A Systematic Review of Subclinical Keratoconus and Forme Fruste Keratoconus

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ABSTRACT

PURPOSE: To identify the definitions used for the terms subclinical keratoconus and forme fruste keratoconus in published articles.

METHODS: This was a prospective, systematic literature review of the electronic database in PubMed, the Cochrane Library, and LILACS Database of all studies using the keywords "subclinical keratoconus" and/or "forme fruste keratoconus" until August 18, 2017. Two independent reviewers analyzed the data. The inclusion criteria for articles were having analyzed subclinical keratoconus or forme fruste keratoconus eyes with a sample size greater than 10 eyes; containing the definition of subclinical keratoconus or forme fruste keratoconus; and the quality of published reports was assessed using standards quality index methods. The following aspects of the selected articles were then analyzed: inclusion criteria for definition and technology used.

RESULTS: A total of 198 and 95 studies, respectively, including the definition of subclinical keratoconus and forme fruste keratoconus were collected in an initial search, of which 165 and 73 studies, respectively, were excluded. Definitions for subclinical keratoconus and forme fruste keratoconus included the criteria of having keratoconus in the fellow eye in 72.72% (24 of 33) and 77.27% (17 of 22) of the articles, respectively. A total of 96.97% (32 of 33) and 90.90% (20 of 22) of the studies used more than one parameter to define subclinical keratoconus and forme fruste keratoconus, respectively. The most common extra parameters included normal slit-lamp examination and cornea on slit-lamp biomicroscopy and inferior-superior asymmetry and/or bowtie pattern with skewed radial axes.

CONCLUSIONS: This review demonstrates the lack of unified criteria to define subclinical keratoconus and forme fruste keratoconus. According to the literature review, the most common subclinical keratoconus definition used refers to an eye with topographic signs of keratoconus and/or suspicious topographic findings under normal slit-lamp examination and keratoconus in the fellow eye and the most common forme fruste keratoconus definition refers to an eye with normal topography, normal slit-lamp examination, and keratoconus in the fellow eye.

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Keratoconus is a progressive and asymmetric disease characterized by steepening, distortion, and apical thinning of the cornea.[1] Inclusion criteria for keratoconus diagnosis are well defined[1-3]; however, terms such as subclinical keratoconus and forme fruste keratoconus are still unclear and imprecise. At times the definitions overlap.

Initially, diagnosis of keratoconus was based on slit-lamp examination and clinical signs, and then topographic signs were included as diagnostic criteria.[1] More recently, with the advent of Scheimpflug imaging analysis and anterior segment optical coherence tomography (OCT), early diagnosis of the disease was achieved due to information such as pachymetric, epithelial, elevation, and aberrometry data, among others.[3] At this point, many indicators have been suggested to diagnose forme fruste keratoconus and subclinical keratoconus. However, there is currently no clear definition of these terms, and considering that the prevalence of keratoconus is higher today than previously reported and that the diagnostic technology allows higher accuracy than was previously used, it is imperative to press deeper into the imprecise field of criteria used in these definitions.

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The purpose of this study was to review the existing literature on subclinical keratoconus and forme fruste keratoconus definitions used for diagnosis and to describe which are the most-used criteria for these two entities to unify criteria.

METHODS

Search Strategy and Inclusion Criteria

A systematic review was performed of primary research articles published in scientific databases, developed under an internationally recommended methodology, to create a reliable and replicable summary of the best evidence available. The protocol was approved by the Scientific Ethics Committee of the Instituto de Ojos Oftalmosalud, Lima, Peru. We searched in the following electronic databases: Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Register of the Eyes and Vision Group); PubMed, using Medical Subject Headings (MeSH) terms and clinical queries; and Latin American and Caribbean Health Sciences Literature Database (LILACS). We reviewed all studies in these databases using the key words "subclinical keratoconus" (all fields) and "forme fruste keratoconus" (all fields) using dates through August 18, 2017. The reference lists of the articles were also examined.

Types of Publication

We primarily searched for articles published in scientific databases. The types of studies included were: prospective comparative studies; prospective cross-sectional, observational studies; prospective case series studies; prospective case–control studies; retrospective comparative studies; retrospective consecutive non-randomized studies; and retrospective cross-sectional studies. The inclusion criteria for articles was having analyzed subclinical keratoconus or forme fruste keratoconus eyes with a sample size greater than 10 eyes; containing the definition of subclinical keratoconus or forme fruste keratoconus; articles without a year-of-publication filter; and English language. Study participants were adult patients with subclinical keratoconus and/or forme fruste keratoconus.

Exclusion Criteria

Duplicated data, studies with a sample size of less than 10 eyes or patients, literature reviews, case reports, letters to the editor, comments to the editor, conferences, protocols, and other unrelated studies were deleted for each study analyzed.

Data Extraction and Assessment of Study Quality

Two independent reviewers analyzed the articles (MAH, MH), and any disagreements were resolved by a third party or by consensus between the reviewers (LI). The two independent authors reviewed the selected articles to find the keratoconus definitions used and the methodological quality and characteristic of each article. The information was entered into an Excel (Microsoft Corporation, Redmond, WA) spreadsheet for analysis.

The following information was extracted: authors, year of publication, title of the study, journal of publication, parameters used to define subclinical keratoconus and forme fruste keratoconus, technology used, and sample size. The quality of published reports was assessed using standard quality index methods adapted from Downs and Black[4] and Deeks et al.[5]

RESULTS

Subclinical Keratoconus

A total of 198 studies concerning the definition of subclinical keratoconus were collected in an initial search, of which 105 were excluded. A total of 93 were selected for a full evaluation and literary review, of which 60 studies were eliminated. In total, 33 articles[6-38] were evaluated for subclinical keratoconus terminology (**Table 1**, **Figure A**, available in the online version of this article).

Studies were evaluated using 14 questions we formulated to assess their quality (**Figure B**, available in the online version of this article). A "yes" answer to each quality-assessment question was considered a positive measure. According to the quality index formulary, 100% (33 of 33) of the sample selected had adequate hypotheses or objectives described and a satisfactory sample size and 93.94% (31 of 33) had main outcomes described in the introduction or methods.

The most frequently cited criterion used to define subclinical keratoconus was to have keratoconus in the fellow eye (72.72%; 24 of 33), followed by "Normal-appearing cornea on slit-lamp biomicroscopy, keratometry, retinoscopy, and ophthalmoscopy" in 45.45% (15 of 33) of the studies. **Table 2** shows the most frequently criteria used in the studies.

Thirty-two (96.97%; 32 of 33) of the studies used more than one parameter to define subclinical keratoconus. Only one study used one criterion to define subclinical keratoconus. Hashemi et al.[12] used the keratoconus severity score as a unique criterion, but it is a grading scheme that included several parameters.

The most frequently cited criteria combinations used to define subclinical keratoconus were: (1) normal-appearing cornea on slit-lamp biomicroscopy, keratometry, retinoscopy, and ophthalmoscopy; (2) inferior–superior asymmetry and/or bow-tie pattern with skewed radial axes; and (3) diagnosis of

TABLE 1

Inclusion Criteria to Define Subclinical Keratoconus Used in Each of the Articles Analyzed

Author, Journal, and Year of Publication	Inclusion Criteria for Diagnosis for Subclinical Keratoconus	Technology Used for Diagnosis
Sideroudi et al.[6] *Ophthalmic Physiol Opt*, 2017	D, E, F	Pentacam
Peña-Garcia et al.[7] *J Biomech*, 2016	F, D, R	ORA, Corvis ST
Shetty et al.[8] *Am J Ophthalmol*, 2017	A, B, C, D	Pentacam, Galilei, or Sirius
Vinciguerra et al.[9] *J Refract Surg*, 2017	D, C, G, H, R	Corvis ST, Pentacam, OPD III, or CSO
Martínez-Abad et al.[10] *Cont Lens Anterior Eye*, 2017	A, B, D, I, J	Sirius
Sideroudi et al.[11] *J Cataract Refract Surg*, 2016	D, E, F	Pentacam
Hashemi et al.[12] *J Curr Ophthalmol*, 2016	M	Pentacam HR
Feizi et al.[13] *J Ophthalmic Vis Res*, 2016	A, B, O, K	Galilei
Li et al.[14] *J Cataract Refract Surg*, 2016	F, B, Q, I	OCT-Fourier
Tummanapalli et al.[15] *J Cataract Refract Surg*, 2015	D, R, F, P	Orbscan IIz
Cui, et al.[16] *Curr Eye Res*, 2016	A, B, C, D	Pentacam
Steinberg et al.[17] *Cornea*, 2015	D, U	Corvis ST
Piñero et al.[18] *Graefes Arch Clin Exp Ophthalmol*, 2015	A, I, D, J	Pentacam
Steinberg et al.[19] *Cornea*, 2015	D, P, U	Pentacam, SS-OCT
Galletti et al.[20] *J Ophthalmol*, 2015	F, T, D	OCT, Placido disk topography, and aberrometry, ORA
Jafarinasab et al.[21] *J Ophthalmic Vis Res*, 2015	A, B, O, K	Orbscan IIz
Steinberg et al.[22] *Acta Ophthalmol*, 2015	D, U	Pentacam
Muftuoglu et al.[23] *J Cataract Refract Surg*, 2015	F, D, L	Pentacam HR
Sahebjada et al.[24] *Optom Vis Sci*, 2014	A, I	IOLMaster, Pentacam
Ruiseñor Vázquez et al.[25] *Am J Ophthalmol*, 2014	D, T	Pentacam HR
Serdarogullari et al.[26] *J Ophthalmic Vis Res*, 2013	A, D, I	Pentacam
Ozgurhan et al.[27] *Am J Ophthalmol*, 2013	A, B, D, J, W	Sirius or ConfoScan 4
de Sanctis et al.[28] *Cornea*, 2013	A, B, C, D	Pentacam
Ramos-López et al.[29] *Optom Vis Sci,* 2013	A, B	CSO
Ahmadi Hosseini et al.[30] *Int Ophthalmol*, 2013	A, B	Pentacam
Arbelaez et al.[31] *Ophthalmology*, 2012	F, D, Q, L, I	Sirius
Uçakhan et al.[32] *J Cataract Refract Surg*, 2011	A, B, D	Pentacam
Mihältz et al.[33] *J Cataract Refract Surg*, 2011	F, E, S, V	Top Model System, Hartmann-Shack wavefront sensor
Piñero et al.[34] *J Cataract Refract Surg*, 2010	A, D, I, J	Pentacam
Bühren et al.[35] *Invest Ophthalmol Vis Sci*, 2010	C, D, F, P	Orbscan IIz, Axial-keratometric data, MATLAB
Lema et al.[36] *Br J Ophthalmol*, 2009	V, N	Biomicroscope, EyeSys Corneal System, Orbscan II
de Sanctis et al.[37] *Ophthalmology*, 2008	A, B, C, D	Pentacam
Bühren et al.[38] *Am J Ophthalmol*, 2007	C, D, M, P, F	Orbscan IIz

ORA = Ocular Response Analyzer; CSO = Costruzione Strumenti Oftalmici; SS-OCT = swept-source optical coherence tomography; OPD = Corneal Topographer Auto Refractor Keratometer
A: Normal-appearing cornea on slit-lamp biomicroscopy, keratometry, retinoscopy, and ophthalmoscopy.
B: Inferior–superior asymmetry and/or bow-tie pattern with skewed radial axes.
C: No history of contact lens use, ocular surgery, or trauma.
D: Diagnosis of keratoconus in the fellow eye.
E: KISA% index between 60% and 100% in the subclinical keratoconus eye.
F: Lack of any keratoconus-related findings/signs in the slit-lamp biomicroscopy.
G: Belin/Ambrósio Enhanced Ectasia total deviation index (BAD-D) from the Pentacam < 1.60 standard deviations.
H: Corvis Biomechanical Index (CBI) score of greater than 0.5 in both eyes.
I: Corneal topography showing an abnormal, localized steepening, or central/inferior steepening or asymmetric bow-tie pattern or claw-shaped pattern on topography.
J: One of the following signs: steep keratometric curvature greater than 47.00 diopters, oblique cylinder greater than 1.50 diopters, or central corneal thickness less than 500 µm.
K: Asymmetric bow-tie pattern without skewed radial axis and/or inferior steepening and/or keratoconus predicting index of 23% to 30% and/or keratoconus severity index of 15% to 30% and/or keratoconus severity index of 15% to 30%.
L: No topography finding significant enough to be diagnosed as clinical keratoconus/corneas with subtle signs of keratoconus but without evidence of clinical keratoconus.
M: Keratoconus Severity Score (no specified which number was used for subclinical keratoconus definition).
N: Simulated central corneal power greater than 47.20 diopters but less than 48.70 diopters.
O: Abnormal biomicroscopic findings including Vogt's striae and Fleischer ring > 2 mm or skewed radial axis > 21° or > 20, or keratoconus predicting index > 30% or > 0.3 or keratoconus severity index > 30%, and abnormal keratoconus index.
P: Inferior–superior asymmetry lower than 1.40 diopters and/or maximum keratometry of 47.00 diopters or less.
Q: Corrected distance visual acuity of 20/20 or better.
R: Normal topography (with no asymmetric bow-tie and no focal or inferior steepening pattern).
S: Maximum keratometry ≥ 47.00 /47.20 diopters.
T: Keratoconus Severity Score of 0, 1, or 2.
U: KISA% index lower than 60%.
V: Paracentral inferior–superior dioptric asymmetry difference in 1.40 to 1.90 diopters gradient.
W: An elevation of the posterior corneal surface (unspecified quantitative value).

TABLE 2

Frequency of Parameters Used in Subclinical Keratoconus Definition in the Analyzed Studies

Parameter	Frequency
Diagnosis of keratoconus in the fellow eye	72.72% (24/33)
Normal-appearing cornea on slit-lamp biomicroscopy, keratometry, retinoscopy, and ophthalmoscopy	45.45% (15/33)
Inferior–superior asymmetry and/or bow-tie pattern with skewed radial axes	36.36% (12/33)
Lack of any keratoconus-related findings/signs in the slit-lamp biomicroscopy	33.33% (11/33)
No history of contact lens use, ocular surgery, or trauma	21.21% (7/33)
Corneal topography showing an abnormal, localized steepening, or central/inferior steepening or asymmetric bow-tie pattern or claw-shaped pattern on topography	21.71% (7/33)
One of the following signs: steep keratometric curvature greater than 47.00 D, oblique cylinder greater than 1.50 D, or central corneal thickness less than 500 µm	12.12% (4/33)
Inferior–superior asymmetry lower than 1.40 D and/or maximum keratometry of 47.00 D or less	12.12% (4/33)
KISA% index between 60% and 100% in the eye with subclinical keratoconus	9.09% (3/33)
KISA% index lower than 60%	9.09% (3/33)
Normal topography (with no asymmetric bowtie and no focal or inferior steepening pattern)	9.09% (3/33)
No topography finding significant enough to be diagnosed as clinical keratoconus/corneas with subtle signs of keratoconus but without evidence of clinical keratoconus	6.06% (2/33)
Keratoconus Severity Score (no specified number was used for subclinical keratoconus definition)	6.06% (2/33)
Abnormal biomicroscopic findings including Vogt's striae and Fleischer ring > 2 mm or skewed radial axis > 21° or > 20°, or keratoconus predicting index > 30% or > 0.3 or keratoconus severity index > 30%, and abnormal keratoconus index	6.06% (2/33)
Corrected distance visual acuity of 20/20 or better (Snellen)	6.06% (2/33)
Keratoconus Severity Score 0, 1, or 2	6.06% (2/33)
Paracentral inferior–superior dioptric asymmetry difference in 1.40 to 1.90 D gradient	6.06% (2/33)
Belin/Ambrósio Enhanced Ectasia total deviation index (BAD-D) from the Pentacam < 1.60 standard deviations	3.03% (1/33)
Corvis Biomechanical Index (CBI) score > 0.5 in both eyes	3.03% (1/33)
Simulated central corneal power > 47.20 D but less than 48.70 D	3.03% (1/33)
Maximum keratometry ≥ 47.00/47.20 D	3.03% (1/33)
Elevation of the posterior corneal surface (unspecified quantitative value)	3.03% (1/33)

KISA% = keratoconus percentage index; D = diopters

keratoconus in the fellow eye in 21.71% (7 of 33) of the studies. **Table 3** shows the most commonly used combinations.

Some criteria have been used in a contradictory, imprecise, or ambiguous way. For example, "Normal-appearing cornea on slit-lamp biomicroscopy, keratometry, retinoscopy, and ophthalmoscopy" was used in 45.45% (15 of 33) of the studies, whereas "Lack of any keratoconus-related findings/signs in the slit-lamp biomicroscopy" was used in 33.33% (11 of 33) of them. "Inferior–superior asymmetry and/or bow-tie pattern with skewed radial axes" was used in 36.36% (12 of 33) of the studies, whereas "inferior steepening or asymmetric bow tie pattern (unspecific value)" was used in 21.71% (7 of 33). "Paracentral inferior–superior dioptric asymmetry difference in 1.40 to 1.90 D" was used in 6.06% (2 of 33) of the studies, whereas "inferior–superior asymmetry lower than 1.40 D" was used in 12.12% (4 of 33) of them. "KISA index between 60% and 100%" was used in 9.09% (3 of 33) of the studies, whereas "KISA% index lower than 60%" was used in 9.09% (3 of 33) of the studies. "Keratoconus Severity Score (without explanation of which value was included)" was used in 6.06% (2 of 33), whereas "KSS of 0, 1, or 2" was used in 6.06% (2 of 33). "Maximum keratometry ≥ 47.00 D" was used in 3.03% (1 of 33), and "Maximum keratometry ≥ 47.00 D" in 12.12% (4 of 33) of the studies.

These were the sample sizes of the articles analyzed for definition of subclinical keratoconus: 30.30% (10 of 33) had fewer than 20 patients, 42.42% (14 of 33) had 21 to 50 patients, 21.21% (7 of 33) had 50 to 100 patients, and 6.06% (2 of 33) had more than 100 patients.

Forme Fruste Keratoconus

A total of 95 studies on the definition of forme fruste keratoconus were collected in an initial search, of which

TABLE 3

Most Frequently Cited Criteria Combinations Used to Define Subclinical Keratoconus and Forme Fruste Keratoconus[a]

Frequently Cited Criteria Combinations Including 3 Parameters	Studies That Used This Combination
To define subclinical keratoconus	
Normal-appearing cornea on slit-lamp biomicroscopy, keratometry, retinoscopy, and ophthalmoscopy	21.71% (7/33)
Inferior–superior asymmetry and/or bow-tie pattern with skewed radial axes	
Diagnosis of keratoconus in the fellow eye	
Inferior–superior asymmetry and/or bow-tie pattern with skewed radial axes	12.12% (4/33)
No history of contact lens use, ocular surgery, or trauma	
Diagnosis of keratoconus in the fellow eye	
Normal-appearing cornea on slit-lamp biomicroscopy, keratometry, retinoscopy, and ophthalmoscopy	12.12% (4/33)
Corneal topography showing an abnormal localized steepening or central/inferior steepening or asymmetric bow-tie pattern or claw-shape pattern on topography	
Diagnosis of keratoconus in the fellow eye	
To define forme fruste keratoconus	
Normal topography	31.81% (7/22)
Normal slit-lamp examination	
Keratoconus in the fellow eye	
Lack of any keratoconus-related findings/signs in the slit-lamp biomicroscopy	9.09% (2/22)
KISA% values between 60% and 100%	
Keratoconus in the fellow eye	

KISA% = keratoconus percentage index
[a]All other combinations that included at least three criteria were used in fewer than three studies for subclinical keratoconus definitions and in only one study in the forme fruste keratoconus definitions.

48 were excluded. A total of 47 were selected for a full evaluation and literature review, of which 25 studies were eliminated. In total, 22 articles[39-59] were evaluated for forme fruste keratoconus analysis (**Table 4**, **Figure C**, available in the online version of this article).

We evaluated the quality of the studies using criteria similar to those described above. All 22 articles (100%) had an adequate sample size, a comparative group, an adequate hypothesis or objective described, a description of patients' characteristics, findings that were clearly described, an appropriate statistical test, and an accurate results measure of value and reliability (**Figure D**, available in the online version of this article).

The three variables most used to define forme fruste keratoconus in the articles evaluated were: keratoconus in the fellow eye in 77.27% (17 of 22), normal topography in 59.09% (13 of 22), and normal slit-lamp examination in 40.90% (9 of 22).

Of these studies, 90.90% (20 of 22) used more than one parameter to define forme fruste keratoconus. Only two studies used one parameter. Zhang et al.[47] used the Keratoconus Severity Score (KSS) as unique criteria, but it is a grading scheme that included several parameters, and Kirwan et al.[58] used a superior–inferior power difference in a 4-mm central zone of more than 1.50 diopters (D).

The most frequently cited criteria combinations used to define forme fruste keratoconus were normal topography, normal slit-lamp examination, and keratoconus in the fellow eye in 31.81% (7 of 22) studies, followed by lack of any keratoconus-related findings of signs in the slit-lamp biomicroscopy, KISA% values between 60% and 100%, and keratoconus in the fellow eye in 9.09% (2 of 22) of the studies (**Table 5**).

Some criteria were used in an unspecific or contradictory way in the articles. For example, "normal-appearing cornea on slit-lamp biomicroscopy, keratometry, retinoscopy, and ophthalmolscopy" was used in 40.90% (9 of 22), and "Lack of any keratoconus-related findings/signs in the slit-lamp biomicroscopy" in 13.63% (3 of 22) of the studies. "Inferior–superior power difference in 4-mm central zone more than 1.50 D" was used in 9.09% (2 of 22) of the studies, whereas "Paracentral inferior–superior dioptric asymmetry ≤ 1.4" was used in 4.54% (1 of 22), and "area of inferior or superior steepening (unspecific value)" was used in 4.54% (1 of 22). "KISA% index be-

TABLE 4

Inclusion Criteria to Define Forme Fruste Keratoconus Used in Each of the Articles Analyzed

Author, Journal, and Year of Publication	Inclusion Criteria for Terminology	Technology Used for Diagnosis
Awad et al.[39] *BMC Ophthalmol*, 2017	A, B, C, D, E	Pentacam
Naderan et al.[40] *Int Ophthalmol*, 2018	A, D, E	OPD Scan II
Pahuja et al.[41] *J Biophotonics*, 2017	A, D, E	Pentacam, OCT
Fujimoto et al.[42] *Invest Ophthalmol Vis Sci*, 2016	A, D, E	OCT
Hashemi et al.[43] *J Curr Ophthalmol*, 2016	F, G, H	Pentacam version 1.17r72
Freitas G de O et al.[44] *Am J Ophthalmol*, 2016	A, E	Pentacam
Ruiz Hidalgo et al.[45] *Cornea*, 2016	E, S	Pentacam
Luz et al.[46] *Am J Ophthalmol*, 2015	K, A, E	ORA
Zhang et al.[47] *J Cataract Refract Surg*, 2015	M	ORA, Orbscan IIz, Galilei
Ayar et al.[48] *Int J Ophthalmol*, 2015	A, D, E	Pentacam, ORA
Mohammadpour et al.[49] *Oman J Ophthalmol*, 2015	I, J, N, O	ORA
Sideroudi et al.[50] *Optom Vis Sci*, 2014	E, L, O	Pentacam
Ye et al.[51] *Br J Ophthalmol*, 2014	A, E	AS OCT, OCT
Fukuda et al.[52] *Br J Ophthalmol*, 2015	A, D, E	3D CAS-OCT, Scheimpflug camera with topography
Smadja et al.[53] *Am J Ophthalmol*, 2013	A, E, O	Galilei
Kozobolis et al.[54] *Eur J Ophthalmol*, 2012	E, L, O	Pentacam, ORA, Topolyzer wavelight
Saad & Gatinel[55] *Invest Ophthalmol Vis Sci*, 2012	A, D, E, P, Q	OPD, Orbscan IIz
Johnson et al.[56] *Cornea*, 2011	E, R, M	ORA, Orbscan IIz
Saad & Gatinel[57] *Invest Ophthalmol Vis Sci*, 2010	P, Q, E	Orbscan IIz, OPD Scan
Kirwan et al.[58] *Ophthalmologica*, 2008	H	ORA
Chan et al.[59] *Cornea*, 2015	A, D	Orbscan IIz, Tomey, SCORE analyzer

OPD = Corneal Topographer Auto Refractor Keratometer; OCT = optical coherence tomography; ORA = Ocular Response Analyzer; AS-OCT = anterior segment optical coherence tomography; 3D CAS-OCT = three-dimensional corneal and anterior segment optical coherence tomography; KISA% = keratoconus percentage index; KSS = Keratoconic Severity Score; NCN = Nidek Corneal Navigator

A: Normal topography.
B: Mean keratometry < 47.00 diopters.
C: Paracentral inferior–superior dioptric asymmetry ≤ 1.4.
D: Normal slit-lamp examination.
E: Keratoconus in the fellow eye.
F: Apex of the cone not centered at the 6-o'clock semi-meridian.
G: Corneal thickness at the apex of the cone is approximately 30 mm thinner than the corresponding distance above the pupil center.
H: Inferior–superior power difference in 4-mm central zone > 1.50 diopters.
I: Area of inferior–superior steepening (unspecific value) or minor topographic asymmetry.
J: Corneal steepness > 47.00 diopters.
K: KISA% index < 60.
L: KISA% values between 60% and 100%.
M: KSS < 3, regardless of the status of the fellow eye.
N: Oblique cylinder > 1.50 diopters.
O: Lack of any keratoconus-related findings/signs in the slit-lamp biomicroscopy.
P: NCN score: null score similarity to suspect keratoconus and keratoconus.
Q: NCN score: non-null score similarity to keratoconus for the contralateral eyes.
R: KSS could be 0, 1, or 2 as long as keratoconic eye had a KSS < 3.
S: Asymptomatic Pentacam tomography and elevation.

tween 60% and 100%" was used in 9.09% (2 of 22) of the studies, whereas "KISA% index less than 60%" was used in 4.54% (1 of 22) of them. "KSS of 1 or 2, regardless of the status of the fellow eye" was used in 9.09% (2 of 22), whereas "KSS of 0, 1, or 2 as long as the other eye with keratoconus has a KSS ≥ 3" was used in 4.54% (1 of 22) of the studies.

The sample size of the articles analyzed for the definition of forme fruste keratoconus were as follows: 22.22% (6 of 22) of the total articles had a sample of 21 to 30 patients; 11.11% (3 of 22) had 31 to 40 patients; 22.77% (5 of 22) had 41 to 50 patients, 7.40% (2 of 22) had 51 to 60 patients; and 13.63% (3 of 22) had 61 to 70 patients.

DISCUSSION

A clinical diagnosis means that the identification of the disease underlying a patient's complaints is based merely on signs, symptoms, and medical history of

TABLE 5

Frequency of Parameters Used on Forme Fruste Keratoconus Definition in the Analyzed Studies

Parameter	Frequency
Keratoconus in the fellow eye	77.27% (17/22)
Normal topography	59.09% (13/22)
Normal slit-lamp examination	40.90% (9/22)
Lack of any keratoconus-related findings/signs in the slit-lamp biomicroscopy	13.63% (3/22)
Inferior–superior power difference in 4-mm central zone more than 1.50 D	9.09% (2/22)
KISA% values between 60% and 100%	9.09% (2/22)
NCN score: non-null score similarity to keratoconus for the contralateral eyes	9.09% (2/22)
Mean keratometry < 47.00 D	4.54% (1/22)
Paracentral inferior–superior dioptric asymmetry ≤ 1.40 D	4.54% (1/22)
Apex of the cone not centered at the 6-o'clock semi-meridian	4.54% (1/22)
Corneal thickness at the apex of the cone is approximately 30 mm thinner than the corresponding distance above the pupil center	4.54% (1/22)
Area of inferior or superior steepening (unspecific value) or minor topographic asymmetry	4.54% (1/22)
Corneal steepness > 47.00 D	4.54% (1/22)
KISA% index less than 60%	4.54% (1/22)
KSS of 1 or 2, regardless of the status of the fellow eye	9.09% (2/22)
Oblique cylinder > 1.50 D	4.54% (1/22)
NCN score: null score similarity to suspect keratoconus and keratoconus	4.54% (1/22)
KSS of 0, 1, or 2 as long as the other eye with keratoconus has a KSS of ≥ 3	4.54% (1/22)
Asymptomatic Pentacam tomography and elevation	4.54% (1/22)

D = diopters; KISA% = keratoconus percantage score; NCN = Nidek Corneal Navigator; KSS = Keratoconus Severity Score

the patient, rather than on laboratory examination or medical imaging. In this way, clinical keratoconus is defined by the evidence of one or more slit-lamp biomicroscopic findings, including conical protrusion of the cornea at the apex, Fleischer rings, Vogt striae, and corneal stromal thinning.[1-3] However, keratoconus diagnosis based only on clinical signs will lead to its diagnosis at the latest stage of the disease, so a commonly used definition is the presence of at least one clinical sign plus topographic criteria. This then ceases to be only a clinical diagnosis; it also includes medical imaging.

The term "subclinical" by dictionary denotation[60] is "not detectable or producing effects that are not detectable by the usual clinical tests"; usual tests for keratoconus diagnosis currently include corneal topography and tomography. Therefore, although many studies may be using the term "subclinical" to mean disease evident on imaging but not on "clinical" examination, this definition appears to be incorrect and outdated. In our review, the three most common variables used in the articles to define subclinical keratoconus were to have: "keratoconus in the fellow eye" in 72.72% (24 of 33); "normal-appearing cornea on slit-lamp biomicroscopy, keratometry, retinoscopy, and ophthalmoscopy" in 45.45% (15 of 33) of the studies; and "inferior-superior asymmetry and/or bowtie pattern with skewed radial axes" in 36.36% (12 of 33) of the studies.

Forme fruste (from the French, "crude, or unfinished, form") is an atypical or attenuated manifestation of a disease or syndrome, with the implications of incompleteness, partial presence, or aborted state. In 1938, Amsler used photographic Placido disk technology to describe early corneal topographic changes and coined the term "form fruste keratoconus."[61-63] The results of our study show that the three variables most used to define forme fruste keratoconus in the articles evaluated were: keratoconus in the fellow eye in 77.27% (17 of 22) of the studies, normal topography in 59.09% (13 of 22) of the studies, and normal slit-lamp examination in 40.90% (9 of 22) of the studies.

The review also shows that most of the articles (subclinical keratoconus: 72.72% [24 of 33] and forme fruste keratoconus: 77.27% [17 of 22]) included having keratoconus in the fellow eye as a diagnostic criterion. This means that a bilateral early diagnosis of the disease without clinical expression is difficult. Also, according to the literature examined, there is no consensus about how many and which signs of a suspicious topography are necessary to distinguish

subclinical keratoconus or forme fruste keratoconus from "keratoconus suspect or abnormal topography" in a patient when neither eye has keratoconus. Thus, to diagnose the early form of keratoconus from an abnormal topography is still a challenge today, and will require consensus on what features are relevant.

A suspicious topography is defined as a topography that includes asymmetric bow-tie, which is asymmetric steepening in any direction greater than 0.50 D but less than 1.00 D as compared with the region 180 degrees opposite the steepest region with no skewed radial axis, and inferior steepening of skewed radial axis, which includes significant skewed radial axis (20 degrees or greater) with or without inferior steepening or 1.00 D or more as compared with the region 180 degrees opposite the steepest region, but an inferior-superior value less than 1.40 D.[44] According to our results, some of the topographic parameters used for both definitions (subclinical keratoconus and forme fruste keratoconus) are not clearly diagnostic criteria for "keratoconus" and can overlap the "suspicious topographic definition."

After analyzing the currently used terminology, the lack of unified criteria is evident. The purpose of the current study is not to generate definitions; however, the most commonly used criteria suggest diagnosing "subclinical keratoconus" only in those eyes with normal slit-lamp examination, topographic/tomographic signs of keratoconus or suspicious topography, and keratoconus in the fellow eye. The diagnosis of forme fruste keratoconus definition was reserved for those eyes with normal slit-lamp examination, normal topography, and keratoconus in the fellow eye. These definitions seem not able to offer initial diagnoses of these conditions in a useful way independent of the condition of the other eye.

This review also reflects some gaps in information. Some criteria related to epithelial imaging,[64] wavefront aberrations,[55] corneal biomechanics,[65] and posterior elevation[66] that have been associated with early diagnosis of keratoconus have not been included as inclusion criteria in the majority of the studies. Finally, it remains doubtful if the term "subclinical keratoconus" is adequate, considering that keratoconus is a bilateral disease and the clinical signs of keratoconus in the fellow eye would mean that the disease was no longer subclinical in its presentation.

This review reflects the lack of unified criteria to define subclinical keratoconus and form fruste keratoconus, and shows that, in the majority of the cases, both definitions require the presence of keratoconus in the other eye, which make it extremely difficult to define the disease in its early form independent of the status of the other eye.

AUTHOR CONTRIBUTIONS

Study concept and design (MAH, LI); data collection (MH); analysis and interpretation of data (MAH, MH); writing the manuscript (MAH, MH); critical revision of the manuscript (MAH, LI); supervision (MAH, LI)

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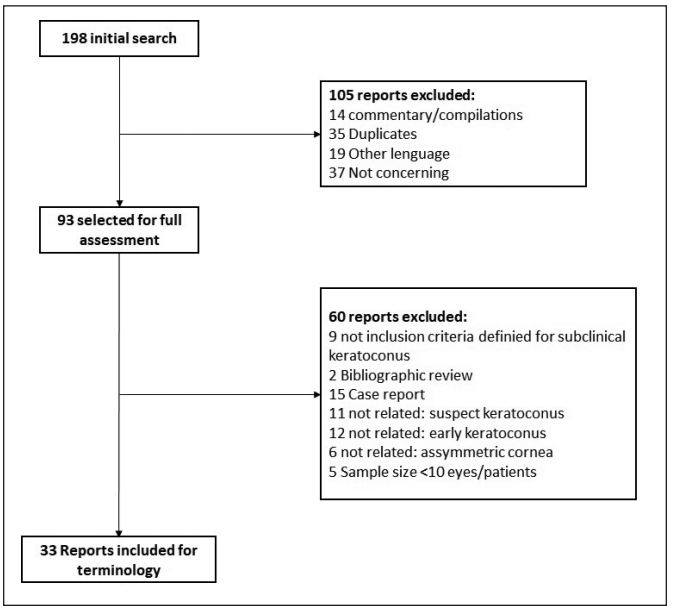

Figure A. Flow chart describing the selection of studies about subclinical keratoconus definition.

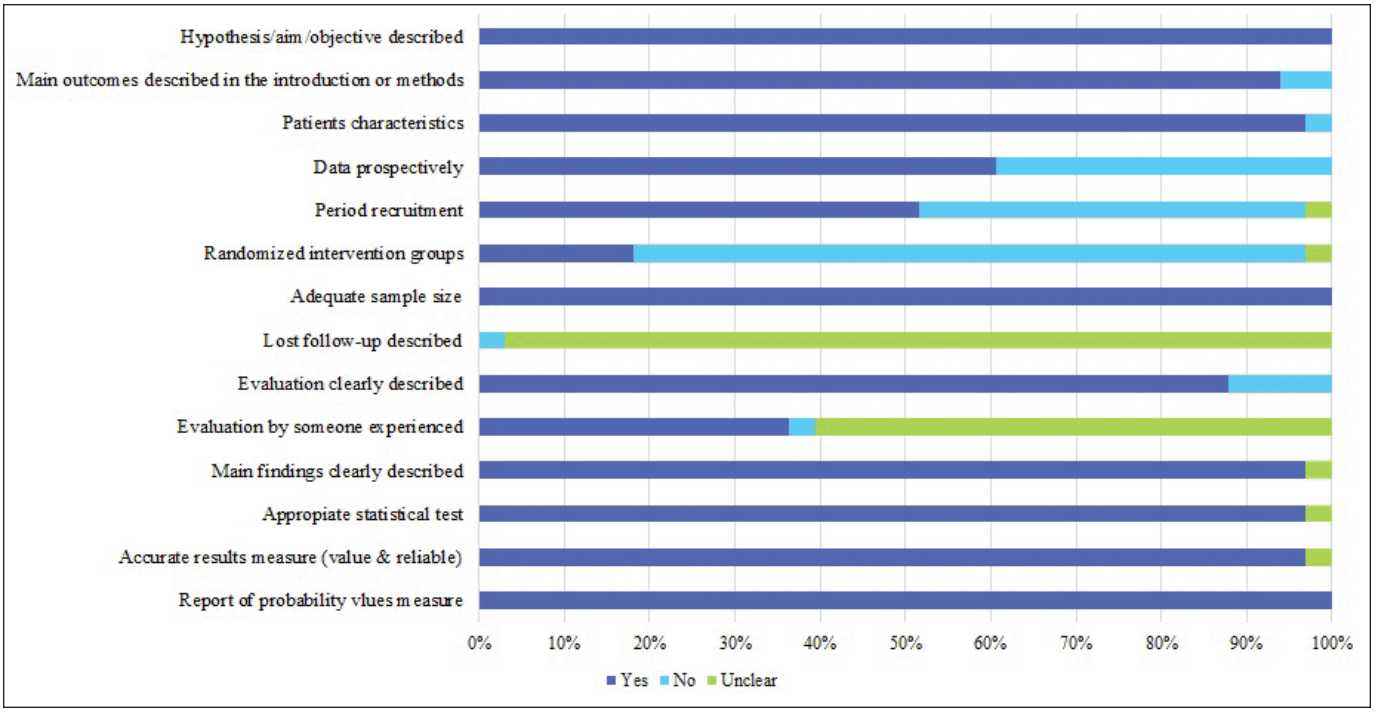

Figure B. Bar graph showing the proportion of studies about subclinical keratoconus terminology: per quality item.

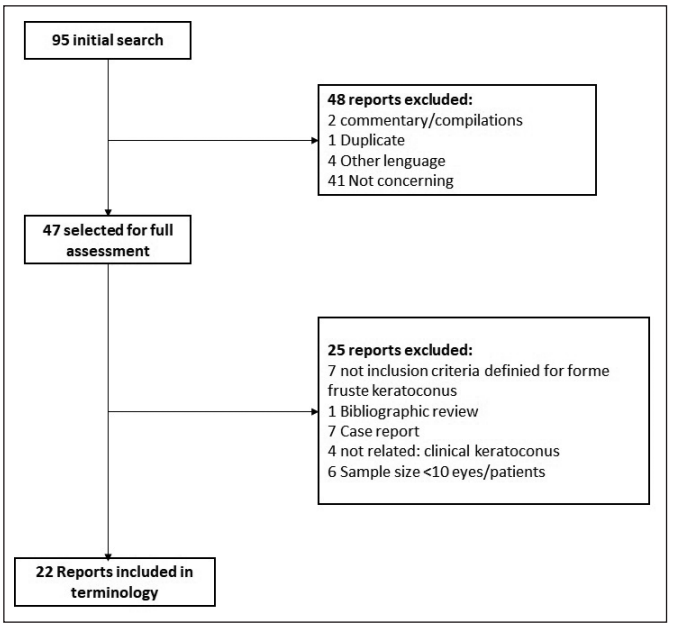

Figure C. Flow chart describing the selection of studies about forme fruste keratoconus definition.

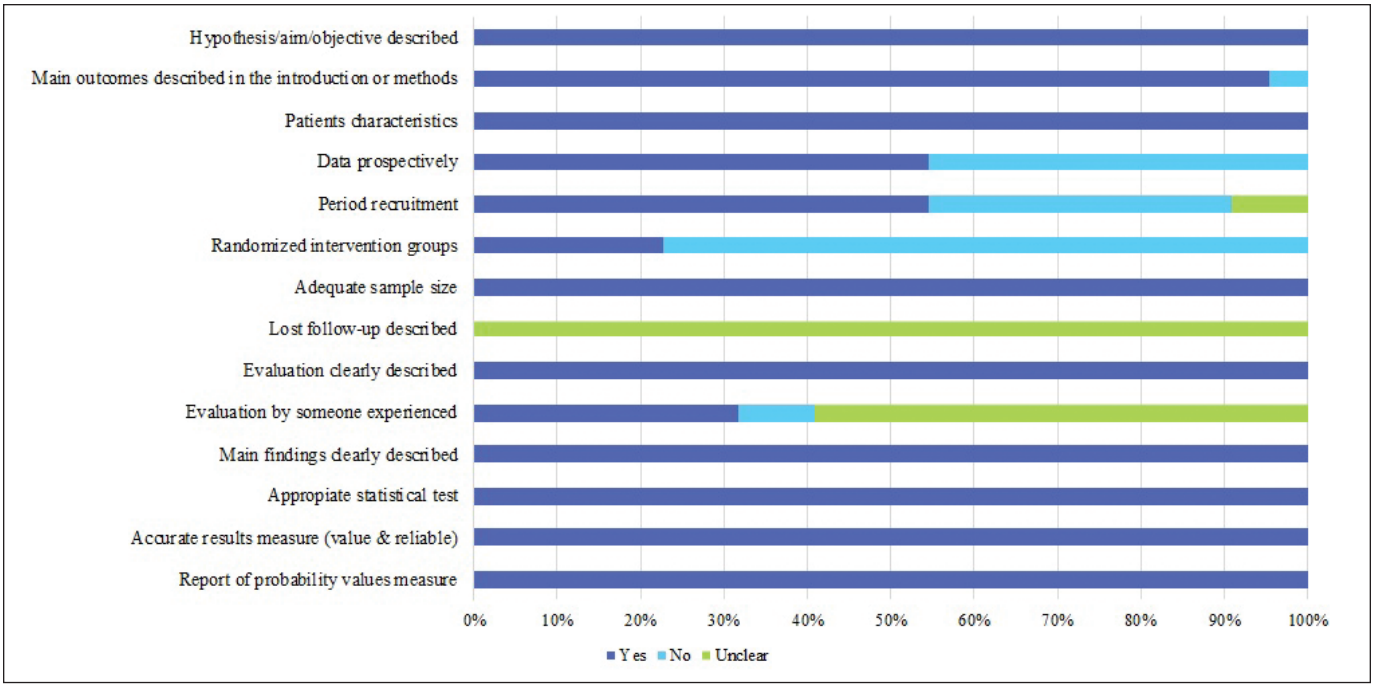

Figure D. Bar graph showing the proportion of studies about terminology and definition of forme fruste keratoconus: per quality item.