Dosage-dependent reduction of macular pigment optical density in female breast cancer patients receiving tamoxifen adjuvant therapy

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Abstract

It is now increasingly common for breast cancer patients to receive adjuvant tamoxifen therapy for a period of up to 10 years. As survival rate increases, managing tamoxifen ocular toxicities is important for patients' quality of life. Macular pigments in photoreceptor cells protect against free radical damage, which can cause macular degeneration. By reducing macular pigment concentration, tamoxifen may increase the risk of macular degeneration. Here, we compared macular pigment optical density (MPOD) and central macular thickness between breast cancer patients on tamoxifen adjuvant therapy (n = 70), and a control group (n = 72). Multiple regression analysis indicated that MPOD decreases with increasing tamoxifen dosage, up to a threshold of about 20 g, after which MPOD plateaus out. Mean MPOD in the treatment group (mean = 0.40) was significantly lower (p-value = 0.02) compared to the control group (mean = 0.47) for the left eye, and for the right eye (treatment mean = 0.39; control mean = 0.48; p-value = 0.009). No significant difference in mean central macular thickness was found between the treatment and the control group (p-values > 0.4). In the control group, MPOD and central macular thickness showed significant correlation (r ~ 0.30; p-values < 0.01) for both eyes. However, in the treatment group, loss of significant correlation was observed in the left eye (r = 0.21; p-value = 0.08). The present results show that MPOD decreases non-linearly as a function of tamoxifen dosage, and highlight the potential of tamoxifen to reduce macular pigment concentration through an unknown mechanism that does not depend on macular thinning solely.

1. Introduction

Long-term adjuvant tamoxifen therapy is now firmly established as an effective clinical intervention that saves the lives of breast cancer patients [1–6]. Originally, adjuvant tamoxifen therapy was continued for up to 5 years; however, data indicating enhanced efficacy with up to 10 years of therapy means that some women will be using tamoxifen for up to a decade [2]. Cumulative evidence from several large randomised clinical trials strongly indicates that tamoxifen is also effective for the prevention of breast cancer in healthy women [7–11]. As more and more women benefit from the use of tamoxifen, the side effects of being exposed to long-term usage of tamoxifen need to be addressed. A potentially life-threatening side effect is the elevation of the risk of endometrial cancer [12]. However, the most commonly reported side effect is postmenopausal symptoms that can impact the patients’ quality of life [13].

Tamoxifen-induced ocular toxicities such as crystalline retinal deposits were first noted in 1978 among women receiving extremely high dosage to tamoxifen (120–320 mg/day) [14]. Other complications include macular edema [15], retinopathy [16] and keratopathy [17]. Patients receiving high-dosage tamoxifen may develop extensive retinal lesions, and become visually impaired as a result of macular edema [18]. The increased risk for developing cataracts when tamoxifen was used for 5 years or more has been
reported [19]. For some women below 50 years old, tamoxifen can affect the optic nerve head by causing subclinical swelling within the first two years of use [20]. Tamoxifen maculopathy in the form of microcystoid maculopathy [21] and crystalline maculopathy [22] have also been reported. While tamoxifen retinopathy may be uncommon (prevalence ~ 3.1%) [23], it can result in foveal cystoid spaces that increase the risk for macula holes [20].

From a theoretical point of view, tamoxifen-induced retinal pigment epithelium (RPE) cell death may be expected to correlate with a reduction in the availability of macular pigment (MP), which is measurable in the form of macular pigment optical density (MPOD). The MP comprises three isomeric carotenoids: meso-zeaxanthin, lutein, and zeaxanthin. These pigments accumulate in high concentrations at the macula [24,25]; they protect the photoreceptor cells by filtering blue light, and by quenching reactive oxygen species (ROS) [26–28]. Furthermore, by attenuating oxidative injury at the macula, MP potentially protects against age-related macular degeneration [29–31]. Supplementing diets with meso-zeaxanthin, lutein, and zeaxanthin is known to improve visual performance [31].

The present study aims to model variation in MPOD as a function of central macular thickness and tamoxifen dosage. To this end, we used a treatment group consisting of female breast cancer patients who received tamoxifen treatment, and a comparable control group.

2. Materials and methods

2.1. Study design

The present study is cross-sectional. It adheres to the Declaration of Helsinki and Good Clinical Practice guidelines. Institutional Review Board approval (MREC ID No. 20164-2395) was obtained from the Medical Ethics Board of University of Malaya Medical Centre (UMMC). Prior to enrolment of each breast cancer patient and control subject, written informed consent was obtained.

2.2. Study population

Breast cancer patients were recruited from the UMMC Breast Clinic, and the UMMC Oncology Clinic. Healthy volunteers were recruited from relatives of accompanying patients, and UMMC hospital staff. The study was conducted from 1 December 2016 until 1 June 2017 at the UMMC Eye Clinic.

2.3. Patient selection

In this study, the case subjects were recruited from female breast cancer patients attending the UMMC Oncology Clinic who received tamoxifen (standard dosage of 20 mg per day) as an adjuvant endocrine therapy. If they received radiotherapy, only those who had it confined to the thoracic region were included. The acceptable cancer stage was limited to stage 0, I or II. Diabetic patients were included only if diabetic retinopathy has been excluded at screening.

Subjects were excluded from the study if they met any of the following criteria: having received chemotherapy, had late stage (stage III) or metastatic breast cancer, had history of radiotherapy applied to the head and neck (inclusive of supraclavicular) region, or had one or more of the following ocular pathologies: pre-existing retinal diseases, macular diseases, glaucoma, cataract or vitreoretinal surgery, ocular trauma, optic neuropathy, intraocular pressure of 21 mmHg or higher, media opacity (corneal scar, dense cataract, dense asteroid hyalosis, etc.), and poor optical coherence tomography (OCT) signal (<6/10). We also excluded patients who

had taken the following medications: hydroxychloroquine, chloroquine, thiordizine, desferoxamine, topiramate, epinephrine, digoxine, sildenafil and/or lutein and zeaxanthin supplements.

Female control subjects were recruited from healthy volunteers who had best corrected visual acuity of 6/12 or better, and normal morphology on spectral domain optical coherence tomography (SD-OCT). As far as possible, the control and the case subjects were matched with respect to age (±3 years difference), ethnicity, and diabetes status.

2.4. Data collection

Subjects who passed the inclusion-exclusion criteria underwent sequential examination consisting of visual and refraction acuity test, spherical equivalent measurement (TopCon KR-8100 Autorefractor Keratometer), undilated slit-lamp biomicroscopy examination, OCT of macula (Model 4000; Carl Zeiss Meditec AG, Germany), measurement of MPOD (MPS II; Tinsley Precision Instruments, UK) and finally, a fully-dilated fundus examination. Relevant demographic and clinical data were collected from the subjects. For calculation of total tamoxifen dosage ever received, the daily consumption dosage of 20 mg/day was multiplied by the number of days from the date of commencing tamoxifen treatment until the day when subjects had their MPOD measured.

2.5. MPOD measurement

MPOD was measured at 0.5° and 7.0° foveal eccentricities. The target was a solid disk of 0.5° arc radius. A small black dot at the centre of the solid disks is meant to facilitate fixation. The wave length composition of the test stimulus alternated between 460 nm (peak MP absorbance) and 540 nm. To measure the parafoveal region, the subjects were asked to fixate on a red light located precisely at 7.0° from the central fixation area.

The patients were trained so that they were able to recognize the null zone (zone of no or minimal flicker). The subjects only had to respond when they first perceive a flicker by pressing a button. Throughout a series of pre-set blue-green luminance ratio, the frequency of blue-green alternation automatically decreases. The MPs in the fovea attenuate the blue component of the stimulus; thus, to perceive a minimal flicker, a greater intensity of blue light is required. This is more so while looking at the stimulus directly as compared to when the stimulus is viewed from the periphery.

Viewing the target eccentrically (while the eye being tested fixates on the peripheral fixation target) means that the observer is actually utilising a part of the retina where MPs are presumed to be absent. As the MPs are absent there, the intensity ratio at which minimum flicker is obtained would differ from the foveal one. The MPOD is calculated as the log_{10} of the ratio of the intensity of blue light needed to perceive minimal flicker directly, to the intensity of blue light needed to perceive minimal flicker from peripheral fixation.

2.6. Statistical analyses

To demonstrate comparability of the control and the treatment group, we performed two-sample t-tests to assess whether mean age, body mass index (BMI), spherical equivalent, and best corrected visual acuity differed significantly between the two groups. For ethnicity and diabetes status, we used the chi-squared test of association between two categorical variables.

For testing whether mean macular thickness and mean MPOD differed between the control and the treatment group, the two-sample t-test was also used. Multiple linear regression analysis was used to evaluate whether central macular thickness, dosage of
tamoxifen, diabetes status, and diabetes-dosage of tamoxifen interaction, were significant predictors of MPOD (full model). The final regression model was built by including only statistically significant predictors from the full model. To investigate the dependence of MPOD on central macular thickness in both eyes for the treatment and the control group, we used the Pearson correlation test. Finally, a polynomial (of degree two — i.e. quadratic) loss curve was used to model the dependence of MPOD on tamoxifen dosage. For all statistical tests, the level of statistical significance was set at 5%. All analyses were done using R Version 3.2.1 [32].

3. Results

3.1. Patient characteristics

A total of 70 female breast cancer patients, and 72 female control subjects, were enrolled into the study. There were 15 female breast cancer patients and 11 control female subjects who had Type 2 diabetes. None of the patients showed obvious tamoxifen-induced maculopathy on clinical examination. Table 1 shows the summary statistics of clinical and demographic variables. Both the treatment and the control group were comparable with respect to these variables, as indicated by the lack of statistically significant differences.

For the treatment group, the majority of breast cancer patients were diagnosed with Stage I (71%; 50/70) breast cancer, followed by Stage II (17%; 12/70) and Stage 0 (11%; 8/70). About 54% (38/70) received breast-conserving surgery, while the remainder received mastectomy (32/70). Median duration of tamoxifen usage was about 20 months (min –1 month; max –54 months). With respect to the three breast cancer markers (ER, PR, HER2), all patients (70/70) were ER positive. About 83% (58/70) were PR positive. HER2 phenotyping was deemed unnecessary for two stage 0 patients; close to half of the patients were HER2 negative (49%; 33/68), a quarter were HER2 positive (24%; 16/68), and about 28% had equivocal results (19/68).

3.2. Multiple linear regression analysis

For the right eye, central macular thickness was a significant predictor of MPOD, and dosage of tamoxifen was marginally significant (Table 2). For the left eye, only central macular thickness was a significant predictor of MPOD. For consistency, the final multiple linear regression model was rerun with only central macular thickness and dosage of tamoxifen for both eyes (Table 3).

The final multiple linear regression model can be interpreted as follows. On average, every increase of 10 \( \mu \text{m} \) in central macular thickness increases MPOD by about 0.02–0.03, and every increase of 10 g in tamoxifen dosage decreases MPOD by about 0.04. This means that, on average, a normal female subject with central macular thickness of 250 \( \mu \text{m} \) has MPOD of 0.5; for a female subject with the same central macular thickness but has taken about 40 g of tamoxifen (the dosage for about 5 years), she is expected to have MPOD of about 0.3.

For the final multiple linear regression model considered, only about 13% (left eye) to 18% (right eye) of variation in MPOD was accounted for by central macular thickness and dosage of tamoxifen, suggesting that a large amount of variation in MPOD is due to variables not included in the present study.

3.3. MPOD as a function of tamoxifen treatment duration

The result of the two-sample t-test shows that mean MPOD differed significantly (\( \text{p-value} = 0.02 \)) between the treatment (mean = 0.40) and the control group (mean = 0.47) by about 0.1 for the left eye, similarly so for the right eye (treatment mean = 0.39; control mean = 0.48; \( \text{p-value} = 0.009 \)). The inclusion of diabetic subjects in both groups did not appear to introduce substantial bias into the estimate of mean MPOD in the control and the treatment group (Table 4), because the difference in estimated mean MPOD between the diabetic subgroup and the non-diabetic subgroup within the control and the treatment group is approximately equal (rounded to 1 decimal place), and the relative size of diabetic to non-diabetic subjects was only about 1 to 4 (Table 1).

The difference in MPOD between the two groups is unlikely to be accounted for by difference in mean central macular thickness, as no statistically significant difference was detected either in the right (treatment mean = 241 \( \mu \text{m} \); control mean = 242 \( \mu \text{m} \); \( \text{p-value} = 0.72 \)) or the left eye (treatment mean = 239 \( \mu \text{m} \); control mean = 242 \( \mu \text{m} \); \( \text{p-value} = 0.46 \)). Consequently, MPOD change can be studied simply as a function of tamoxifen dosage in the treatment group. There appears to be a trend for MPOD to decrease as tamoxifen dosage increases, in both the right (Fig. 1a) and the left

### Table 1

Patient characteristics in the treatment and the control group. The rightmost column gives the \( \text{p-value} \) for tests of equality of mean (t-test) between the treatment and the control group (Age, BMI, spherical equivalent, best corrected visual acuity), and chi-squared tests of independence (ethnicity, diabetes). Summary statistics for age and BMI are given as mean ± 1 standard deviation (SD).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Treatment</th>
<th>Control</th>
<th>( \text{p-value} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>54 ± 7</td>
<td>54 ± 7</td>
<td>0.76</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>27 ± 6</td>
<td>27 ± 7</td>
<td>0.83</td>
</tr>
<tr>
<td>Spherical equivalent (D)</td>
<td>−0.93 ± 2.91</td>
<td>−0.83 ± 2.34</td>
<td>0.82</td>
</tr>
<tr>
<td>Best corrected visual acuity (logMAR)</td>
<td>0.03 ± 0.05</td>
<td>0.02 ± 0.05</td>
<td>0.28</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malay</td>
<td>31 (44.3%)</td>
<td>28 (38.5%)</td>
<td>0.57</td>
</tr>
<tr>
<td>Chinese</td>
<td>29 (41.4%)</td>
<td>29 (40.3%)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indian</td>
<td>10 (14.3%)</td>
<td>15 (20.8%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>55 (78.6%)</td>
<td>61 (84.7%)</td>
<td>0.47</td>
</tr>
</tbody>
</table>

### Table 2

Estimates of the slope parameters of central macular thickness, dosage of tamoxifen, diabetes status and the interaction between dosage of tamoxifen with diabetes status for both the right and the left eye. A statistically significant result is indicated with an asterisk, whereas a marginally significant result is indicated with a cross. For both eyes, the intercept estimate was not significantly different from 0 and therefore omitted.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Eye</th>
<th>Slope</th>
<th>( \text{p-value} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central macular thickness</td>
<td>Right</td>
<td>0.003</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>0.002</td>
<td>0.003*</td>
</tr>
<tr>
<td>Dosage of tamoxifen</td>
<td>Right</td>
<td>−0.0056</td>
<td>0.04*</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>−0.0026</td>
<td>0.39</td>
</tr>
<tr>
<td>Diabetes status</td>
<td>Right</td>
<td>0.056</td>
<td>0.27</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>0.077</td>
<td>0.17</td>
</tr>
<tr>
<td>Dosage of tamoxifen x diabetes status</td>
<td>Right</td>
<td>0.0020</td>
<td>0.51</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>−0.0018</td>
<td>0.57</td>
</tr>
</tbody>
</table>

### Table 3

Estimates of the slope parameters of central macular thickness and dosage of tamoxifen for both the right and the left eye. A statistically significant result is indicated with an asterisk. For both eyes, the intercept estimate was not significantly different from 0 and therefore omitted.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Eye</th>
<th>Slope</th>
<th>( \text{p-value} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central macular thickness</td>
<td>Right</td>
<td>0.0029</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>0.0024</td>
<td>0.002*</td>
</tr>
<tr>
<td>Dosage of tamoxifen</td>
<td>Right</td>
<td>−0.0040</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>−0.0042</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>
eye (Fig. 1b), up to about 20 g, followed by a plateau phase. According to the fitted polynomial (of degree 2) loess curve, from a mean of 0.55 (at minimal dosage of ~0.8 g), mean MPOD gradually decreased to about 0.35, at a dosage of about 20 g, whence it more or less remained constant with increasing dosage afterwards. Estimate of mean MPOD beyond 40 g was unreliable due to limited availability of data in the present study for higher tamoxifen dosage (third quartile ~ 19 g; max = 54 g).

3.4. Correlation between MPOD and central macular thickness

In the control group, both eyes showed significant, modest sample correlation of about 0.3 between MPOD and central macular thickness. In contrast, an asymmetric result was seen in the treatment group. The estimated correlation became statistically not significant in the left eye, as well as having a reduced magnitude ($r = 0.21$) compared to those of the control ($r = 0.3$). However, the estimated correlation ($r = 0.36$) was significant for the right eye (Table 5).

4. Discussion

Due to difficulties in recruiting early breast cancer patients, we did not exclude diabetic patients (except those diagnosed with diabetic retinopathy). Recently, Scanlon et al. found, using a total sample size of 150 individuals, that MPOD is significantly lower in people with Type 2 diabetes (mean = 0.33; SD = 0.21), compared with people with Type 1 diabetes (mean = 0.49; SD = 0.23), and with normal controls (mean = 0.48; SD = 0.35) [33]. Our observations are generally consistent with their findings (Table 4), in that mean MPOD was lower in the diabetic subgroup in both the treatment and the control group. However, since the ratio of non-diabetic to diabetic subjects (~4:1) was about equal in both the treatment and the control group, the biases in both groups approximately cancel off one another. Finally, the lack of sufficient numbers of patients on long term tamoxifen adjuvant therapy in this study (possibly losses after some period of therapy are increased because of death, voluntary withdrawal, or withdrawal due to loss of financial support) makes the estimated loess curve difficult to interpret at high tamoxifen dosage.

Despite the observed general trend of decreasing mean MPOD

<table>
<thead>
<tr>
<th>Diabetes subgroup</th>
<th>Right Eye</th>
<th>Control</th>
<th>0.49 ± 0.02</th>
<th>0.44 ± 0.05</th>
<th>−0.05</th>
<th>−0.06</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment</td>
<td></td>
<td>0.42 ± 0.03</td>
<td>0.32 ± 0.04</td>
<td>−0.10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Left Eye</td>
<td>Control</td>
<td>0.48 ± 0.03</td>
<td>0.43 ± 0.04</td>
<td>−0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment</td>
<td>0.41 ± 0.03</td>
<td>0.35 ± 0.06</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4: Mean MPOD ± 1 standard error for the control and the treatment group stratified by diabetes status, for both eyes. The mean effect of including diabetic subjects was to reduce MPOD by an amount ~0.1 (rounded to 1 decimal place) within the control and the treatment group.

<table>
<thead>
<tr>
<th>Group</th>
<th>Sample Pearson correlation, $r$</th>
<th>95% CI for Pearson correlation</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>Left Eye 0.21</td>
<td>[-0.03,0.42]</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>Right Eye 0.36</td>
<td>[0.13,0.55]</td>
<td>0.002*</td>
</tr>
<tr>
<td>Control</td>
<td>Left Eye 0.29</td>
<td>[0.06,0.49]</td>
<td>0.01*</td>
</tr>
<tr>
<td></td>
<td>Right Eye 0.30</td>
<td>[0.07,0.49]</td>
<td>0.01*</td>
</tr>
</tbody>
</table>

Table 5: Sample Pearson correlation, 95% confidence interval (CI) and p-values of the correlation test between MPOD and central macular thickness for the treatment and the control group. A statistically significant result is indicated with an asterisk.

Fig. 1. Scatterplot of MPOD against tamoxifen dosage for the (a) right eye and the (b) left eye. A degree-2 polynomial loess curve was fitted to the treatment data, and the dashed lines indicate the 95% confidence bands. Symbols: cross = control; circle = treatment.
with increasing mean tamoxifen dosage (Fig. 1), MPD at different tamoxifen dosage had wide range. This observation may be partly due to genetic polymorphisms in genes involved in tamoxifen metabolism (e.g., the cytochrome P450 (CYP) gene family [34,35]) among the subjects. For example, in a study involving Chinese, Malay and Indian subjects in Singapore, Lim et al. found that two CYP2D6 polymorphisms were significantly associated with lower concentrations of endoxifen and higher N-desmethyltamoxifen (NDM) - two important tamoxifen metabolites [36,37], in the blood plasma [38]. Additionally, they observed that Chinese and Malays had similar allelic frequencies for the polymorphisms examined, but that Indians usually had significantly different allelic frequencies. Future studies may include genotyping of CYP2D6 genetic polymorphisms to assess the potential correlation of genotype with MPD variation at particular tamoxifen dosages.

Maenpää et al. reported that tamoxifen could hamper glutamate transport, leading to a condition referred to as “glutamate neurotoxicity” [39], which is characterised by increased damage of cellular components that eventually causes cell death [40]. This hypothesis could apply to the ganglion cells of the retina, in which the MPs are mainly concentrated. Additionally, glutamate is an important source for the synthesis of alpha-ketoglutarate, which is an intermediate in Krebs cycle. Thus, impaired glutamate transport could deprive the Krebs cycle of this intermediate. The resulting energetic disruption can be expected to ultimately result in the death of the ganglion cells (hence loss of MP).

In normal eyes, the positive correlation between MPD and central macular thickness is well supported in the literature [41–44]. However, we observed loss of correlation between MPD and central macular thickness for the left eye in the treatment group. In addition, we also found that mean central macular thickness did not significantly differ between the treatment and the control groups, but that mean MPD increased with increasing mean dosage of tamoxifen. On the basis of these observations, we speculate that the tamoxifen produg and its metabolites [45] possibly interact with molecules in a yet unknown pathway by interfering with zeaxanthin and lutein transport and their storage in the macula, in addition to induction of retinal cell death.

5. Conclusion

Increased tamoxifen dosage appears to reduce MPD in female breast cancer patients (mean age = 54 ± 7 years) up to some threshold dosage. The observed loss of correlation between MPD and central macular thickness in the left eye of the tamoxifen treatment group suggests that tamoxifen-induced depletion of MP concentration need not occur through induced retinal cell death.

Acknowledgments

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