was significantly higher than that in the serum ($P < 0.001$, respectively) (Fig. 1).

Discussion

To investigate the association of serum and vitreous estradiol with idiopathic macular hole in postmenopausal women, this study included 30 IMH patients and 32 controls at First Affiliated Hospital of Zhengzhou University in China. A number of previous studies have reported that elderly women are at a higher risk of developing an IMH than men (4,14,15), and in this study, we found that serum and vitreous E2 levels have a strong association with the occurrence of IMH in postmenopausal women.

As is known that aged population are more prone to develop an IMH, especially in the elderly women. As one of the important gonadal hormones for women, E2 also plays a part in the eyes besides the reproductive function. Changes in E2 levels may lead to changes in vitreous metabolism. Previous studies reported that E2 can restrain collagen gel from contraction through the regulation of retinal pigment epithelium (RPE) cells, and hence the decrease of E2 may erase the inhibition and affect vitreous collagen metabolism (16). In addition, E2 may influence vitreous collagen or the vitreoretinal interface through the intervention of the synthesis and metabolism of glycosaminoglycans (17,18), which is related to PVD, and then progress to IMH (19). It is also reported that E2 has an effect on hyaluronic acid metabolism from the influences of E2 on the production of hyaluronic acid in skin (20) and differences of the hyaluronic acid in the rabbit vitreous body after hormonal treatment (21). The biological activities of E2 are mainly mediated by their interaction with ERs. The expression of ER- α founded in the retina and RPE of young women, is undetected within the eyes of postmenopausal women, which indicates that age affects the expression of ERs (9).

In our study, E2 in the vitreous body is higher than that in the serum of IMH patients. Higher intraocular E2 levels in IMH patients supports the previous observation that E2 could be locally synthesized in retina (7). The formation of E2 in retina reportedly depends on the process of cholesterol synthesis and testosterone aromatization by the enzymatic activity regulations of cytochrome P450 side-chain cleavage enzyme (P450scc) and aromatase (7). The synthesis of E2 begins with the process of cholesterol synthesis that is converted into pregnenolone after the catalytic action of the cytochrome P450scc (7,22). And then, pregnenolone is converted into progesterone and androgen metabolites, and eventually into E2 with the action of aromatase (7,23).

Several reports have shown that cell migration and cell proliferation play a leading role in IMH pathogenesis (24). Migration of activated glial cells such as astrocytes and Müller cells from the retina to the vitreous surface can be induced by α -2-macroglobulin (α 2M) (25). Cell Proliferation along the vitreous surface and rearrangement of fibers in the vitreous cortex contribute to the vitreoretinal traction, which is widely thought an important mechanism in the formation of IMH (3). Furthermore, it has been found that epiretinal cell proliferation of glial cells occurs in the inner limiting membrane (ILM) at all stages of IMH (3,26). ILM is a scaffold of superficial hyperplasia tissue, and its centrifugal tension participates in the process of expanding the hole (27).

Reactive astrocytes are found conducive to the production of E2 by manifesting aromatase when injuries occur in the brain (28). Evidence also shows that expression of aromatase in embryonic rat RPE (29) and

the capillary of choroid of rats (30). Assuming that the glial cells in brain and retina are of the same characteristics, reactive astrocytes that migrate from the retina to the vitreous surface may express aromatase to promote E2 synthesis through testosterone aromatization procedure. However, the vitreous E2 in the control group was similarly higher than that in the serum, which may be due to the presence of a certain degree of vitreoretinal disorder, as we can not obtain the normal human vitreous. However, the reason for the difference in E2 levels between vitreous and serum has yet to be identified, and further investigation is required.

There are some limitations to this study that must be addressed. First, our subjects were selected from the Chinese population, so the findings may not be entirely used to determine IMH in other ethnic individuals. Second, we chose the patients undergoing a vitrectomy for uncomplicated primary RD as the control group due to the limited collection of the normal human vitreous. Therefore, it was unable to compare the E2 levels of IMH with normal people.

Conclusion

In conclusion, the findings of this study suggest that lower E2 levels in the serum and higher E2 levels in the vitreous body after menopause are associated with the occurrence of IMH. While further research should be undertaken to explore the reason for the difference in E2 between the eyes and blood circulation, and the role of E2 in the prevention and treatment of IMH.

Abbreviations

IMH:idiopathic macular hole; SD:standard deviation; E2:Estradiol; ERs:estradiol receptors; RD:retinal detachment; RPE:retinal pigment epithelium; P450scc:P450 side-chain cleavage enzyme; α 2M: α -2-macroglobulin; ILM:inner limiting membrane;

Declarations

Acknowledgements

Not applicable

Authors' contributions

KX for study design, acquisition, analysis, interpretation of data and drafting of the manuscript; RX, and GW for data collection, analysis and interpretation of data. GW for study concept, design, and supervision. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests

Funding

The current study was supported by the National Natural Science Foundation of China (NO. 81970824), the National Key R&D Program of China (NO. 2018YFA 0107304, NO. 2017YFA 0105000), the Plan For Scientific Innovation Talent of Henan Province (NO. 184200510005), Henan Natural Science Foundation Project (NO. 182300410363) and Medical Scientific and Technological Project of Henan Province (NO. 201601003).

Availability of data and materials

Not applicable.

Ethics approval and consent to participate

This study received the approval of the ethics committee of the First Affiliated Hospital of Zhengzhou University and written informed consent of all patients.

Consent for publication

The study was undertaken with the consent of all patients.

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Figures

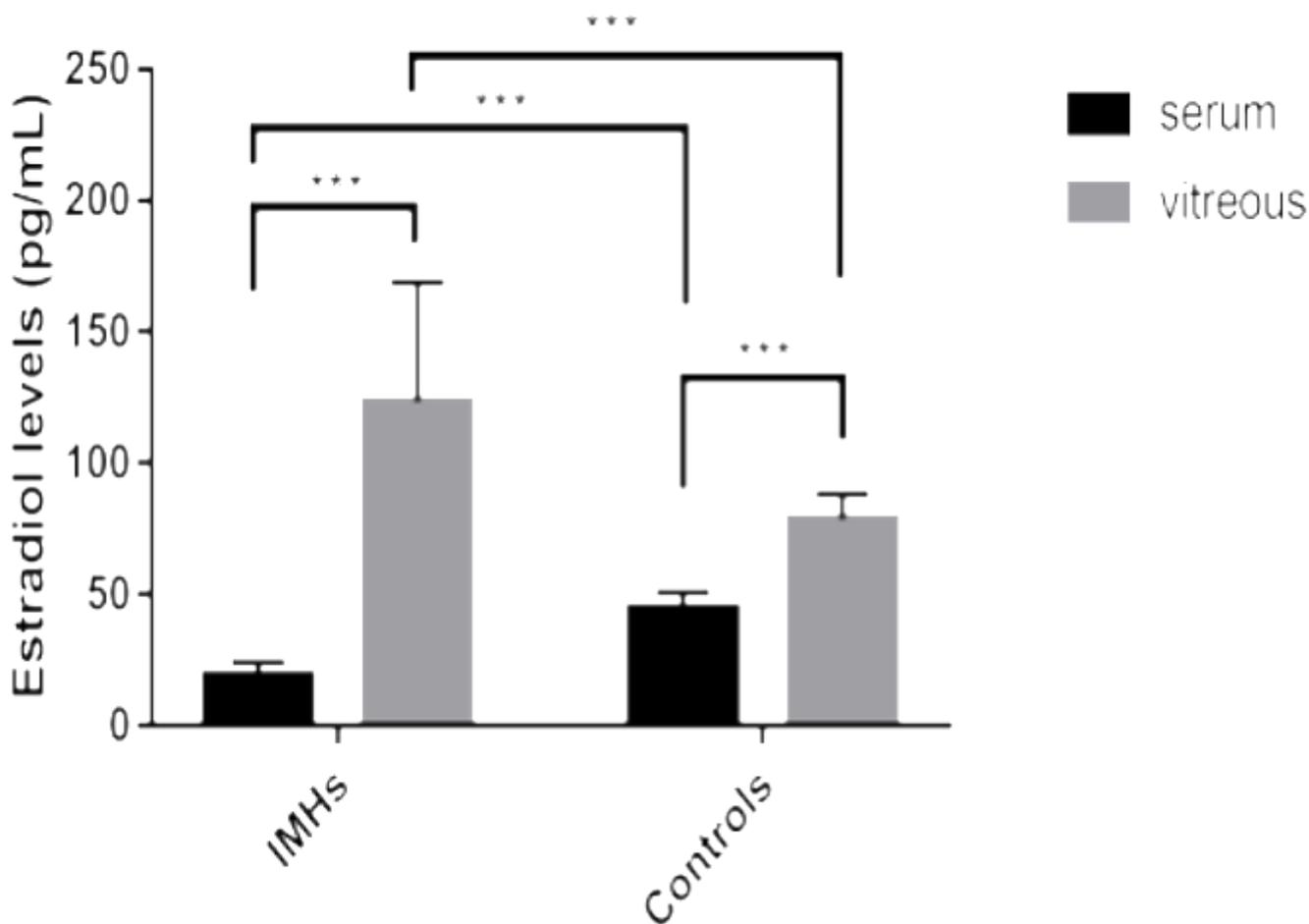


Figure 1

E2 levels (pg/mL) in the serum and vitreous in the postmenopausal IMH patients and the controls. The mean E2 level in the serum from the postmenopausal IMH patients was significantly lower than that in the controls. The mean E2 level in the vitreous from the postmenopausal IMH patients was significantly

higher than that in the controls. In the two groups, the E2 level in the vitreous body was significantly higher than that in the serum. Abbreviations: E2, estradiol; IMH, patients with an idiopathic macular hole.
*** P < 0.001