An objectıve method to determıne corneal changes durıng menopause

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Summary

Objective: We hypothesized that menopause has a measurable effect on corneal thickness. The aim of this study was to evaluate central corneal thickness (CCT) differences between women in the premenopausal and postmenopausal period. *Methods*: A prospective, case-control, single-blind study was designed. Two groups were included: Group I (premenopausal period) and Group II (postmenopausal period). Forty women were recruited in each group. The correlation between CCT with age, estradiol (E2) and follicle stimulating hormone (FSH) levels were evaluated. *Results*: CCT was significantly decreased in postmenopausal women compared to premenopausal women (521.18 ± 37.97 μm 561 ± 42.84 μm, respectively, $p < 0.005$). Similarly, there was a linear correlation between CCT and serum E2 levels of patients overall ($p < 0.01$). *Conclusion:* The data presented in this study suggest that menopause causes corneal changes, which may be documented by central corneal thickness measurement.

Key words: Cornea; Eye; Menopause; Estradiol.

Introduction

The ovary is unique in that age associated with a decline in function (to frank failure) appears to have remained constant, despite the increase in longevity experienced by women over the last century. Because the loss of ovarian function has a profound impact on the hormonal milieu in women, and also on the subsequent risk for the development of disease via the loss of estrogen production, improving our understanding of reproductive aging is critical to care for all women. It is now accepted that the cessation of menses for one year and/or increase in serum FSH levels above 40 IU/ml and decrease in serum estradiol levels below 100 pg/ml are essential for a diagnosis of menopause. Menopause occurs at a median age of 51.4 years, with the normal age range in women being 42-58 years. The age of menopause appears to be determined largely by genetics, and it is due to exhaustion of the oocyte pool. Menopause and the years preceding are characterized by hormonal changes, decline in reproductive potential, and increased risk for physical and psychological changes [1].

Several visual system abnormalities have been reported with menopause and hormonal status. Corneal changes are the most common. In the United States, it has been reported that 3.2 million women who are over 50 years old are inflicted with dry eye and corneal problems [2-5]. Epidemiologic studies reported that corneal variables including corneal thickness, curvature, and sensitivity could be regulated by sex hormones; however, the mechanism of this phenomenon is not apparent. These variables of the cornea are considered to be important parameters for contact lens wear, or a patient who is a candidate for corneal surgery. A change in thickness during the menstrual cycle of women and each trimester of pregnancy has also been reported [6, 7]. These cyclic changes are attributed to hormonal influences. Variations in corneal thickness may be enough to cause changes in visual performance. No report has been published about the changes of corneal thickness between premenopausal and postmenopausal women.

In this study our aim was to evaluate the central corneal thickness differences between women in the premenopausal and postmenopausal period.

Materials and Method

Study design

A prospective randomized, single-blind, case-control study was undertaken in 2006. Two groups were formed: Group I (premenopausal period) and Group II (postmenopausal period). Forty women aged between 40 and 50 years were recruited in each group to check for differences in corneal changes during menopause. Women over 50 years old were excluded. Thus, both Group I and II were in the same age group ($p > 0.05$). Women undergoing hormone replacement therapy, suffering from hypertension, diabetes mellitus, wearers of contact lenses, who had previously had corneal pathology, and who had had prior ocular surgery or dry eyes were also excluded from the study. We assessed FSH and E2 levels in the blood samples of postmenopausal women and undertook routine examinations of the premenopausal women on the third day of menstruation. This was done to standardize the time during which E2 levels were evaluated. Women who had had cessation of menses for one year and serum FSH levels above 40 IU/ml were defined as being in the postmenopausal period. The study was performed in accordance with the ethical standards that were reviewed in the Helsinki Declaration. Approval of the ethical committee of the institution was obtained. All subjects were informed of the study, and they participated of their own will and gave written consent.

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Measurment of the corneal thickness

All women were recruited from the outpatient clinic of the Department of Obstetrics and Gynecology, University of Istanbul. These women were sent to the Department of Opthalmology of the university, in accordance with the single-blind study design. Central corneal thickness values were taken and ultrasound (US) was used for evaluation (ultrasound pachometry is the most reliable method for the measurement of central corneal thickness [8]). The mean inter-observer difference for US pachometry was 0.001 mm (SD 0.009; SE 0.0015) and the mean intra-observer difference was 0.002 mm (SD 0.011; SE 0.0019)(5). Central corneal thickness (CCT) was measured by a Alcon Handheld Ultrasonic Pacimeter (Alcon, INC, Irvine, CA, USA). Measurements were taken in the sitting position, a local anesthethic (one drop of benoxinate) was applied, and the patients were asked to look straight ahead. The corneal center was detected by determining corneal light reflex where the US probe was set at 1.5 mm temporal to light reflex. The CCT was measured five times for each eye and the average of these readings was taken. Measurements were recorded from 10 a.m. to 12 p.m. to prevent diurnal variation.

Statistical analysis

Age is expressed as the median (min-max) values. Central corneal thickness and E2 levels are expressed as the mean ± SD values. The differences in Groups I and II according to the variables were evaluated by the t-test. Correlations between central corneal thickness and E2 levels were evaluated by Pearson's correlation test.

Results

Mean age of Groups I and II was 43.65 ± 2.85 (range 40-49) and 46.05 ± 2.56 (range 41-49). There was no significant statistical difference between the two groups according to age (Table 1).

Mean ± SD E2 levels in Groups I and II were 250.14 ± 190.62 pg/ml; and 33.11 ± 24.80 pg/ml, respectively. As expected E2 levels were significantly lower in the postmenopausal group compared to the premenopausal women ($p < 0.005$, u = 0.00) (Table 1).

Mean ± SD CCT values in Groups I and II were 561 ± 42.84 and 521.18 ± 37.97 μm, respectively. In Group II, central corneal thickness was significantly lower ($p < 0.005$, t = 3.12) (Table 1).

Correlation tests between CCT and E2 levels were performed. Central corneal thickness significantly correlated with menopause and E2 levels ($p < 0.01$, r = –0.051).

Table 1. — *Comparison of central corneal thickness, E2 and age in the groups*.

	CCT Mean ± SD (micrommeters)	E2 Mean ± SD (pg/ml)	Age Mean ± (year)
Group I (premenopausal period n = 40)	561 ± 42.84	250.14 ± 190.62	43.65 ± 2.85 (range 40-49)
Group II (postmenapausal period n = 40)	521.18 ± 37.97	33.11 ± 24.80	46.05 ± 2.56 (range 41-49
p values for pairwise group*	$p < 0.005$ t = 3.12	$p < 0.005$ u = 0.00	ns

*$p < 0.05$ is statistically significant (t-test values); CCT = central corneal thickness; E2 = estradiol; ns = not significant.

Discussion

Sex steroid hormones are present in all tissues of the body as they are circulated through the blood; however, their effects are seen only in cells that are armed with the corresponding receptors. Studies have shown the presence of sex steroid hormone receptors in various ocular tissues such as the lens, retina, choroid, cornea, iris, ciliary body, lacrimal gland, meibomian gland, lid, and palpebral and bulbar conjunctiva. They are also found in the nuclei of human corneal epithelial, stromal and endothelial cells [9-11].

Some of the earlier epidemiologic and laboratory studies revealed that the effect of sex steroids cause changes in the eye with increased age such as age-related macular degeneration (AMD), an idiopathic full-thickness macular hole, age-related cataract, tear function and dry eye [12-17]. Although specific sex hormone receptors have been shown in some tissues of the eye, the pathophysiologic process of sex steroids is not clear.

Menstrual cycle variations of corneal thickness, curvature, and sensitivity have been reported [18]. Millodot and Lamot suggest that the change in corneal sensitivity during the premenstrual phase may be due to a generalized increase in water retention or an increase in intraocular pressure [19]. Kiely *et al*. found steepening central curvatures in both horizontal and vertical meridians at the beginning of the cycle with flattening occurring after ovulation; in addition, cyclic changes in corneal thickness during the menstrual cycle and thickening of the cornea at ovulation were also found [20]. Giuffre *et al*. investigated that the thinnest cornea at the beginning of the cycle with significantly thicker at ovulation and at the end of the cycle, without substantial differences between the last two time points. Therefore, the thicker central cornea is found immediately after the peak of plasma E2 that occurs during the cycle [21].

Moreover, Sanchis-Gimeno *et al*. studied and compared corneal thickness values of postmenopausal women with and without dry eye [2]. They showed that postmenopausal women with dry eye had reduced corneal thickness values at each corneal location when compared with postmenopausal women without dry eye. They advocated that the decrease in corneal thickness was because of eye dryness, and this was not specific to menopause. They believed that a longer duration of dry eye symptoms might be the cause of reduced corneal thickness values found in postmenopausal women. However, they did not study and compare the corneal thickness values of premenopausal women with that of postmenopausal women. We have not found any literature studies of such comparison.

This study measured the corneal thickness values of postmenopausal women and compared the results with those of premenopausal women. We found that corneal thickness had significantly lower mean values in postmenopausal than in premenopausal women. Some evidence seems to confirm that hormones may play a role in corneal thickness, especially estrogen. Weinreb *et al*. showed that pregnant women had a central corneal thick-

ness that was greater than the control group, and they suggest that hormonal changes during pregnancy leads to retention of water in the cornea, with a concomitant increase in corneal thickness [22]. Affinito *et al*. studied the effects of hormone replacement therapy (HRT) on corneal thickness in postmenopausal women and discovered a thicker cornea in subjects receiving HRT with 17β-estradiol compared with untreated, control women, although the difference between the two groups was not significant [23]. However, there was a significant linear correlation between corneal thickness and serum E2 levels in our study. We found elevated E2 levels on the third day of menstruation. In our opinion, there were two reasons for this result: first, even though we accepted cyclic women with a 28-day period, E2 levels of women aged 40-50 years were unstable. Second, in five patients, E2 levels were higher than expected, thus the median was calculated as above the standard level, so the standard deviation was high.

A potential indirect mechanism of estrogen that could also have an impact on corneal thickness needs to be taken into account. Stefano *et al*. reported that physiological doses of estrogen immediately stimulate nitric oxide release from human endothelial cells through activation of a cell-surface estrogen receptor that is coupled with increase in intracellular calcium [24]. Yanagiya *et al*.*'s* investigations on the rabbit cornea suggested that nitric oxide is produced in the corneal endothelium, and that the nitric oxide/cyclic GMP pathway is involved in the maintainance of corneal thickness [25]. Thus estrogen may have an indirect impact on the cornea.

These reports seem to show a strong association between corneal thickness and female hormone levels, particularly estrogen levels. Estrogens reach the cornea through the tears and aqueous humor, and it is not apparent whether a hormonal influence is exerted through direct interaction in the cornea or via the secondary effects such as systemic water retention by estrogen-induced up-regulation of the renin-aldosterone system, dry eye, and nitric oxide mechanism. Further and more detailed studies are needed to reevaluate the reasons why postmenopausal women have thinner corneas.

Conclusion

The results of this study suggest that corneal thickness is significantly correlated with menopause and E2 levels. These data merit further study to evaluate the role of central corneal thickness measurements to document corneal changes during menopause in women, with the intention of objective clinical visual system evaluation.

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