

Prevalence of keratoconus in persons with Down syndrome: a review

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ABSTRACT

Purpose Keratoconus is a vision-threatening condition, and there is a need for knowledge about the occurrence in subgroups of the population. The progression of the disease can be effectively stopped, and vision may be restored, if keratoconus is diagnosed at an early stage. The purpose of this review was to evaluate the literature of the prevalence of keratoconus in persons with Down syndrome.

Methods We conducted a literature review of keratoconus prevalence in persons with Down syndrome. A thorough search was performed in Pubmed (Medline), and the quality of evidence was evaluated.

Results The literature review identified 20 relevant studies, which reported keratoconus in 0%–71% of persons with Down syndrome. These studies varied greatly in design, patient selection, sample sizes and mean age, and the quality of evidence concerning estimates for the prevalence of keratoconus was generally evaluated as low. Most studies that included adults reported high prevalences of keratoconus—in many studies more than 10-fold the prevalence in the general population. No large screening studies in persons with Down syndrome were identified.

Conclusions The present review showed that the prevalence of keratoconus in persons with Down syndrome is higher than in the general population. However, estimates from previous studies vary widely. Screening for keratoconus in this group should be considered.

INTRODUCTION

Keratoconus is characterised by thinning and a conical shape of the cornea leading to refraction errors and visual complaints.¹ As the disease progresses, the corrected distance visual acuity is affected. At this stage, further examinations are often performed, and corneal tomography usually leads to the diagnosis.

Keratoconus was previously considered quite rare, with a reported prevalence of 54.5 per 100 000 population in an often-cited study from 1986.² However, some recent studies have reported markedly higher prevalences; 0.2%–0.3% in the general population^{3 4} and more than 1% in some subgroups.^{5–7} Higher rates may be a consequence of more sophisticated diagnostics and increased awareness of the disease in recent years. Additionally, the threshold for referral and more diligent

follow-up of these patients are likely lowered as a result of corneal collagen crosslinking (CXL), which has been shown as a successful treatment for stopping the disease progression.^{8–11} The introduction of CXL has led to a decreased demand for keratoplasties in keratoconus patients.^{11 12}

Persons with Down syndrome have an increased risk of several medical diseases. Ocular conditions include epicanthus, strabismus, lens opacifications and refraction errors.^{13–15} An increased risk of keratoconus has also been mentioned,^{15–19} although the exact reason for this association remains unknown. Studies have found varying frequencies of keratoconus in persons with Down syndrome. While some have reported a markedly higher prevalence than in the general population, other studies have reported no keratoconus cases.^{13 15 16 18–30}

In the literature, no clear consensus appears to have been established regarding the true prevalence of keratoconus in persons with Down syndrome. Many studies seem to be limited by small sample sizes, furthermore, prevalence estimates are affected by whether studies have examined subgroups of patients or specific age groups (eg, children). A thorough evaluation of these aspects seemed to be required. Knowledge about the occurrence of keratoconus in persons with Down syndrome is essential for both clinicians and policymakers, in terms of determining the threshold for referral to eye examination for individual patients, for resource allocation and for evaluating whether keratoconus screening should be recommended in this group. In this literature review, we aimed to investigate the prevalence of keratoconus in persons with Down syndrome as well as to evaluate the quality of the current knowledge.

MATERIALS AND METHODS

In this review, we conducted a literature search of all published articles that have presented original research with numbers and/or proportions of the occurrence of keratoconus in persons with Down syndrome.



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We used the following search strategy to find relevant publications on PubMed (Medline): ((*keratoconus*[Title/Abstract]) AND (*prevalence*[Title/Abstract] OR *incidence*[Title/Abstract])) AND *Down syndrome*[Title/Abstract]. An additional search was performed without the terms *prevalence* and *incidence*. We also searched the reference lists of the included articles, in case some relevant publications had not been identified. The search was restricted to English-language publications and had no time restrictions. It was conducted by two independent reviewers (OK and LD) and was finished in November 2020. The quality of evidence and risk of bias of the included studies were evaluated.

RESULTS

Results of the literature search

The main literature search yielded 21 articles, 13 of which reported rates of keratoconus in persons with Down syndrome.^{13 15 18–22 24 25 27 30–32} In the additional literature search with a total of 54 articles, we identified another six articles for inclusion.^{16 23 26 28 29 33} Thus, a total of 19 articles met the inclusion criteria for the review. In addition, we have included results from our recently published nationwide register study of the keratoconus prevalence in persons with Down syndrome.³⁴ As shown in [table 1](#), the reported rates in these publications ranged from 0% to 71%. Another three studies were considered relevant, although they did not quantify the rate of keratoconus: one study found a high proportion of astigmatism and myopia in persons with Down syndrome¹⁴; another found a steeper corneal curvature on topography in persons with Down syndrome compared with controls³⁵ and a third showed that corneal topographic changes in persons with Down syndrome were more similar to mild keratoconus than in controls.³⁶ Furthermore, a large retrospective longitudinal cohort study of keratoconus patients found an adjusted OR of 6.22 for Down syndrome.³⁷

Quality of evidence evaluation

A quite high proportion of the included studies had small sample size in terms of determining the prevalence of keratoconus in persons with Down syndrome. The number of individuals with Down syndrome in the included studies ranged from 31 to 4342 ([table 1](#)). The studies varied in terms of whether they reported specific inclusion criteria in detail. Some studies did only include hospitalised patients. Seven studies focused on children.^{16 20 23–26} Ten studies either did not include corneal tomography or did not comment on the use of such diagnostic instruments.^{18–21 24–26 28–30} In general, higher rates (>10%) were reported in studies that included corneal topography as standard.^{13 15 16 22 23 27 31 32} Our recently published study was the only one that included the whole population of a country.³⁴ Still, its quality of evidence was limited by the lack of detailed clinical data. Two studies were screened for keratoconus in selected samples of the population with Down syndrome,^{22 32} otherwise, we identified no large population-based screening studies.

DISCUSSION

Persons with Down syndrome have an increased risk of developing keratoconus.^{17–19} Our literature search identified several studies that have reported increased rates in this population—in one study as high as 71%.³¹ However, previous studies vary greatly; furthermore, their estimates have primarily been based on small sample sizes and often on selected hospital populations or children.^{13 15 16 18–30} Only one study reported nationwide numbers, estimating a keratoconus prevalence of 5.5% among persons with Down syndrome.³⁴

Most previous studies have estimated a keratoconus prevalence in the range of 17.5–86 per 100 000 in general populations.^{2 38–42} However, markedly higher numbers have been reported in some recent studies of general populations, with an estimated prevalence of 0.2% in Norway,⁴ 0.3% in the Netherlands³ and 1.2% in a younger population in Australia.⁷ Furthermore, even higher rates have been found in subgroups of the population in India, Jerusalem, New Zealand and Saudi Arabia.^{5 6 43 44} Although knowledge is limited concerning the aetiology of keratoconus, a number of publications have indicated that specific conditions are associated with an increased risk, including atopy, allergy, eye rubbing, Leber's congenital amaurosis, mitral valve prolapse and connective tissue disease.^{17 45 46} In addition, an association with Down syndrome has been clearly demonstrated.^{17–19}

Down syndrome is caused by an extra copy of chromosome 21. The occurrence seems to vary across countries, in the range of 0.7–1.4 per 1000 live births.^{47 48} The proportion in the general population is expected to be slightly lower, as persons with Down syndrome have a shorter life expectancy.^{49 50} Rates of approximately 0.8 per 1000 people in the general population have been reported.^{49 51} Suggested links with keratoconus are collagen-related abnormalities and that keratoconus is linked to chromosome 21.^{17 45} Additionally, it has been argued that Down syndrome is associated with more eye rubbing and possibly also a higher frequency of atopy.^{15 17 30 45 52} Moreover, a thinner cornea has been found in the eyes of persons with Down syndrome without manifest keratoconus.^{15 16}

This literature review identified studies that have reported keratoconus in as many as 8%–36% of persons with Down syndrome.^{15 16 18 22 23 27–30 33} and in one study even in 71%.¹³ However, several of these studies had small sample sizes and a biased patient selection ([table 1](#)). Furthermore, other studies have reported no keratoconus in persons with Down syndrome.^{19 20 25 26} This inconsistency is likely due to study design, completeness of the data, disease criteria, the diagnostics used and ethnicity (it has been speculated that the proportion of keratoconus is considerably lower in Asians with Down syndrome).⁵³ In addition, age seems to be an important factor to the variation in prevalence, as several of the studies (especially those from Asia) seem to have only included children, whereas keratoconus usually develops in adolescence or early adulthood. Furthermore, corneal

Table 1 Proportions with keratoconus in persons with Down syndrome (studies identified by literature review)

| | n DS | n (%) KC | Location | CT | Patient group and age |
|--|------|------------------------------|-----------------|---------|--|
| Walsh ¹⁸ | 91 | 7 (8%) | Sweden | No | Institutionalised mentally retarded persons (5–60 years). |
| Wong and Ho ¹⁹ | 140 | 0 (0%) | Hong Kong | No | Children (3 months–13 years) in hospital. |
| Van Allen <i>et al</i> ²⁹ | 38 | 6 (15.8%) | USA | No | Adults (30–68 years old) in residential centre. |
| Haugen <i>et al</i> ¹⁵ | 47 | 5 (10.6%) | Norway | Yes | Case–control study (all ages) |
| Kim <i>et al</i> ²⁵ | 123 | 0 (0%) | Korea | No | Children (6 months–14 years), non-institutionalised. |
| Van Splunder <i>et al</i> ³⁰ | 409 | 36 (9%) | Netherlands | No | Cross-sectional survey. Adults (≥18 years) |
| Liza-Sharmini <i>et al</i> ²⁶ | 60 | 0 (0%) | Malaysia | No* | Children (1 month–17 years) in hospital. |
| Fimiani <i>et al</i> ²⁰ | 157 | 0 (0%) | Italy | No | Children (1 month–18 years) in hospital. |
| Karlica <i>et al</i> ²⁴ | 153 | 2 (1.3%) | Split-Dalmatia | No | Children (0–18 years). |
| Fong <i>et al</i> ²¹ | 91 | 1 (1%) | Hong Kong | No† | Cross-sectional survey. Adults (≥18 years) |
| Aslan <i>et al</i> ¹⁶ | 27 | 21.1% (11 eyes) | Helsinki | Yes | Children (5–12 years). Clinical trial. Identified early subclinical keratoconus. |
| Li <i>et al</i> ³³ | 20 | 36.3% (12 eyes) | Hong Kong | Yes‡ | Adult patients scheduled for cataract surgery (tertiary eye hospital) |
| Real de Asua <i>et al</i> ²⁸ | 144 | 10 (7%) | Spain | Unknown | Retrospective review of medical records. Adults (17–65 years) |
| Alio <i>et al</i> ¹³ | 59§ | 42 (71.3%) | Spain and Egypt | Yes | Multicentre case–control study. Age 3 months–60 years. |
| Marsack <i>et al</i> ²⁷ | 140 | 11.8%–20.8%¶ (26–46 eyes) | USA | Yes | Case–control study. Age 8–55 years |
| Hashemi <i>et al</i> ²² | 226 | 28 (12.4%) | Iran | Yes | Population-based cohort study. Age 10–30 years. |
| Imbornoni <i>et al</i> ²³ | 31 | 10 (32%) | USA | Yes | Children/young adults (4–24 years) in hospital. |
| Mathan <i>et al</i> ³² | 98 | 30 (30.6%) ** | New Zealand | Yes | Screening of paralympics athletes (age 15–53 years) |
| Bermudez <i>et al</i> ³¹ | 1207 | 331 (27.2%) | Brazil | Yes‡ | Retrospective review of medical records. Adults (all ages) |
| Kristianslund and Drolsum ³⁴ | 4342 | 238 (5.5%) | Norway | Yes†† | Population-based register study. All ages. |

*Placido disc used to detect keratoconus.

†Corneal thickness measured.

‡when KC suspected and the patient cooperated.

§Number of patients that cooperated with eye examination.

¶Proportion above threshold on detection metric (two types used).

**Presents several numbers.

††Performed in many cases when indicated and the patient cooperated, however, proportion unknown.

CT, corneal topography/tomography; DS, Down Syndrome; KC, keratoconus; n, number.

topography was not always included as part of the ocular examination. This review identified rates in the range of 10.6%–71.3% in studies that included corneal topography as part of the examination of mainly adult patients (table 1).^{13 15 16 22 23 27 31 32}

In a study from Norway, we reported a national prevalence of keratoconus in persons with Down syndrome using data from a nationwide patient registry,³⁴ thereby avoiding the risk of selection bias. We found a keratoconus rate of 5.5% in this subgroup, which is 30 times the estimated keratoconus prevalence in the general Norwegian population.⁴ The Norwegian Patient Registry

is nationwide and mandatory for public specialist care; thus, making it possible to study the national occurrence of keratoconus in persons with Down syndrome and compare it with the corresponding rate in the general population. However, even in national register studies, some uncertainty remains as to whether patients have been correctly coded. In addition, the true prevalence of keratoconus in patients with Down syndrome is probably higher, as no routine screening is performed for this condition.

Few other studies of keratoconus in persons with Down syndrome have been carried out in Northern



Europe.^{15 16 18} A case-control study by Haugen *et al*¹⁵ found a thinner cornea, higher keratometry values and more keratoconus in the Down syndrome group, as 5 out of 47 (11%) individuals with Down syndrome had keratoconus, compared with 1 out of 51 (2%) controls. In studies from various other regions throughout the world, lower proportions than the one we found in Norway have been reported in young patients,^{20 24–26} whereas higher proportions have often been reported in selected hospital populations.^{13 18 22 28 29} In a study from Brazil, Bermudez *et al*³¹ reviewed the medical records of 1207 patients with Down syndrome and found a keratoconus rate of 27.2%. They describe an ophthalmological outpatient clinic for Down syndrome patients, which included corneal topography if keratoconus was suspected and the patient cooperated. Thus, their numbers possibly approaches a realistic prevalence if screening for keratoconus is performed in persons with Down syndrome.

It seems reasonable to suspect a substantial number of undiagnosed cases of keratoconus, particularly in persons with Down syndrome, since the detection of this eye condition depends on adequate communication of symptoms, timely referral and good cooperation during the eye examinations. Early keratoconus may be challenging to diagnose in the slit lamp only, and cooperation with corneal tomography is often a challenge in persons with Down syndrome. Retinoscopy may be valuable by searching for abnormal motions of the retinoscopy reflex.¹⁵

Several studies from general populations have found a male predominance for keratoconus,^{3 6 40 54–56} although this finding has not been consistent.^{2 5 39 57} In this literature review, we identified one publication that found a similar gender distribution among persons with Down syndrome and keratoconus,²² which is consistent with our recent publication,³⁴ otherwise, the gender distribution does not seem to have been in focus. There seem to be slightly more male than female persons with Down syndrome.^{50 58} We were, therefore, surprised to find a similar gender distribution for keratoconus in persons with Down syndrome in our study from Norway, as we have previously identified a quite pronounced male predominance for keratoconus in general in the total Norwegian population.⁴ Several predisposing factors seem to influence the development of keratoconus, and we hypothesise that the predominant factor in persons with Down syndrome is not related to gender or hormonal factors. However, this is speculation, and further research is needed.

Results from this literature review indicate a considerably higher proportion of keratoconus in persons with Down syndrome compared with the general population. An implication from this finding is that screening should be considered for this group,^{30 39} especially since several of these patients are less able to communicate their symptoms. Health economic aspects should be included in such evaluations. Marsack *et al*²⁷ demonstrated keratoconus suspect findings in 11.8%–20.8% of eyes of persons with Down syndrome, using two detection metrics on corneal topographies. If keratoconus is detected, and

CXL treatment is performed in early stages, a good visual acuity can hopefully be maintained. Furthermore, this may avoid persons reaching advanced stages, where corneal transplantation with a long postoperative follow-up may become necessary; a treatment that is particularly complicated in Down syndrome patients.⁶⁰ A considerable proportion of persons with Down syndrome has visual impairment,²¹ and advanced stage keratoconus is likely one of the reasons.

In conclusion, the present review found a great variation in the reported prevalence of keratoconus in persons with Down syndrome; however, most studies of adolescents and adults reported a markedly higher prevalence than in the general population. Still, it seems likely that a significant number of keratoconus cases in persons with Down syndrome are undiagnosed. This indicates that screening for keratoconus in these individuals should be considered, to detect candidates for CXL treatment at an early stage. Also, large screening studies in persons with Down syndrome using slit lamp examinations and corneal tomography in cooperative individuals could provide more answers regarding the true prevalence.

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