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Evaluation of the Effect of Postmenopausal Hormone Replacement Therapy on Pupil Size

Postmenopozal Hormon Replasman Tedavisinin Pupil Boyutuna Olan Etkisinin Değerlendirilmesi

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ABSTRACT Objective: Corneal refractive surgery has been gaining popularity among postmenopausal women over the past several years. Previous studies with different methods showed increased adrenergic activity in the postmenopausal period and suppressed sympathetic response with hormone replacement therapy. As pupil size may alter with sympathetic activity, we hypothesized that the success rate of corneal refractive surgery may be affected by hormone replacement therapy. The aim of this study was to evaluate the effects of hormone replacement therapy on pupil diameter. **Material and Methods:** Sixty-five healthy postmenopausal women who received hormone replacement therapy that was consisted of conjugated estrogen and medroxyprogesteron acetate have participated in this study. Pupil diameter was measured with an infrared pupillometer [OPD-Scan II Pupillometer/Corneal Wavefront Analyser ARK-10000 system (Nidek, Japan)] at the time of study enrollment and atleast 3 months (4.9 ±1.3) after the initiation of hormone replacement therapy. **Results:** Mean pupil diameters under mesopic/photopic conditions were 5.84±0.86mm/ 4.60±0.79mm before hormone replacement therapy and, 5.85±0.77mm/4.62±0.76 mm after hormone replacement therapy. The differences between 'before hormone replacement therapy' and 'after hormone replacement therapy' assessments were statistically insignificant (p=0,860 ve p=0,552 respectively). **Conclusion:** The effect of hormone replacement therapy on pupil size, either directly or via autonomic nervous system, was insignificant in postmenopausal women. However, it is recommended that the results of our study need to be confirmed by more detailed studies.

Keywords: Menopause; pupil size; hormone replacement therapy; autonomic nervous system

ÖZET Amaç: Son yıllarda korneal refraktif cerrahi, postmenopozal kadınlar tarafından da giderek daha fazla rağbet görmektedir. Farklı yöntemler ile yapılan daha önceki birçok çalışma menopoz sonrası dönemde adrenerjik aktivitenin arttığını ve hormon replasman tedavisi ile sempatik cevabın baskılandığını göstermiştir. Pupil çapının sempatik aktivite ile değişkenlik gösterdiği düşünülürse, hormon replasman tedavisinin korneal refraktif cerrahi başarısını etkileyebileceği öngörülmüştür. Bu çalışmanın amacı hormon replasman tedavisinin pupil çaplarına olan etkisini değerlendirmektir. **Gereç ve Yöntemler:** Konjuge östrojen ve medroksiprogesteron asetat içeren hormon replasman tedavisi kullanan 65 sağlıklı postmenopozal kadın çalışmaya dahil edildi. Pupil çapı, hormon replasman tedavisi kullanımı öncesi ve tedavi başlangıcından en az 3 ay geçtikten sonra (4,9±1,3), infrared pupillometre [OPD-Scan II Pupillometer/ Corneal Wavefront Analyser ARK-10000 sistem (Nidek, Japan)] ile ölçüldü. **Bulgular:** Mezopik ve fotopik koşullarda ortalama pupil çapları hormon replasman tedavisi öncesi sırasıyla 5,84±0,86 mm /4,60±0,79 mm ve hormon replasman tedavisi sonrası sırasıyla 5,85±0,77 mm / 4,62±0,76 idi. Hormon replasman tedavisi öncesi ve sonrası yapılan pupil çapı ölçümleri arasındaki fark istatistiksel olarak anlamlı değildi (sırasıyla p=0,860 ve p=0,552). **Sonuç:** Sonuç olarak, çalışmamızda hormon replasman tedavisinin, post menopozal kadınlarda direkt veya otonom sinir sistemi aracılığı ile pupil çapını anlamlı düzeyde etkilemediği saptanmıştır. Ancak, çalışmamızda elde ettiğimiz bu sonuçların çok daha geniş kapsamlı araştırmalarla desteklenmesi gerekmektedir.

Anahtar Kelimeler: Menopoz; pupil çapı; hormon replasman tedavisi; otonom sinir sistemi

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For many years, there has been increasing interest in the use of corneal refractive surgery in the elderly, especially on postmenopausal women with hormone replacement therapy (HRT). The pupil has a considerable impact on the surgical outcome.[1-4] If there are large changes in the pupil size, there could be a significant amount of decentration in the ablation zone.

Increased sympathetic activity is reported to occur in postmenopausal women.[5,6] Hormone replacement therapy has been found to decrease sympathetic activity and serum norepinephrine levels in postmenopausal women.[7,8] Determination of pupil size in response to light serves information about the sympathetic and parasympathetic innervation of the pupil. We know also the presence of estrogen and progesterone receptors in various ocular tissues including the iris.[9] Therefore the pupil size can be affected by hormonal and autonomic changes and also its innervational features can serve to analyze autonomic dysfunctions.[10-12] In the previous study, we found that HRT has no effect on refractive status and wavefront aberrations of the eye.[13]

In this study, we hypothesized that HRT can affect the pupil diameter via reducing sympathetic-adrenergic reactivity or directly by stimulating estrogen and progesterone receptors found in the iris and we investigated the effect of HRT on pupil size under mesopic and photopic conditions in postmenopausal women.

MATERIAL AND METHODS

The present study was started after the approval of Gulhane Military Medical Academy Ethics Committee (Y.ETIK KRL.:1491-367-07), Turkey and conducted in accordance with international agreements and the Declaration of Helsinki. Sixty-five healthy postmenopausal women participated in the study. Informed consent was obtained from each patient. Only the right eyes of the subjects were included in the study. None of the subjects had previously received any form of HRT.

They had more than one year from their last menstrual period and serum estradiol concentration was 40 pg/mL or less before study enrollment. Subjects were excluded if they had a history of systemic or neurologic disorder affecting pupil size including diabetes, intraocular surgery or trauma throughout the previous years, use of ocular medications during the last one year and patients with pupil abnormalities (e.g. Holmes-Adie syndrome). Those currently using systemic medications known to affect pupil size or tone such as opioids, autonomic agents, and migraine medications were also excluded. Patients meeting these criteria underwent an extensive evaluation including a comprehensive ophthalmic history and examination.

All patients received HRT that consisted of 0.625 mg/day conjugated estrogen and 5 mg/day medroxyprogesterone acetate in a continuous combined regimen (Premelle®, Wyeth).

Pupil size measurements were performed using the pupillometer incorporated in the Optical Path Difference Scan (OPD-Scan, Nidek Co., Gamagori, Japan). It uses an infrared detector to capture the pupil image in different illumination conditions. The software automatically provides pupillometric measurements (Figure 1). Two measurements were performed for each participant, first as a baseline before HRT and the second least 3 (4.9±1.3) months after starting the HRT. All measurements were performed in the afternoon (3:00 -5:00 PM). The pupil camera captured images of each eye in a closed, dark room under two natural undiluted illumination conditions

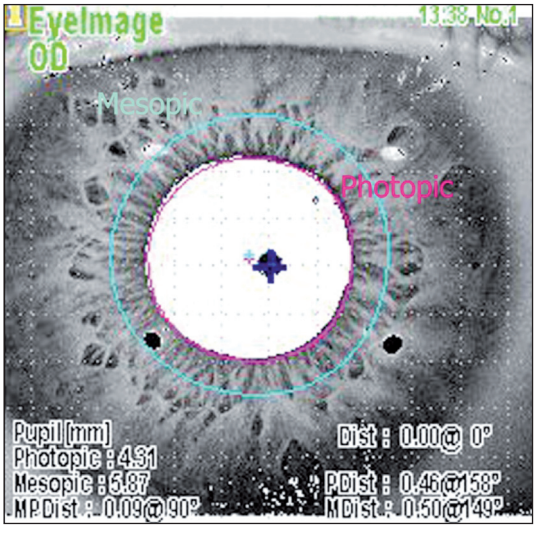

FIGURE 1: An OPD scan image of a patient's right eye. Inner purple circle represents the border of photopic pupil position which is 4.31 mm and outer cyan circle represents the border of mesopic pupil position which is 5.87 mm.

(mesopic: 10 lux, photopic: 100 lux) that is automatically provided with the device (Figure 1).

Results were evaluated with statistical analysis software (SPSS 15.0 for Windows, SPSS Inc., USA). Normality of the data was first tested using the normal probability plots, Kolmogorov-Smirnov, and Shapiro-Wilk tests. Statistical differences were considered significant at $p<0.05$. Means before and after the HRT were statistically evaluated using the Wilcoxon signed ranks test.

RESULTS

Follow-up examinations were completed in all patients. The mean patient age was 50.8±2.6 (range: 47-56) years and the mean duration of menopause was 2.6±0.7 (range: 1.5-3.4) years.

No significant difference was noted in the mean pupil diameter under photopic and mesopic conditions before and after HRT (p=0,552 and p=0,86 respectively) (Table 1).

DISCUSSION

There are many reports about decreased adrenergic activity and circulating catecholamines in postmenopausal women who receive HRT.[8,14,15] Besides, the magnitude of the reduction of circulating noradrenaline was found to be related to the magnitude of the increase in circulating estradiol.[14] The suggested mechanisms of effects of estrogens on norepinephrine secretion are induction of catecholamine synthesis, provoked adrenergic response via increased gamma2-adrenergic and beta2-adrenergic receptor numbers and cell membrane reactivity by acting through the Ca^{+2} channel.[9,16-18] It is well known that decreased sympathetic activity causes miosis. Because of the decreased sympathetic response and noradrenaline levels after HRT, it was expected that the pupil diameter would be smaller. However, in our study, both mesopic and photopic pupil diameters did not significantly change after HRT. Besides, although not significant, both mean mesopic and photopic pupil diameters were larger after HRT. This might be due to the unresponsiveness of pupil diameter to HRT or some other mechanisms that can counteract against the decreased adrenergic effects of HRT such as stimulation of sex steroid hormone receptors that are found in the iris.[9,19]

An exact measurement of pupil diameter is an important key point in corneal refractive surgery. During preoperative patient evaluation, laser ablation size is determined in accordance with mesopic pupil size. If mesopic pupil size is greater from than the ablation size, patients may suffer significant visual complaints such as night glare, haloes and image ghosting after surgery.[20] Therefore; pupil size, especially in mesopic conditions, and medications that affect pupil size are important in preventing visual complaints. Pupil size is also important during cataract surgery. A small pupil which is resistant to pupil dilation attempts may complicate a cataract surgery.[21] Whence, cataract surgeons may be cocerned about suppressed sympathetic response that may cause difficulty in pupil dilation. Thankfully, pupil size does not seem to be effected by HRT.

It is well known that the pupil diameter decreases with age.[1] Despite this fact, in a recent study, Khanani et al. could not find a significant variation

TABLE 1: Mean pupil diameters in millimeters under mesopic and photopic conditions, before and after HRT.

Pupil condition	Before HRT (mm) Mean±SD (range)	After HRT (mm) Mean±SD (range)	p*
Photopic	4.6±0.79 (2.63 to 6.09)	4.62 ±0.76 (3.16 to 6.14)	0.552
Mesopic	5.84±0.86 (3.26 to 7.55)	5.85 ±0.77 (4.13 to 7.34)	0.860

HRT: Hormone replacement therapy; SD: standard deviation, *Wilcoxon signed ranks test.

in the dark-adapted pupil diameter in healthy subjects over a 6-month period. They proposed that the decrease in pupil diameter occurs in decades, not over a short period such as six months.[22] Therefore; we would not expect that there would be a significant contribution of aging to pupil diameter in 6 months, in our study.

Our patients received oral HRT consisted of 0.625 mg/day conjugated estrogen and 5 mg/day medroxyprogesterone acetate in a continuous combined regimen. However, the effects of HRT might change depending on the dosage and the administration route. In our study, oral HRT was used, whereas transdermal HRT might have better bioavailability. In this study, we did not measure the serum estradiol concentration at the sixth-month follow-up that might show the differences in the bioavailability of the treatment among patients, despite a standard constant regimen. This is the main drawback of this study. Moreover, the effects of HRT might change depending on the duration of the therapy. Therefore, studies with longer follow-up, with larger groups and perhaps with different administration routes are called for further to investigate the effects of HRT on the pupil diameter.

In this era of surgical correction of refractive errors, a thorough evaluation of all the factors should be sought to obtain a perfect visual outcome, especially in those under medications affecting dependable factor of the refractive status of the eye and the pupil.

CONCLUSION

In conclusion, we showed that HRT does not significantly affect the pupil size in photopic and mesopic state in postmenopausal women directly or indirectly with autonomic system. We propose that refractive surgeons shouldn't hesitate to perform keratorefractive surgery because of pupil size alterations in postmenopausal women under HRT.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Üzeyir Erdem, Salih Altun, Ümit Yolcu;* ***Design:*** *Üzeyir Erdem, Salih Altun, Abdullah İlhan, Ümit Yolcu;* ***Control/Supervision:*** *Üzeyir Erdem;* ***Data Collection and/or Processing:*** *Abdullah İlhan, Ümit Yolcu;* ***Analysis and/or Interpretation:*** *Abdullah İlhan, Ümit Yolcu, Salih Altun;* ***Literature Review:*** *Abdullah İlhan, Ümit Yolcu;* ***Writing the Article:*** *Abdullah İlhan, Ümit Yolcu;* ***Critical Review:*** *Üzeyir Erdem, Salih Altun;* ***References and Fundings:*** *Üzeyir Erdem,* ***Materials:*** *Ümit Yolcu, Salih Altun.*

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