Original Article

Thyroid gland dysfunction and keratoconus

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ABSTRACT

Background: The association between keratoconus and thyroid gland dysfunction (TGD) remains controversial. We aimed to determine the frequency of keratoconus among patients with laboratory-confirmed, treatment-naive TGD compared with that of age- and sex-matched healthy controls. Moreover, we investigated the potential relationship between TGD and corneal topographic and tomographic parameters.

Methods: This multicenter, cross-sectional study recruited individuals with treatment-naive, laboratory-confirmed TGD and sex- and age-matched healthy controls. Demographic and ophthalmic data of all participants were recorded. All participants underwent comprehensive ocular examinations and corneal tomography. Patterns of symmetric bowtie, asymmetric bowtie, asymmetric bowtie/superior steep, asymmetric bowtie/inferior steep, or asymmetric bowtie pattern with a skewed radial axis were documented if present. Furthermore, the maximum simulated keratometry value (Kmax), corneal thinnest thickness (CTT), and back elevation (BE) values were recorded. We measured the serum concentrations of thyroid-stimulating hormone (TSH) and thyroid hormones (free thyroxine [FT4] and free tri-iodothyronine [FT3]) using an immunoassay method.

Results: We included 200 eyes of 200 individuals with TGD and 200 eyes of 200 healthy age- and sex-matched controls, with female predominance in both groups. The mean FT4 concentration was significantly higher and the TSH concentration was significantly lower in the TGD group than in the control group (both $P < 0.0001$), whereas the FT3 level was comparable between groups ($P > 0.05$). In the TGD group, the frequencies of hyperthyroidism and hypothyroidism were 190 (95%) and 10 (5%), respectively. We found significantly lower mean CTT, higher Kmax, and greater BE values with a significantly higher frequency of abnormal topographic patterns among eyes in the TGD group than in controls (all $P < 0.05$). The frequency of eyes with keratoconus was significantly higher in the TGD (7.5%) group than in the control (0.5%) group ($P < 0.0001$). Except for a statistically significant correlation of Kmax ($r = -0.23$, $P < 0.05$) and CTT ($r = +0.15$, $P < 0.05$) with TSH level in the TGD group, no significant correlation was found between corneal characteristics and thyroid profile in either group (all $P > 0.05$).

Conclusions: We observed a higher frequency of keratoconus, with female predominance, in the TGD group. TGD was associated with significant changes in certain corneal topographic and tomographic parameters. Compared with healthy controls, individuals with TGD demonstrated increased Kmax and BE values with more corneal thinning, highlighting the potential association between keratoconus and TGD. However, further large-scale longitudinal studies are essential to confirm our findings.

KEYWORDS

keratoconus, thyroid gland, primary hyperthyroidism, primary hypothyroidism, corneal topography, thyroid-stimulating hormone, T4 thyroid hormone, T3 thyroid hormone

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INTRODUCTION

Keratoconus is a multifactorial, asymmetric, bilateral, ectatic corneal disease that results in progressive thinning and steepening of the cornea, leading to irregular astigmatism with visual deterioration [1]. Eye rubbing, eczema, asthma, a family history of keratoconus, and allergy are known risk factors for keratoconus development [1-8]. In addition, genetic inheritance, vernal keratoconjunctivitis, hormonal changes, pregnancy, lactation, oxidative damage, immunological disorders such as Hashimoto's thyroiditis, and environmental factors are among associated factors. Early detection and advancements in screening methods have improved its diagnosis [1-8].

The prevalence and incidence rates of keratoconus vary widely, ranging from 0.2–4790 cases per 100 000 persons and 1.5–25 cases per 100 000 persons annually, respectively, with the highest rates in young adults of Middle Eastern and Asians ethnicities aged 20–30 years. Keratoconus is more prevalent in countries having hot, dry climate and geographic areas with greater ultraviolet light exposure, including Egypt [1, 8-11].

The association between keratoconus and thyroid gland dysfunction (TGD) is controversial [7, 12-20]. Although some studies have revealed a higher prevalence of TGD among patients with keratoconus [7, 12-15], others have failed to find a significant association [16-20]. However, differences in study design, sample size, racial background of participants, and geographical area [16-20] may determine whether this association is observed.

We aimed to determine the frequency of keratoconus among patients with laboratory-confirmed, treatment-naive TGD and to analyze the potential relationship between TGD and corneal tomographic/topographic parameters compared to that of healthy individuals.

METHODS

This multicenter, cross-sectional study was approved by the ethics committee of Fayoum Faculty of Medicine, Fayoum University, Fayoum, Egypt, and adhered to the tenets of the Declaration of Helsinki. The study was conducted between April 2020 and March 2022. All participants provided written informed consent before enrollment.

We included 400 randomly selected eyes of 400 consecutive eligible participants with or without TGD during the study period. Individuals in the TGD group were recruited from endocrinology clinics at Fayoum University Hospital, Fayoum, Egypt, and Cairo University Hospital, Cairo, Egypt. Individuals in the control group were sex- and age-matched healthy individuals recruited from ophthalmology outpatient clinics at Fayoum, Cairo, Sohag, and Alexandria University Hospitals, Egypt.

The inclusion criterion for the TGD group was treatment-naive, laboratory-confirmed hyperthyroidism or hypothyroidism [21-23] without surgical history. The inclusion criterion for the control group was laboratory-confirmed euthyroid status [21-23] without history of TGD. The exclusion criteria for both groups were concomitant ocular pathology other than keratoconus, previous ocular diseases or surgeries, pregnancy, lactation, history of systemic medications or surgeries, and presence of other systemic comorbidities.

Demographic and ophthalmic data of all participants were recorded. All participants underwent complete ophthalmological examinations, including measurement of best-corrected distance visual acuity using a Snellen chart (ACP-8R automatic chart projector; Topcon Corp., Tokyo, Japan), intraocular pressure measurement using the Goldmann applanation tonometer (AT900; Haag-Streit, Koniz, Switzerland), and undilated and dilated slit-lamp biomicroscopy examination (SL-D2; Topcon) for detailed assessment of the anterior and posterior segments.

Corneal tomography was performed using Pentacam HR (Oculus Optikgerate GmbH, Wetzlar, Germany). Patterns of symmetric bowtie (SB), asymmetric bowtie (AB), AB/superior steep (AB/SS), AB/inferior steep (AB/IS), or AB pattern with a skewed radial axis (AB/SRAX) were documented, if present, using an anterior axial map [24-26]. Furthermore, the maximum simulated keratometry value (Kmax) (abnormal value ≥47 diopter [D]), corneal thinnest thickness (CTT; abnormal value ≤470 μm), and back elevation (BE) (abnormal value >17 mm) were recorded [24-27].

We measured the serum concentrations of thyroid-stimulating hormone (TSH) and thyroid hormones using an immunoassay method [28]. Hyperthyroidism was characterized as a low serum TSH concentration (μU/mL) and elevated serum concentrations of thyroid hormones. Subclinical hyperthyroidism was characterized as a low serum TSH concentration with normal serum free thyroxine (FT4; ng/dL) and free tri-iodothyronine (FT3; pmol/L) concentrations. Hypothyroidism was defined as a TSH concentration above the reference range and FT4 concentration below the reference range [21-23]. Data analysis was performed using the Statistical Package for the Social Sciences software version 22.0 (IBM Corp., Armonk, NY, USA). The Kolmogorov–Smirnov test was used to assess the normality of data distribution.

The independent samples *t*-test, Mann–Whitney U test, or chi-square test was used for comparison between groups when applicable. Data are summarized as frequency (%) or mean (standard deviation [SD]). Possible correlations of Kmax, CTT, and BE with TSH or thyroid hormones were analyzed using Pearson's correlation test. Statistical significance was set at $P < 0.05$.

RESULTS

We included 200 eyes of 200 individuals with TGD and 200 eyes of 200 healthy age- and sex-matched controls, with female predominance in both groups (Table 1). The mean (SD) FT4 concentration was significantly higher in the TGD group than in the control group (6.20 [3.90] and 1.33 [0.23] ng/dL, respectively; $P < 0.0001$). Despite a numerically higher mean (SD) FT3 level in the TGD group than in the control group, the difference was not statistically significant (3.80 [9.31] and 2.68 [0.88] pmol/L, respectively; $P = 0.43$). The mean (SD) TSH concentration was significantly lower in the TGD group than in the control group (0.84 [2.35] and 2.87 [1.24] μU/mL, respectively; $P < 0.0001$). In the TGD group, the frequencies of hyperthyroidism and hypothyroidism were 190 (95%) and 10 (5%), respectively. All individuals in the control group were euthyroid.

Table 2 summarizes the corneal characteristics of the study groups. We found significantly lower mean CTT, higher Kmax, and greater BE values in the TGD group than in the control group (all $P < 0.05$). Considering axial map patterns, the frequencies of AB/SS, AB/IS, and AB/SRAX patterns were significantly higher in the TGD group than in the control group ($P < 0.05$; Table 2). The frequency of eyes with keratoconus was significantly higher in the TGD group (n = 15 eyes, 7.5%) than in the control group (n = 1 eye of a male participant, 0.5%; $P < 0.0001$) (Table 2).

In subgroup analysis of the TGD group, of 15 eyes with keratoconus, 14 were eyes of participants with hyperthyroidism (nine females and five males), and one was the eye of a participant with hypothyroidism (one female; $P = 0.04$). Comparing the hyperthyroidism and hypothyroidism subgroups, we observed a significantly lower mean (SD) CTT (523.40 [46.77] and 575.00 [30.21] μm, respectively; $P = 0.002$), higher Kmax (45.90 [4.36] and 43.10 [1.05] D, respectively; $P = 0.0009$), and greater BE (6.30 [5.94] and 2.50 [1.53] μm, respectively; $P = 0.001$) in the hyperthyroidism subgroup. Table 3 summarizes the correlation between corneal characteristics and thyroid profile in the study groups. In the TGD group, we found a statistically significant negative correlation between Kmax and TSH level (r = - 0.23, $P < 0.05$), a positive correlation between CTT and TSH level (r = + 0.15, $P < 0.05$), and no significant correlation between BE and TSH level, and between Kmax, CTT, or BE and FT3 or FT4 level (all $P > 0.05$; Table 3). The strength of the observed significant relationship of TSH level with Kmax or CTT was weak or negligible. In the control group, no significant correlation was found between corneal characteristics and thyroid profile (all $P > 0.05$; Table 3). We instructed all participants with keratoconus to continue follow-up in both the Outpatient Cornea and Endocrinology Units in the setting of a multidisciplinary team approach.

Table 1. Demographic characteristics of study groups

Variables	TGD group (n = 200)	Control group (n = 200)	*P*-value
Age (y), Mean ± SD	35.3 ± 6.6	34.1 ± 7.3	0.09
Sex (Male / Female), n (%)	40 (20) / 160 (80)	28 (14) / 172 (86)	0.1

Abbreviations: TGD, thyroid gland dysfunction; n, number of participants; y, years; SD, standard deviation; %, percentage.

Table 2. Comparison of corneal characteristics between study groups

Variables	TGD group (n = 200)	Control group (n = 200)	*P*-value
Kmax (D), Mean ± SD	45.80 ± 4.10	43.20 ± 2.75	**0.001**
CTT (μm), Mean ± SD	534.90 ± 53.96	544.40 ± 27.17	**0.02**
Back elevation (μm), Mean ± SD	7.60 ± 5.63	6.30 ± 5.04	**0.008**
SB pattern, n (%)	143 (71.5)	177 (88.5)	**0.001**
AB pattern, n (%)	3 (1.5)	13 (6.5)	
AB/SS pattern, n (%)	21 (10.5)	6 (3.0)	
AB/IS pattern, n (%)	32 (16.0)	4 (2.0)	
AB/SRAX pattern, n (%)	1 (0.5)	0 (0.0)	
Corneal opacity, n (%)	2 (1.0)	1 (0.5)	0.06
Keratoconus, n (%)	15 (7.5)	1 (0.5)	**< 0.0001**

Abbreviations: TGD, thyroid gland dysfunction; n, number of eyes; %, percentage; Kmax, maximum simulated keratometry reading; D, diopters; SD, standard deviation; CTT, corneal thinnest thickness; μm, micrometers; SB, symmetric bowtie; AB, asymmetric bowtie; AB/SS, asymmetric bowtie/superior steep; AB/IS, asymmetric bowtie/inferior steep; AB/SRAX, asymmetric bowtie pattern with a skewed radial axis. Note: *P*-values < 0.05 are shown in bold.

Table 3. Correlation between corneal characteristics and thyroid profile.

Thyroid profile	Kmax, Correlation Coefficient (*P*-value)	CTT, Correlation Coefficient (*P*-value)	BE, Correlation Coefficient (*P*-value)
TGD group (n = 200 eyes)			
FT3	r = - 0.09 (0.2)	r = - 0.07 (0.3)	r = + 0.11 (0.12)
FT4	r = + 0.002 (0.9)	r = - 0.05 (0.5)	r = + 0.05 (0.4)
TSH	**r = - 0.23 (0.001)**	**r = + 0.15 (0.03)**	r = - 0.09 (0.2)
Control group (n = 200 eyes)			
FT3	r = - 0.11 (0.1)	r = - 0.04 (0.5)	r = - 0.06 (0.5)
FT4	r = + 0.12 (0.09)	r = - 0.03 (0.7)	r = - 0.02 (0.8)
TSH	r = + 0.04 (0.6)	r = + 0.02 (0.8)	r = + 0.05 (0.4)

Abbreviations: Kmax, maximum simulated keratometry reading; CTT, corneal thinnest thickness; BE, back elevation; TGD, thyroid gland dysfunction; n, number of eyes; FT4, free thyroxine; FT3, free tri-iodothyronine; TSH, thyroid-stimulating hormone; r, correlation coefficient. Note: *P*-values < 0.05 are shown in bold.

DISCUSSION

We found a significantly higher frequency of keratoconus in individuals with treatment-naive, newly diagnosed, laboratory-confirmed TGD than in age- and sex-matched healthy controls. In parallel with a higher frequency of keratoconus, compared with controls eyes, the TGD group had significantly lower mean CTT, higher Kmax, and greater BE values, with a higher frequency of AB/SS, AB/IS, and AB/SRAX patterns that are compatible with clinical characteristics of keratoconus. As expected, those with TGD had significantly higher FT4 and lower TSH levels than controls. Except for a significant but weak or negligible correlation between TSH level and Kmax or CTT in the TGD group, we found no significant correlation between thyroid profile and other corneal characteristics in either group. Most participants in the TGD group had hyperthyroidism, accounting for 95% of cases, and 93% of eyes with keratoconus in the TGD group were within this subgroup. Likewise, eyes in the hyperthyroidism subgroup had significantly lower CTT, higher Kmax, and greater BE values.

The potential role of TGD in keratoconus development and progression has been postulated [7, 13-15, 29-37]; however, some studies have not supported this association [16-20]. We found a significantly higher frequency of keratoconus in individuals with TGD than in healthy controls, with rates of 7.5 and 0.5%, respectively. Thanos et al. [12] reported a TGD rate of 13.6% (21 patients) in 154 patients with keratoconus, of whom 90% (19 patients) had hypothyroidism and 10% (two patients) had hyperthyroidism. The TGD rate was six times higher than that of a previous study in the general population. Among 21 patients with keratoconus and TGD, 15 and six patients had severe and moderate keratoconus, respectively. The authors found a significantly higher tear T4 concentration in eyes with keratoconus and TGD, and in eyes with keratoconus but without overt clinical TGD, compared with that of controls. However, the tear T4 concentrations were comparable between individuals with keratoconus and TGD versus those having keratoconus without TGD [12]. As in our study, the researchers observed female predominance among patients with TGD and keratoconus [12]. The current study did not measure tear T4 concentrations in eyes with keratoconus in the TGD group. Further studies addressing this limitation could provide better understanding of the effect of TGD on keratoconus severity.

In a population-based cohort study [38] with a decade of follow-up, the incidences of keratoconus among individuals with hyperthyroidism, hypothyroidism, and euthyroidism were 8.287, 6.019, and 6.227 individuals per 100 000 person-years, respectively, with a female predominance in keratoconus incidence. The researchers found no statistically significant differences; however, there was a higher hazard ratio of developing keratoconus in those with hyperthyroidism than in euthyroid individuals after age and sex adjustment [38]. Likewise, we found that most patients with TGD and keratoconus had hyperthyroidism, and we observed a female predominance in those with keratoconus and TGD (n = 10 females, 67%).

Awad et al. [30] recruited 177 patients having keratoconus without previously diagnosed TGD along with 85 age- and sex-matched healthy controls with normal corneas and no systemic comorbidities. All participants underwent quantitative measurement of thyroid indices (TSH, FT4, and FT3 concentrations) with evaluation of vitamin D receptor polymorphisms. They observed significantly higher keratometry (flat K, steep K, and Kmax) and lower pachymetry values in patients with keratoconus than in controls. They found significantly higher TSH and FT4 levels, with a higher frequency of TGD, in patients than in healthy controls [30]. Logistic regression analysis identified TSH and T4 levels,

hypothyroidism, and insufficient or deficient vitamin D level as risk factors for keratoconus [30]. We recruited those with laboratory-confirmed, treatment-naive TGD and found a higher frequency of keratoconus when compared with age- and sex-matched controls. Considering that Awad et al. [30] found a higher frequency of TGD among those with keratoconus, and the current study observed a higher frequency of keratoconus among those with TGD, we recommend that every patient with TGD be examined for the coexistence of keratoconus, and vice versa.

Gatzioufas and Thanos [31] reported a case of acute keratoconus with mild hypothyroxinemia in a 33-year-old woman at the 19th week of pregnancy who had a 6-year history of bilateral keratoconus [31]. Although we excluded pregnant or breastfeeding women, the only participant with hypothyroidism and keratoconus was female in the TGD group. Bassiouny et al. [29] conducted a case-control study in Egypt recruiting 100 eyes of 50 patients having TGD and 100 eyes of 50 healthy controls. They compared Pentacam parameters between study groups and assessed potential correlations of serum FT4 and TSH levels with Pentacam parameters. They found significantly higher values for steep keratometry, Kmax, central corneal thickness, and thinnest pachymetry in those with hypothyroidism than in those with hyperthyroidism or healthy controls [29]. BE, however, was significantly higher in the eyes of patients with hyperthyroidism than in those with hypothyroidism or healthy controls. Serum TSH and FT4 levels had moderate positive and negative correlations with central corneal thickness and thinnest pachymetry, respectively [29]. We found significant positive and negative correlations of serum TSH with Kmax and CTT, respectively. However, no correlations were found between FT4 or FT3 level and corneal parameters in either group. The mean values for CTT, Kmax, and BE were significantly different between groups. Eyes of individuals with hyperthyroidism had a significantly lower CTT, higher Kmax, and greater BE. These findings may indicate that hyperthyroidism could affect corneal characteristics more than hypothyroidism. However, considering the unequal numbers of participants with hyperthyroidism and hypothyroidism in the TGD group, further age- and sex-matched longitudinal studies including similar numbers of participants are needed to verify this hypothesis.

Meyer [39] reported preliminary outcomes in 429 patients with severe keratoconus who underwent corneal transplantation and had a 3% rate of diagnosed or treated TGD (13 of 429 patients), of whom 2.3% had hypothyroidism (10 of 429 patients). He observed a higher prevalence rate for women (10 of 178 women, 5.6%) than men (3 of 251men, 1.2%). He concluded that, based on an official report involving a similar population that had TGD prevalence rates of 5.9 and 1.2% in women and men, respectively, the rate of TGD among the study participants with severe keratoconus did not differ from that of the general population [39]. We observed a significantly higher frequency of keratoconus in those with laboratory-confirmed, treatment-naive TGD than in healthy controls. This observed discrepancy between results of the two studies could be due to a difference in inclusion criteria, as Meyer [39] included those with severe keratoconus who underwent corneal transplantation and retrospectively reviewed their thyroid profiles without including a control group [39]. However, our participants had laboratory-confirmed TGD, keratoconus was detected in 7.5%, with a wide spectrum of severity, and the findings were compared and confirmed using age- and sex-matched healthy controls.

In a cross-sectional study comparing 187 patients having keratoconus without previously known TGD to 187 sex- and age-matched healthy controls, El-Massry et al. [7] reported a 5.3% prevalence rate of TGD among patients with keratoconus versus 1.1% in controls without keratoconus. They found a significantly higher mean (SD) TSH value in those with keratoconus (3.35 [1.1] μU/mL) than in controls (2.66 [1.37] μU/mL). However, serum FT3 and FT4 levels were comparable. Of 187 patients with keratoconus, 10 (5.3%) had TGD, and the rate of TGD in controls was lower at 1.1% (two patients); however, the difference did not reach statistical significance. The researchers reported the treatment outcomes of patients with keratoconus and TGD with a follow-up range of 1–8 years [7]. In a population with a racial background similar to that included by El-Massry et al. [7], the current study revealed a prevalence of 7.5% for keratoconus among those with laboratory-confirmed TGD. This may indicate an association between TGD and keratoconus; however, a causal relationship must be confirmed using prospective, longitudinal cohort studies with robust designs.

The present study provides evidence of an association between TGD and keratoconus, exploiting both laboratory investigations and Pentacam imaging to report detailed findings. However, the study had a small sample size, lack of age subgrouping, and no inclusion of corneal biomechanical characteristics [32] or tear T4 concentration measurements [15]. Considering the findings of the current and previous studies [12, 30], we recommend examining for potential coexistence of keratoconus among those with TGD, and vice versa. Further studies including immunohistochemical evaluation of the cornea in patients with TGD and keratoconus who underwent corneal transplantation may clarify

the pathogenesis of this observed association. Moreover, current evidence on the suitability of artificial intelligence (AI) in diagnosing, staging, grading, pretreatment assessment, and treatment decisions for thyroid eye disease [40, 41] suggests a potential application of AI in screening for TGD among patients with confirmed keratoconus or assessing for preclinical keratoconus in patients with TGD.

CONCLUSIONS

We found a higher frequency of keratoconus, with a female predominance, in individuals with TGD than in healthy controls. TGD was associated with significant changes in certain corneal topographic and tomographic parameters. Increased Kmax and BE values with more corneal thinning in the TGD group may indicate an association between keratoconus and TGD. However, further longitudinal studies are needed to confirm these preliminary findings.

ETHICAL DECLARATIONS

Ethical approval: This study was approved by the ethics committee of Fayoum Faculty of Medicine, Fayoum University, Fayoum, Egypt, and adhered to the tenets of the Declaration of Helsinki. All participants provided written informed consent before enrollment.

Conflict of interest: None.

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