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The effect of preoperative total antioxidant capacity on short-term outcomes after kerato-lenticule extraction surgery

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To evaluate influence of total antioxidant capacity expression (TAC) on outcome of kerato-lenticule extraction (KLEx). A prospective non-randomized trial was conducted and patients received KLEx were categorized via TAC concentration. A total of 56 and 36 eyes were enrolled into the low TAC and high TAC groups. The main outcomes are the postoperative un-corrected visual acuity (UCVA), refraction and superficial keratitis between groups. The generalized liner model was applied for statistical analysis. One month after the KLEx surgery, the UCVA was significantly higher in the high TAC group ($P = 0.028$), and low TAC group associated with superficial keratitis risk compared to high TAC group ($P = 0.035$). The trends of TAC and ascorbic acid (AA) decrements were more significant in the low TAC group (both $P < 0.05$). Low TAC population and old age correlated to poor UCVA (both $P < 0.05$) while the thick CCT correlated to better UCVA ($P = 0.030$). Besides, the low TAC population ($P = 0.032$) correlated to higher superficial keratitis rate, while old age ($P = 0.018$) correlated to lower superficial keratitis rate. The presence of low TAC expression correlated to worse UCVA and higher risk of superficial keratitis after KLEx.

Keywords Kerato-lenticule extraction, Un-corrected visual acuity, Superficial keratitis, Ascorbic acid, Total antioxidant capacity

Abbreviations

KLEx	Kerato-lenticule extraction
UCVA	Un-corrected visual acuity
D	Diopter
DED	Dry eye disease
AA	Ascorbic acid
TAC	Total antioxidant capacity
OZ	Optic zone
IOP	Intraocular pressure
CCT	Central corneal thickness
AXL	Axial length
ACD	Anterior chamber depth
LT	Lens thickness
aOR	Adjusted odds ratio
CI	95% Confidence interval
N	Number
SD	Standard deviation

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The keratorefractive surgeries had been applied for the correction of myopia, hyperopia, and astigmatism and several types of keratorefractive surgeries had been developed[1]. The current types of corneal refractive surgery include photorefractive keratectomy, laser in situ keratomileusis (LASIK, a flap was created by either specific blade or femtosecond laser and lifted then the excimer laser strike and evaporate the corneal stroma that account for the targeted refractive error), and the kerato-lenticule extraction (KLEx, a corneal lenticule that account for the targeted refractive error and a corneal incision were created by femtosecond laser then the corneal lenticule was removed from the incision by spatula and forceps)[2], and the numbers of patients received KLEx surgery have increased in the past decades[3]. The visual and refractive results of KLEx surgery is fair in which more than 90% of patients received KLEx surgery achieved un-corrected visual acuity (UCVA) of 20/20 and refractive spherical equivalent within ± 1.00 diopter (D) from target values[4]. Still, the corneal optical density was higher in KLex surgery than LASIK surgery during early postoperative intervals[5].

Although the safety of KLEx may be acceptable, certain postoperative complications of KLEx surgery can disturb visual outcome[6]. The postoperative corneal wound healing process is a major concern for keratorefractive surgeries and delayed corneal healing could lead to irritation and guarded visual acuity[7]. Besides, the dry eye disease (DED) is the most frequent postoperative complications of refractive surgeries including the KLEx surgery which can reduce the speed of visual recovery[2,8,9]. Although the rate of severe DED was lower in KLEx surgery than LASIK surgery, the advanced DED can occur in individuals who have received KLEx surgery[10]. In the severe form of DED, the prominent superficial keratopathy and microbial keratitis may develop and the presence of visual impairment is not-uncommon[2,11], thus the retardation of DED after KLEx surgery is crucial.

The oxidative stress expression is a fundamental component in several systemic and ocular morbidities[12,13]. The higher oxidative stress had been demonstrated as a major risk factor for the DED and ocular surface injury due to the intracellular stress signaling, ocular surface epithelial and goblet cell dysfunction, and the loss of tear film stability[14]. Moreover, the corneal alkali injury can be lessened by antioxidant including N-acetyl-L-cysteine and ascorbic acid (AA) usages, which may because the antioxidant can suppress the reactive oxygen species produced during the alkali injury of ocular surface and the following inflammation and harmful angiogenesis would decrease[15,16]. About the correlation between the ocular surgery and oxidative stress, the retinal surgery like the trans pars plana vitrectomy can contribute to elevated postoperative oxidative stress and increase the risk of developing glaucoma[17]. Besides, the oxidative stress would be produced during the cataract surgery which may contribute to the corneal endothelial cell damage[18]. Regarding the keratorefractive surgery, the elevated oxygen-derived free radicals and corresponding corneal injury were observed in the patients received LASIK surgery which can be alleviated by the application of antioxidant[19].

Still, the correlation between preoperative antioxidant level and postoperative condition of KLEx surgery had not been elucidated. Because the oxidative stress associated with post-KLEx surgery complication like DED[10,14], the preoperative antioxidant level may influence the postoperative condition of KLEx surgery. The KLEx surgery is a surgery that rapidly develop and renew nowadays[20], and the oxidative stress-related disease like DED may contribute to permanent ocular pain after refractive surgery which may influence the quality of life[21]. Thus, the potential factor that could reduce the postoperative outcome after KLEx surgery, including the oxidative stress-related etiology, should be evaluated to discover the high-risk population and establish possible management.

As a consequence, we aim to investigate the postoperative outcomes of KLEx surgery in patients with different preoperative total antioxidant capacity (TAC). The effects of other preoperative parameters on KLEx surgery results were also analyzed.

Materials and methods

Ethics statement

The present study obeyed the declaration of Helsinki in 1964 and related amendments. Moreover, the present study was approved by the Institutional Review Board at the Linkou Chang Gung Memorial Hospital (Project Code: 202200858B0A3). The written informed consents were completed by all the participants and our clinical trial was registered in the ClinicalTrial.gov (Registration Number: NCT05905237, actual study start date: July 12, 2022, estimated study completion date: September 6, 2024).

Selection process

A prospective non-randomized study was conducted in Nobel Eye Institute which is an ophthalmic institution specialized in cataract and refractive surgeries. The participants of this study was recruited during August 10, 2022 to September 24, 2022. The individuals included in the present study achieved our inclusion criteria: (1) age between 20 and 50 years, (2) myopic status for at least − 1.00 D, (3) receipt the KLEx surgery in Nobel Eye Institute, and (4) participant realized all details of the present project. Also, the following exclusion criteria was applied to assure the homogeneity of participants as fair as possible: (1) un-corrected visual acuity (UCVA) lower than hand motion level, (2) any forms of cataract, (3) both the clinical significant or subclinical keratoconus or any corneal ectasic diseases, (4) severe retinal disorder like proliferative diabetic retinopathy or retinal detachment, (5) any uncontrolled or end-stage glaucoma, (6) active corneal lesions, central corneal scars, and microbial keratitis, (7) advanced ptosis that cover the whole pupil, (8) optic neuritis and optic nerve atrophy, (9) unstable refractive status which fluctuated more than 0.5 D during the past one years, (10) pregnant status, and (11) active systemic inflammatory diseases such Sjogren syndrome and rheumatic arthritis. A total of 92 eyes from 46 participants that received KLEx were included in the present study. These patients were further divided into two groups according to the level of TAC which demonstrated in the following section.

Surgical technique

The KLEx surgeries in the present study were done by one experienced refractive specialist (C.-K.C.). The KLEx surgery was completed using one femtosecond laser lenticule extraction device (Visuamax 500, Carl Zeiss, Göschwitzer Str., Jena, Germany). The optic zone (OZ) was set as 5.5–6.9 mm based on the patients' pupil size and ablation depth, and a 3.0 mm corneal was created at 105 degrees. After the coaxially sighted corneal light reflex was confirmed manually by microscope with the assistance of topography, the cornea was fixed by the suction ring of the femtosecond laser lenticule extraction device. Then the device emitted femtosecond laser which creates the lenticule around 23 s which based on the refraction-related lenticule thickness. After the creation of the corneal lenticule, a spatula was used to dissect the lenticule, and then the corneal lenticule was extracted by a forceps. After the KLEx surgery, the topical prednisolone and levofloxacin eyedrops were instilled four times per day for one week, then switched to topical sulfamethoxazole and fluorometholone eyedrops four times per day for another three weeks. Preservative-free artificial tear was instilled pro re nata with a baseline frequency of four times per day for at least 8 weeks.

Ophthalmic examination

All the patients received identical examinations in the Nobel Eye Institute. The pre-operative exams included the following items: UCVA, best corrected visual acuity (BCVA), intraocular pressure (IOP) value via pneumatic tonometry (NT-530, NIDEK, Gamagori, Aichi, Japan), cyclopegic refraction of sphere/cylinder power via autorefractor (KR-8900, Topcon, Itabashi-ku, Tokyo, Japan), corneal cylinder power and central corneal thickness (CCT) via tomographic device (Oculus Pentacam, OCULUS Optikgeräte GmbH, Münchholzhäuser, Wetzlar, Germany), and Schirmer II test. For the details of Schirmer II test, a Schirmer strip was applied after topical anesthesia, and the patients closed their eyes and waited for 5 min. The length of the wet portion of Schirmer strip was recorded after the removal of the Schirmer strip from the patients' eye. The postoperative exams of KLEx surgery involved the UCVA (presented as value in Snellen chart), sphere power, cylinder power, CCT, and IOP in which same preoperative device was applied. Moreover, the ophthalmologist evaluated the corneal surface via slit-lamp biomicroscope with fluorescein stain and decided whether postoperative superficial keratitis presented. The presence of superficial keratitis was regarded as grade 3 (prominent central puntate keratitis) to 5 (diffuse puntate keratitis at the whole cornea) according to Oxford Scheme[22]. The data before the surgery, one week after the surgery, and one month after the surgery were obtained and put in the statistical analyses.

Antioxidant agent determination

The TAC and AA concentrations were collected and analyzed with the similar methods illustrated in the previous publications[23–25]. The tear film of each patient was obtained via the Schirmer strip in three time points: (1) preoperatively, (2) one week postoperatively, and (3) one month postoperatively. The tear film samples were taken near the incision of KLEx surgery which means the superior-temporal site (around 11 clock hours) from right eye and superior-nasal site (near 1 clock hour) from left eye. The Schirmer strip was put near the limbal region of corneal incision in KLEx for 5 min, and the tear film sample in the Schirmer strip was transported in liquid nitrogen (– 196 °C) and stored in a refrigerator at -80 °C. The assessments of TAC and AA concentrations were performed via the colorimetric OxiSelect™ Ascorbic Acid Assay Kit (FRASC, Cell Biolabs, Inc., San Diego, CA, USA), which examined the reduction of ferric ions by the application of ascorbic oxidase. Before analysis, tear film samples that restored in refrigerator at – 80 °C were thawed to about 4 °C, and 35 µL of each tear film sample was diluted by the assay buffer of OxiSelect™ to a one-twentieth concentration. After the dilution, colorimetric assessments were completed within the light ranges of 540–600 nm wavelength via the absorbance microplate reader (Sunrise™ Tecan, Switzerland). Finally, the expressions of TAC and AA were checked via the utilization of colorimetric OxiselectTM Ascorbic Acid Assay Kit. Concerning the unit of antioxidant, the quantification of both TAC and AA concentrations was described in units of millimoles per liter (µmol/L or µM). To ensure the accuracy of tear film samples, all tear film samples were examined for three times and the average value of the examinations were used in the subsequent analysis.

Statistical analysis

The SPSS version 20.0 (SPSS Inc., Chicago, Illinois, USA) was conducted for all analyses mentioned in the present study. The Shapiro–Wilk test was applied to check the normal distribution of the whole KLEx population and normal distribution was confirmed ($P > 0.05$). The whole KLEx population was then divided into the low TAC group (56 eyes) and high TAC group (36 eyes) according to the TAC concentration of 820µM which is the mean TAC value of all participants. The descriptive analysis was adopted to present the baseline data of the low TAC and high TAC groups, and the independent T test and Fisher's exact test were applied to compare the difference of baseline data between the two groups according to the types of data. Then the independent T test and Fisher's exact test were also utilized to compare the postoperative data between the two groups. After that, the trend of TAC and AA changes after the KLEx surgery between the two groups were analyzed via the generalized estimate equation, which can adjusted the influence of repeated measurements for some parameters like age and sex, with the adjustment of age, sex, preoperative refraction, corneal cylinder, IOP, CCT, results of Schirmer test, OZ and lenticule thickness. The adjusted odds ratio (aOR) and corresponding 95% confidence interval (CI) of TAC and AA changes in high TAC group compared to low TAC group was yielded. In the next steps, the generalized linear model was applied to analyze the correlation between preoperative factors and UCVA one month postoperatively and the postoperative superficial keratitis. The generalized linear model also adjusted the effect of age, sex, preoperative refraction, corneal cylinder, IOP, CCT, Schirmer test results, and surgical parameters then aOR with 95% CI were produced. Also, the generalized linear model was applied to evaluate

the correlation between old age and both TAC and AA concentrations. A *P* value lower than 0.05 was defined as statistical significance and the *P* value lower than 0.001 was presented as $P<0.001$.

Results

The baseline features between the low TAC and high TAC groups are demonstrated in Table 1. The mean age was 32.33 ± 7.26 years and 34.12 ± 6.28 years in the low TAC and high TAC groups, respectively, without significant difference ($P=0.241$). Similarly, the sex distribution (male to female) was 8:20 and 7:11 in the low TAC and high TAC groups, respectively. The difference of sex distributions between the two groups was non-significant ($P=0.246$). The other baseline features including IOP, systemic diseases, presence of DED, preoperative refractions, topographic indexes, Schirmer test results and surgical parameters showed similar values between the two groups (all $P>0.05$) (Table 1).

The initial concentrations of TAC and AA were 1199.03 ± 205.48μM and 597.00 ± 143.03μM in the high TAC group which were significantly higher than the 359.20 ± 148.83μM and 219.32 ± 95.17μM in the low TAC group (both $P<0.001$). After the follow-up period of one month, the change of TAC were − 384.14 ± 81.87μM (32.04%) in the high TAC group and − 229.50 ± 69.14μM (63.89%) in the low TAC group, respectively (Fig. 1). Besides, the change of AA were − 65.45 ± 43.86μM (10.96%) in the high TAC group and − 83.40 ± 58.54μM (38.03%) in the low TAC group, respectively (Fig. 2). The trends of TAC (aOR: 3.368, 95% CI: 1.158–9.793, $P<0.001$) and AA (aOR: 2.049, 95% CI: 1.646–5.260, $P<0.001$) decrements were more significant in the low TAC group compared to high TAC group.

One week after the KLEx surgery, the amount of UCVA, sphere, cylinder and IOP illustrated similar values between the two groups (all $P>0.05$). One month after the KLEx surgery, however, the UCVA was significantly higher in the high TAC group (1.00 ± 0.02) than the low TAC group (0.94 ± 0.15) ($P=0.028$) while the difference of sphere, cylinder and IOP remain insignificant between the two groups (all $P>0.05$) (Table 2). On the other hand, the CCT value after KLEx surgery demonstrated insignificant difference between the two groups ($P=0.353$), while the low TAC group associated with more cases with superficial keratitis compared to high TAC group ($P=0.035$) (Table 2).

About the predictors for UCVA one month postoperatively, the low TAC population (aOR: 0.948, 95% CI: 0.906–0.992, $P=0.022$), old age (aOR: 0.995, 95% CI: 0.992–0.999, $P=0.009$) correlated to poor UCVA while the thick CCT (aOR: 1.003, 95% CI: 1.001–1.005, $P=0.030$) correlated to better UCVA. The other preoperative parameters showed no significant association to UCVA one month postoperatively (all $P>0.05$) (Table 3). Concerning the predictors for the development of postoperative superficial keratitis, the low TAC population (aOR: 2.897, 95% CI: 1.075–7.058, $P=0.032$) correlated to higher rate of postoperative superficial keratitis, while old age (aOR: 0.763, 95% CI: 0.609–0.956, $P=0.018$) correlated to lower rate of postoperative superficial keratitis. The other indexes did not influence the incidence of postoperative superficial keratitis (all $P>0.05$) (Table 4). The old age was not significantly related to the TAC and AA concentrations (both $P>0.05$).

Discussion

Briefly, the patients with low initial TAC demonstrated a worse UCVA and higher rate of superficial keratitis than the patients with high initial TAC after KLEx surgery. Moreover, the trend of TAC and AA decrements were more prominent in the patients with low TAC levels compared to those with high TAC levels. On the other hand, the old age and thick CCT is positively and negatively correlated to worse postoperative UCVA while old age associated with fewer episodes of superficial keratitis after the KLEx surgery.

Feature (mean ± SD)	Low TAC group (*N* = 56)	High TAC group (*N* = 36)	*P* value
Age	32.33 ± 7.26	34.12 ± 6.28	0.241
Sex (male: female)	8:20	7:11	0.246
Systemic disease[#]	2	0	0.667
Pre-existing DED	18	19	0.082
BCVA	1.00 ± 0.02	1.00 ± 0.01	0.850
Sphere	− 5.35 ± 1.95	− 4.67 ± 1.81	0.104
Cylinder	− 1.06 ± 0.66	− 1.01 ± 0.81	0.761
Corneal cylinder	− 1.42 ± 0.55	− 1.44 ± 0.61	0.894
IOP	16.39 ± 2.53	16.29 ± 2.24	0.843
Schirmer test	13.41 ± 6.07	11.53 ± 6.88	0.183
CCT	545.00 ± 29.23	541.71 ± 31.43	0.618
OZ	6.53 ± 0.18	6.55 ± 0.31	0.711
Lenticule thickness	124.50 ± 22.06	118.12 ± 21.93	0.094

Table 1. The preoperative features of the whole study population. *BCVA* best corrected visual acuity, *CCT* central corneal thickness, *DED* dry eye disease, *IOP* intraocular pressure, *N* number, *OZ* optic zone, *SD* standard deviation, *TAC* total antioxidant capacity. [#]Two patients diagnosed with thyroid diseases in low TAC group.

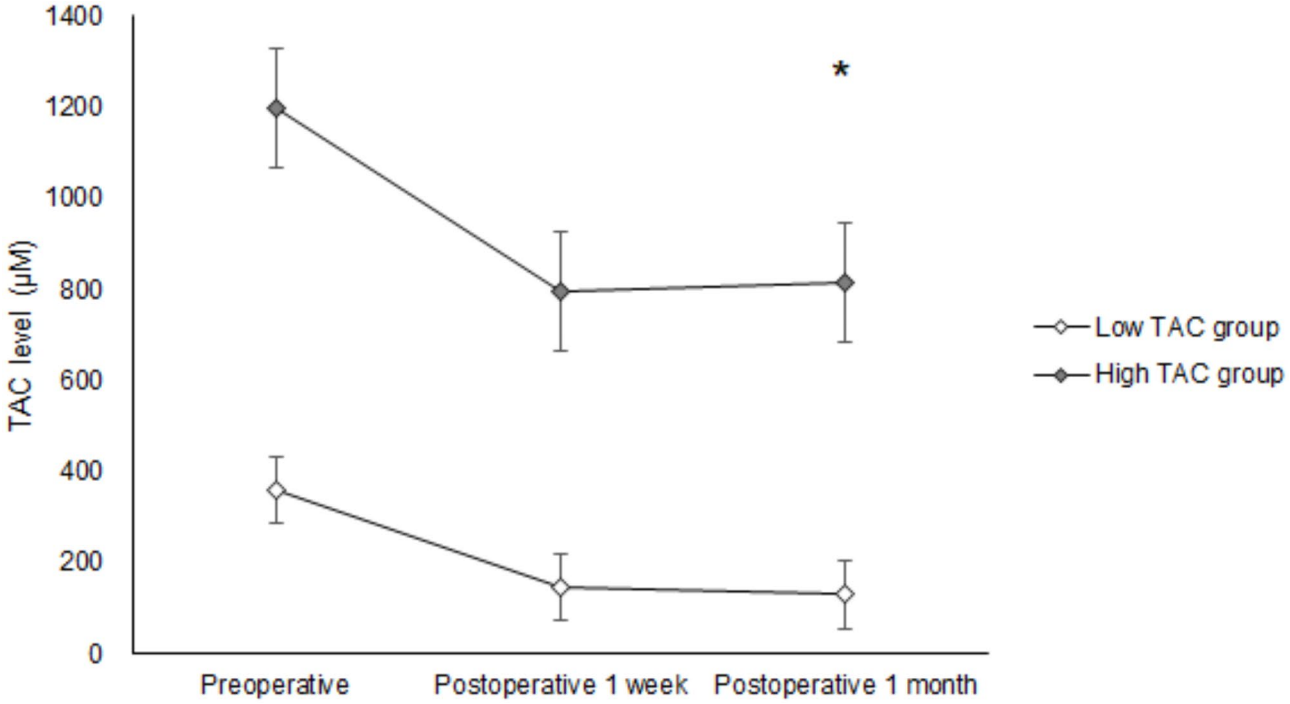

Fig. 1. The trend of total antioxidant capacity change between the two groups. TAC: total antioxidant capacity. *Denotes significant difference of TAC decrement between the two groups after adjusting age, sex, preoperative refraction, corneal cylinder, IOP, CCT, Schirmer test results, OZ and lenticule thickness.

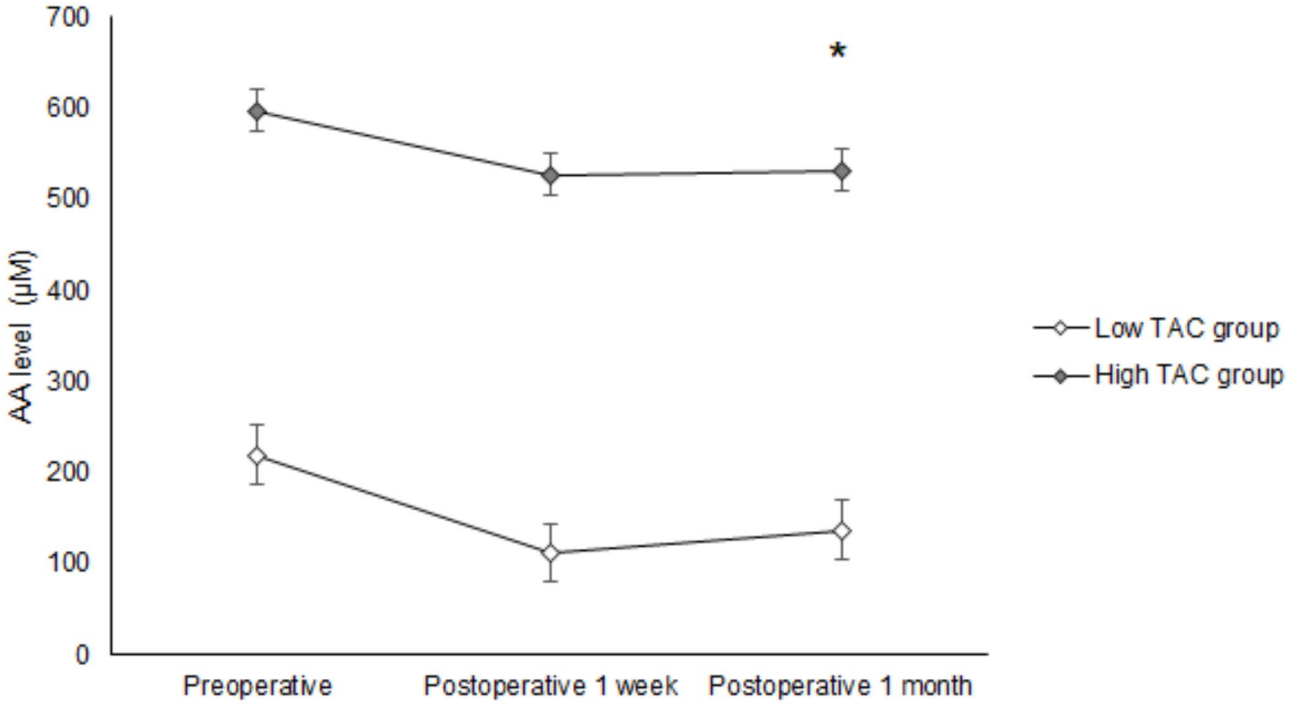

Fig. 2. The trend of ascorbic acid change between the two groups. AA: ascorbic acid. *Denotes significant difference of AA decrement between the two groups after adjusting age, sex, preoperative refraction, corneal cylinder, IOP, CCT, Schirmer test results, OZ and lenticule thickness.

Feature	Low TAC group (*N* = 56)	High TAC group (*N* = 36)	*P* value
Postoperative 1 week			
UCVA	0.92 ± 0.13	0.95 ± 0.12	0.291
Sphere	− 0.02 ± 0.48	− 0.09 ± 0.46	0.505
Cylinder	− 0.60 ± 0.33	− 0.52 ± 0.30	0.256
IOP	10.69 ± 1.82	10.57 ± 2.00	0.769
Postoperative 1 month			
UCVA	0.94 ± 0.15	1.00 ± 0.02	0.028*
Sphere	− 0.18 ± 0.54	− 0.15 ± 0.45	0.846
Cylinder	− 0.61 ± 0.33	− 0.49 ± 0.27	0.063
IOP	10.66 ± 2.12	10.55 ± 2.68	0.844
CCT	441.70 ± 28.60	448.48 ± 38.89	0.353
Superficial keratitis	9	1	0.035*

Table 2. The postoperative outcomes between the two groups. *CCT* central corneal thickness, *IOP* intraocular pressure, *N* number, *TAC* total antioxidant capacity, *UCVA* un-corrected visual acuity. *Denotes significant difference between the two groups.

Parameters	aOR	95% CI	*P* value
Low TAC	0.948	0.906–0.992	0.022*
Age	0.995	0.992–0.999	0.009*
Sex	0.950	0.902-1.000	0.050
Preoperative BCVA	0.752	0.209–2.704	0.663
Preoperative sphere	1.002	0.985–1.018	0.853
Preoperative cylinder	1.050	0.993–1.111	0.085
Preoperative corneal cylinder	0.970	0.906–1.039	0.387
Preoperative IOP	1.003	0.992–1.014	0.568
Preoperative Schirmer test	0.997	0.994–1.001	0.140
Preoperative CCT	1.003	1.001–1.005	0.030*
OZ	0.955	0.834–1.094	0.508

Table 3. The relationship of each parameter to postoperative un-corrected visual acuity. *aOR* adjusted odds ratio, *BCVA* best corrected visual acuity, *CI* confidence interval, *CCT* central corneal thickness, *IOP* intraocular pressure, *OZ* optic zone, *TAC* total antioxidant capacity. *Denotes significant difference between the two groups.

In the present study, the low baseline TAC correlated to the worse UCVA one month after the KLEx surgery compared to the individuals with high baseline TAC level. In previous publication, the worse UCVA that warranted enhancement after KLEx surgery could associate with intraoperative suction loss, high preoperative myopia and high preoperative astigmatism[26]. Moreover, both the preoperative and postoperative DED correlated to a worse visual quality after keratorefractive surgeries[27]. Nevertheless, the molecular predictor for the visual outcome after KLEx surgery had not been established. To our knowledge, our results may be a preliminary experience to demonstrate the positive correlation between low baseline TAC and poor postoperative visual outcome. Furthermore, this correlation was re-checked by the generalized linear model which incorporates the effect of age, sex, preoperative refractive status and the tear secretion function. As a consequence, the low baseline TAC may serves as independent risk factor for the poor UCVA after KLEx surgery. The laser application during KLEx surgery would contribute to postoperative inflammation in the corneal stroma which resulted from the thermal effect[28]. In previous study, the inflammation in the anterior segment of eye are associated with higher levels of oxidative stress[29]. On the other side, the persistent ocular surface inflammation, oxidative stress and subsequent DED after kertorefractive surgeries could impair the postoperative visual recovery[30]. We speculate that the individuals with lower baseline TAC concentrations may experience a prolonged course of high oxidative stress status because the low antioxidant capacity cannot promptly compensate the oxidative stress produced by KLEx. Accordingly, the postoperative visual recovery would be slower in the population with low baseline TAC.

In addition to the worse postoperative UCVA, the individuals with lower baseline TAC also presented with higher incidence of postoperative superficial keratitis than the high baseline TAC population. The development of superficial keratitis is a not-uncommon, but not universal, complication after the performance of refractive surgeries[31,32]. In previous literature, the incidence of superficial keratitis or corneal epithelial defect was lower in the KLEx surgery than the LASIK surgery[33]. In the present study, we highlight the possible molecular predictor

Parameters	aOR	95% CI	*P* value
Low TAC	2.897	1.075–7.058	0.032*
Age	0.763	0.609–0.956	0.018*
Sex	0.571	0.084–3.887	0.567
Preoperative BCVA	1.030	0.005–2.314	0.965
Preoperative sphere	1.244	0.645–2.399	0.515
Preoperative cylinder	1.588	0.179–4.121	0.478
Preoperative corneal cylinder	0.890	0.292–1.217	0.210
Preoperative IOP	0.989	0.692–1.416	0.954
Preoperative Schirmer test	0.910	0.775–1.068	0.249
Preoperative CCT	1.022	0.990–1.055	0.189
OZ	0.640	0.466–7.681	0.456

Table 4. The relationship of each parameter to postoperative superficial keratitis. *aOR* adjusted odds ratio, *BCVA* best corrected visual acuity, *CI* confidence interval, *CCT* central corneal thickness, *IOP* intraocular pressure, *OZ* optic zone, *TAC* total antioxidant capacity. *Denotes significant difference between the two groups.

for the formation of postoperative superficial keratitis. Similar to the UCVA-related analysis, we also applied generalized linear regression that adjusted the effect of several confounders for postoperative DED/corneal damage. Although the preoperative DED may contribute to postoperative corneal defects[34], the preoperative tear secretion function between the two groups were similar and we adjusted the effect of preoperative DED in the multivariable analysis. Thus the low baseline TAC concentration could also be an independent risk factor for the development of post-KLEx superficial keratitis. The oxidative stress can lead to various ocular surface disorders including the anterior segment and posterior segment of eye[35]. The higher oxidative stress was observed in the individuals with DED which resulted from the deficiency of tear film and the antioxidant it contains[35]. On the other side, the corneal injury like the alkali-induced corneal erosion is accompany with higher level of oxidative stress[36], and the usage of antioxidant can reduced such corneal damage[16]. Because the KLEx and other keratorefractive surgeries could induce the oxidative stress elevation[28,29], the delayed reduction of oxidative stress in those with lower baseline TAC expression could insult the corneal surface more easily than those with adequate baseline TAC.

About the trend of antioxidant changes between the low TAC and high TAC groups, the percentage of TAC decrement was significantly higher in the low TAC group than that in the high TAC group which confirmed by the generalized estimate equation. In previous studies, the postoperative oxidative stress could be elevated after keratorefractive surgeries[28,29], thus it is reasonable that the prominent reduction of TAC between the KLEx in the present study. Our result imply that the patients with higher TAC concentration were under better protection for oxidative stress-related event like the KLEx surgery, and the residual TAC may be adequate for the oxidative stress resulted from postoperative DED which may persisted up to 6–12 months[2]. On the other hand, the overall AA decrements in the both group were even lesser than the TAC loss. The possible explanation for this results is that the TAC consists of multiple antioxidants on ocular surface[12,37], and some of these antioxidants may be consumed firstly to compensate the oxidative stress induced by keratorefractive surgeries thus the concentration of AA did not decrease prominently as other antioxidant. Nevertheless, further study is warranted to verify this hypothesis.

Concerning the other parameters that associate with the worse postoperative UCVA and the presence of postoperative superficial keratitis, the old age positively correlates to worse postoperative UCVA and lower risk of postoperative superficial keratitis. In the previous study discussing the postoperative outcome of KLEx, the age was a significantly risk factor for the poor postoperative visual acuity[26,38]. Moreover, the old age would delay the visual recovery in both our clinical experience and an earlier publication[38]. Because the follow-up period in the present study was only one month, the patients with old age may not fully recovered and presented with worse postoperative visual acuity. Interestingly, the patients with old age presented with lower risk of developing postoperative superficial keratitis which is contrast to previous concept that the older patients related to higher incidence of DED and corneal damage[39]. The possible reason is that the individuals with older age used the smart phone with lower frequency compared to their younger counterpart[40], thus avoid a prominent risk factor for DED and possible superficial keratitis development. On the other hand, the thick preoperative CCT correlates to better postoperative UCVA after the adjustment of preoperative sphere and cylinder powers, which means the protective effect of thick CCT on postoperative UCVA was independent of lenticule thickness. Since postoperative irregular astigmatism and corneal ectasia often occurred in those with thin cornea[41], the lower risk of mild postoperative irregular astigmatism in patients with think CCT may lead to better postoperative vision.

There are some limitations in the present study. Firstly, the case numbers of the present study is relative few in which only a total of 92 eyes was enrolled. Although the normality of the study population was confirmed by Shapiro–Wilk test, the relative small study population may lead to statistical bias and reduce the reproducibility and generalizability of our results. Secondly, we only demonstrate the statistical association between preoperative TAC and postoperative UCVA while the causal relationship and the exactly mechanism was not examined and

confirmed, so the significance and importance of our findings may not be high. Besides, the one month follow-up period of the present study is short, and subsequent visual and corneal recovery cannot be accessed. Moreover, the site of tear film collection was not the exact site of laser strike during the KLEx surgery: the femtosecond laser strike on the corneal surface and stroma while we took the tear film sample at the surface of conjunctiva-limbus junction. Thus, the reduction of TAC and AA may not directly resulted from the application of KLEx surgery and would be influenced by the condition of ocular surface. Finally, the numbers and expressions of reactive oxygen species were not measured in the present study and the exact mechanism of antioxidant reduction could remain unclear, and the pH measurement and densitometry exam were also not performed.

In conclusion, the individuals with lower TAC correlates to worse UCVA and high risk of superficial keratitis after KLEx surgery after adjusting multiple covariates. Furthermore, the percentage of TAC and AA decrements were more significant in the low-TAC population. Consequently, the topical or systemic antioxidant supplement might be suggested for the individuals with low baseline TAC who scheduled for KLEx surgery. Further large-scale prospective study to evaluate whether the preoperative application of antioxidant in the low-TAC population can preserve the postoperative visual recovery and corneal integrity after KLEx surgery is mandatory.

Data availability

The data used in this study is available from the corresponding author upon reasonable request.

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C.-K.C.: conceptualization. C.-Y.L., H.-C.C., and S.-F.Y.: methodology. C.-K.C. and Y.-J.H.: data curation. C.-K.C.: software. CKC and J.-Y.H.: formal analysis. C.-Y.L., H.-C.C., and S.-F.Y.: writing—original draft preparation. C.-K.C.: writing—review and editing. C.-K.C.: validation. C.-K.C.: visualization. C.-K.C.: supervision. All authors reviewed and agreed the submission version of our manuscript.

Declarations

Competing interests
The authors declare no competing interests.

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