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META-ANALYSIS

The Association Between Keratoconus and Mitral Valve Prolapse: A Meta-Analysis

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ARTICLE HISTORY

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Abstract: ***Objective*****:** The debate pertaining to the association between Keratoconus (KC) and Mitral Valve Prolapse (MVP) continues to occur among physicians. The results of cross-sectional studies attempting to present the co-existing prevalence of these two diseases remain indeterminate. We compiled the first meta-analysis to determine the pattern of prevalence between the two diseases.

Methods**:** Two separate literature searches for cross-sectional studies were performed for this meta-analysis. The first search encompassed finding literature comparing the prevalence of KC between patients with MVP and a control group. The second search pertained to finding studies comparing the prevalence of MVP patients with KC and a control group.

Results**:** Six studies reported the prevalence of MVP in patients with KC and a control group. The prevalence was 41.6% in patients with KC and 11.5% in patients without KC (OR = 7.06 [95% CI = 2.41-20.64]). There was a significant heterogeneity among the studies (I^2 = 84%). Two studies showed the prevalence of KC in patients with MVP and a control group. The prevalence was 17.0% in patients with KC and 2.9% in the control group (OR = 5.07 [95% CI = 1.08-23.83]). There was no heterogeneity within the analysis (I^2 = 0%).

Conclusion**:** There is a statistically significant co-existing prevalence between MVP and KC. Patients with KC are more likely to present with MVP, and patients with MVP are more likely to present with KC.

Keywords: Keratoconus, mitral valve prolapse, association, epidemiology, cardiology, ophthalmology.

1. INTRODUCTION

Beardsley and Foulks first proposed an association between keratoconus and mitral valve prolapse in 1982 [1]. Since then, studies further emphasized the possible association between the two diseases. However, some studies have found no association between them, and the ones that do find a correlation comprised of small sample sizes [1-7]. There has not been a published meta-analysis that associates these two diseases. The following meta-analysis compiles all the data from these studies to show if there is a significant prevalence of mitral valve prolapse in patients with keratoconus in addition to a significant prevalence of keratoconus in patients with mitral valve prolapse.

2. METHODS

2.1. Data Collection

An electronic search was performed for cross-sectional studies containing a study group of patients with keratoconus or mitral valve prolapse and a control group to assess the prevalence of the other disease that was not common throughout the study group; publications included either a study group composed of patients with keratoconus to assess the prevalence of mitral valve prolapse or a study group composed of patients with mitral valve prolapse to assess the prevalence of keratoconus. Databases included Google Scholar and PubMed.

Abstracts were then reviewed. Irrelevant articles and smaller studies containing the same patients included in another larger study were removed. Baseline characteristics and prevalence rates of each sample group were extracted and recorded in an electronic datasheet for further analysis.

2.2. Statistical Analysis

The meta-analysis was compiled with Review Manager Version 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark). Forest plots were created using the application to include DerSimonian and Laird random effects models to reduce heterogeneity. An I^2 of more than 50% was considered to have significant heterogeneity. Reported values were two-tailed. An Odds Ratio (OR) with a confidence interval

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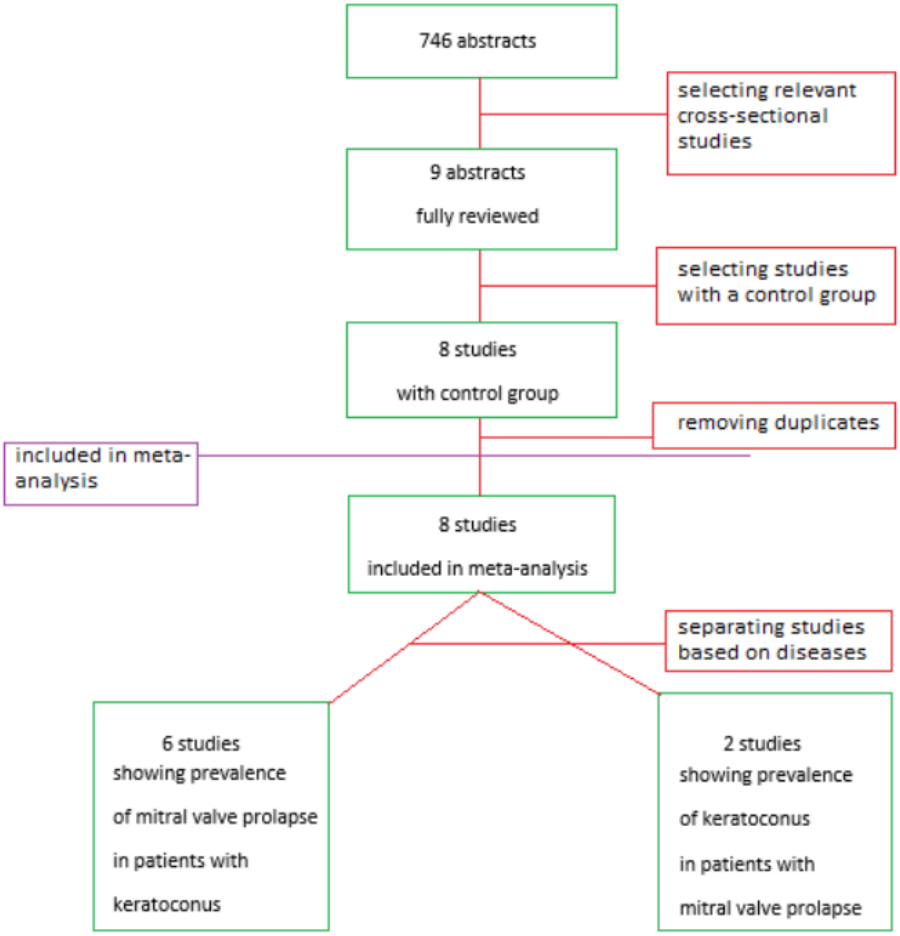

Fig. (1). Flowchart illustrating the study selection process. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

of 95% was reported using the Mantel-Haenszel method. A *p* value of less than 0.05 was considered statistically significant.

3. RESULTS

3.1. Selected Studies

The electronic search identified 746 publications (Fig. **1**). Selecting for cross-sectional studies which assessed the number of mitral valve prolapse cases in patients with keratoconus or vice versa reduced the number of publications to 9. One publication was removed due to not having a control group. No publications had identical patients. This allowed for 8 publications to be used for the analysis (Table **1**).

From the 8 publications, 2 studies identified the prevalence of mitral valve prolapse in patients with keratoconus and 6 studies determined the prevalence of keratoconus in patients with mitral valve prolapse. Baseline characteristics are listed on Tables **2** and **3**, respectively (Table **2**, Table **3**). The baseline characteristics are similar among the studies. The study by Mohammady *et al*. did not report the age or gender of their patients but stated that both the study group and control group were matched in terms of those characteristics [7]. Street *et al*. split patients into two groups according to whether they were older or younger than 40 years, therefore, making it difficult to discern the exact numbers for inclusion in the baseline analysis [5]. Sharif *et al*. contributed information on age and gender of the patients in the study group, but only described the patients in the control group as matched with those of the study group [4].

3.2. Prevalence of Mitral Valve Prolapse in Patients with Keratoconus

Six studies reported the prevalence of mitral valve prolapse in patients with keratoconus and compared it to a control group (Fig. **2**). The prevalence was 41.6% in patients with keratoconus and 11.5% in the patients without keratoconus (OR = 7.06 [95% CI = 2.41-20.64]; p = 0.0004). There was significant heterogeneity among the studies (I^2=84%).

3.3. Prevalence of Keratoconus in Patients with Mitral Valve Prolapse

Two studies showed the prevalence of keratoconus in patients with mitral valve prolapse and compared it to a group of patients without keratoconus (Fig. **3**). The prevalence was 17.0% in the patients with keratoconus and 2.9% in the control group (OR = 5.07 [95% CI = 1.08-23.83]; p = 0.04). There was no heterogeneity within the analysis (I^2 = 0%).

Table 1. Details of selected studies.

Study Name	Prevalence Investigated	No. Patients	Results	Comments
Akcay *et al*. (2014)	KC in patients with MVP	97 (MVP = 52; Control = 45)	KC in MVP = 5.7%; KC in Control = 1.1% (p = 0.25)	Mention a group of patients with suspected KC, but only the definite KC patients were used in our meta-analysis.
Lichter *et al*. (2011)	KC in patients with MVP	61 (MVP = 36; Control = 25)	KC in MVP = 22.2%; KC in Control = 4.0% (p = 0.08)	-
Rabbanikhah *et al*. (2011)	MVP in patients with KC	160 (KC = 32; Control = 128)	MVP in KC = 65.6%; MVP in Control = 9.0% (p < 0.01)	The patients with KC also had acute corneal hydrops while the patients in the control group had no ophthalmic diseases.
Javadi *et al*. (2007)	MVP in patients with KC	229 (KC = 62; Control = 167)	MVP in KC = 22.6%; MVP in Control = 6.6% (p < 0.01)	The odds ratio for MVP increased with each decade (lower than third decade, third decade, and fourth decade and above noted).
Mohammady *et al*. (2001)	MVP in patients with KC	60 (KC = 30; Control = 30)	MVP in KC = 90.0%; MVP in Control = 40.0% (p < 0.01)	-
Sharif *et al*. (1992)	MVP in patients with KC	100 (KC = 50; Control = 50)	MVP in KC = 58.0%; MVP in Control = 7.0% (p < 0.01)	-
Street *et al*. (1991)	MVP in patients with KC	191 (KC = 95; Control = 96)	MVP in KC = 21.1%; MVP in Control = 17.7% (p = 0.56)	-
Beardsely *et al*. (1982)	MVP in patients with KC	45 (KC = 22; Control = 23)	MVP in KC = 40.9%; MVP in Control = 13.0% (p = 0.04)	-

Abbreviations: KC = Keratoconus; MVP = Mitral Valve Prolapse.

Table 2. Baseline characteristics of combined studies.

Characteristic	MVP Prevalence in KC Patients		KC Prevalence in MVP Patients	
	KC Patients	Control Patients	MVP Patients	Control Patients
Age [mean (range)]	29 (17-64)	29.8 (15-65)	44.5 (19-79)	41.1 (20-78)
Gender [total male/ total female]	164/95	269/137	44/44	36/34
Total patients	291	494	88	70

Abbreviations: MVP = mitral valve prolapse; KC = keratoconus.

Table 3. Contributions to baseline characteristics.

Study	Baseline Characteristic Contributed
Akcay *et al*.	Age, Gender, Total (KC in MVP patients)
Lichter *et al*.	Age, Gender, Total (KC in MVP patients)
Rabbanikhah *et al*.	Age, Gender, Total (MVP in KC patients)
Javadi *et al*.	Age, Gender, Total (MVP in KC patients)
Mohammady *et al*.	Total (MVP in KC patients)
Sharif *et al*.	Age and Gender only of patients in study group, Total (MVP in KC patients)
Street *et al*.	Gender, Total (MVP in KC patients)
Beardsely *et al*.	Age, Gender, Total (MVP in KC patients)

Abbreviations: KC = Keratoconus; MVP = Mitral Valve Prolapse.

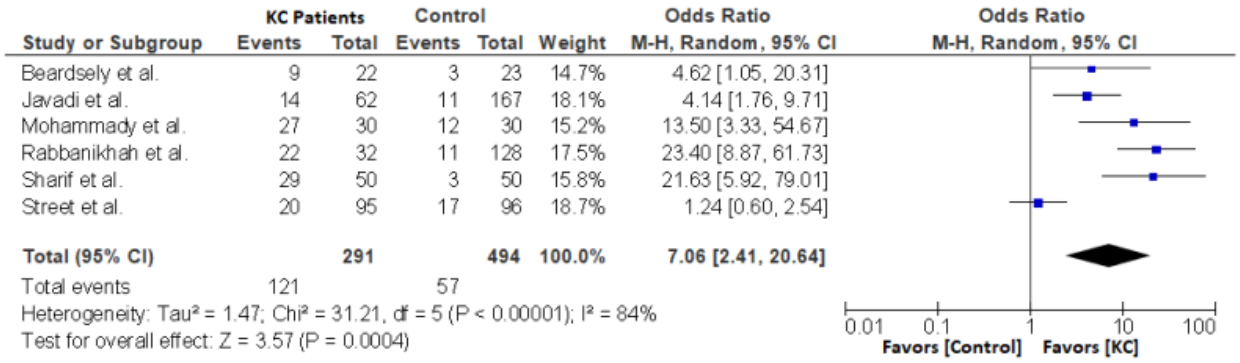

Fig. (2). Prevalence of mitral valve prolapse in patient with keratoconus compared to controls. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

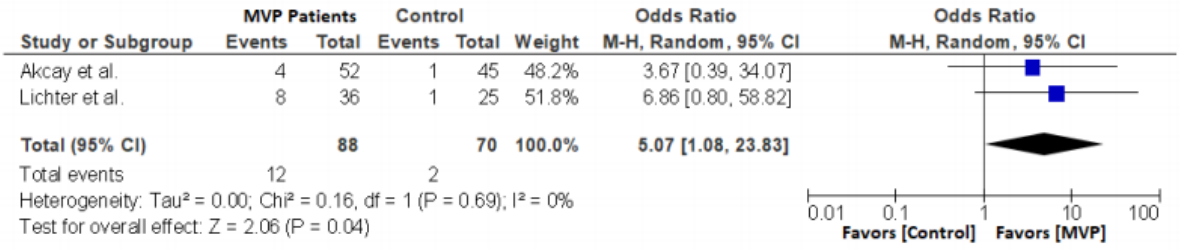

Fig. (3). Prevalence of keratoconus in patients with mitral valve prolapse compared to controls. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

4. DISCUSSION

Heart valves, similar to the cornea, are composed of collagen types I and V along with a small proportion of collagen type III. Patients with mitral valve prolapse *via* myxomatous degeneration (whether by fibroelastic deficiency or Barlow disease) have abnormal deposition of acid mucopolysaccharides, including chondroitin sulphate and hyaluronic acid [4, 8, 9]. Keratoconus is a non-inflammatory corneal thinning disorder with particular degeneration of collagen types I and V along with an abnormal distribution of glycosaminoglycans.[4, 10-12] Similar pathogenesis of both diseases has driven suspicion of their association in particular systemic disorders.

Myxomatous degeneration of the cornea has characteristics similar to those found in keratoconus including disruption of Bowman's membrane and the myofibroblastic differentiation of stromal keratocytes [13]. Similar to keratoconus patients, the corneas of patients with mitral valve prolapse are thinner, more fragile, and more prone to deformation than those found in the general population [2, 14, 15]. Since keratoconus and mitral valve prolapse involve similar collagen defects, it is possible that an embryogenic phenomenon occurring in the sixth to seventh week of fetal life could alter corneal stroma and atrioventricular valves together [16, 17]. Lysyl oxidase impairment in both diseases further enhances the suspicion of association [18].

Both keratoconus and mitral valve prolapse have been associated with multiple systemic collagen disorders, including pseudoxanthoma elasticum, Marfan's syndrome, Ehlers-Danlos syndrome, and osteogenesis imperfecta [4, 8, 17, 19, 20]. Down syndrome can present with keratoconus and mitral valve prolapse as well as joint hypermobility and atlantoaxial subluxation [20, 21]. However, studies by Street and Lichter failed to show an association between keratoconus, mitral valve prolapse, and joint hypermobility [5, 22].

4.1. History of Association

The association between mitral valve prolapse and keratoconus was initially suggested by Beardsely and Foulks in 1982. They found that 38% of patients with keratoconus had mitral valve prolapse, but this was found in a small group of 32 keratoconus patients [1]. The association was further emphasized by Sharif *et al*., showing that 58% of patients that required corneal transplantation for severe keratoconus had mitral valve prolapse [4]. However, Street *et al*. failed to discover an association of mitral valve prolapse in keratoconus patients [5]. Nevertheless, many studies have shown a statistically significant occurrence of mitral valve prolapse in patients with keratoconus with a recorded prevalence of 23-66% compared to 7-13% in the general population [1, 3, 4]. Our meta-analysis combines all these studies and supports the concept that patients with keratoconus are more prone to concomitant mitral valve prolapse.

The prevalence of mitral valve prolapse is higher in patients with severe levels of keratoconus. Sharif *et al*. showed that patients undergoing corneal transplantation due to severe keratoconus have a greater prevalence of mitral valve prolapse than those reported in the general population or with milder forms of keratoconus [4]. Rabbanikhah *et al*. found that keratoconus patients with acute corneal hydrops further had an odd ratio of 26.7 for having mitral valve prolapse, which is much higher than observed in the general population or in keratoconus patients without corneal hydrops [3].

While studies have shown a high prevalence of mitral valve prolapse in patients with keratoconus, the inverse-prevalence of keratoconus in patients with mitral valve prolapse- is not as evident. Lichter *et al*. recorded keratoconus in 22.2% of patients with myxomatous-degenerative mitral valve prolapse, which was considered as a weak, but statistically significant association in their study ($p = 0.049$). When compared to the 4% prevalence of keratoconus in the control group, there was no statistical significance of keratoconus prevalence in either group ($p = 0.08$) [22]. Akcay *et al*. discovered keratoconus in six eyes of four patients (5.7%) and possible keratoconus in eight eyes of five patients (7.7%) with mitral valve prolapse; only one eye of one patient (1.1%) had keratoconus in the control group ($p = 0.035$) [2]. The statistical significance exists if the patients with suspected keratoconus are included as having the disease. If only the ones with definitive keratoconus are labeled as having the disease, there is no statistical significance in the prevalence of keratoconus in mitral valve prolapse patients ($p = 0.25$). However, despite using the scenarios without significance in our meta-analysis, our study showed a statistically significant prevalence of keratoconus in patients with mitral valve prolapse.

Another study by Javadi *et al*. reported no cases of keratoconus in 392 patients with mitral valve prolapse [23]. This study was not included in our meta-analysis due to lack of a control group. Nevertheless, a large clinical trial is needed in order to establish a higher prevalence of keratoconus in patients with mitral valve prolapse.

5. LIMITATIONS

The meta-analysis is limited by the number of publications included in the forest plots. While the first forest plot concerning the prevalence of mitral valve prolapse in patients with keratoconus includes six studies, the other forest plot pertaining to the prevalence of keratoconus in mitral valve prolapse patients only includes two studies. Furthermore, the total number of patients in each group is small; there are less than 500 patients in each group in the first forest plot and less than 100 in each group in the second forest plot.

Heterogeneity and publication bias also exist in this meta-analysis. Although there is no heterogeneity in the second forest plot, there is significant heterogeneity found in the first plot. Removing studies by Street *et al*. and Javadi *et al*. would reduce the heterogeneity significantly ($I^2 = 16\%$). The main reason may be from the fact that both the studies contain a greater number of total patients compared to the other publications. Removal of these studies would still show a significant prevalence of mitral valve prolapse in patients with keratoconus ($p < 0.00001$).

CONCLUSION

Keratoconus and mitral valve prolapse tend to present together. There is a significant association of patients with keratotoncus that have mitral valve prolapse and vice versa. Physicians should remember this relation in their patients to aid in screening and diagnosis.

CONSENT FOR PUBLICATION

Not applicable.

STANDARD OF REPORTING

PRISMA guidelines and methodologies have been followed.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

REFERENCES

[1] Beardsley TL, Foulks GN. An association of keratoconus and mitral valve prolapse. Ophthalmology 1982; 89(1): 35-7. http://dx.doi.org/10.1016/S0161-6420(82)34857-5 PMID: 7070771

[2] Kalkan Akcay E, Akcay M, Uysal BS, *et al.* Impaired corneal biomechanical properties and the prevalence of keratoconus in mitral valve prolapse. J Ophthalmol 2014; 2014402193 http://dx.doi.org/10.1155/2014/402193 PMID: 24864193

[3] Rabbanikhah Z, Javadi MA, Rostami P, *et al.* Association between acute corneal hydrops in patients with keratoconus and mitral valve prolapse. Cornea 2011; 30(2): 154-7. http://dx.doi.org/10.1097/ICO.0b013e3181e846a2 PMID: 21045676

[4] Sharif KW, Casey TA, Coltart J. Prevalence of mitral valve prolapse in keratoconus patients. J R Soc Med 1992; 85(8): 446-8. PMID: 1404188

[5] Street DA, Vinokur ET, Waring GO III, Pollak SJ, Clements SD, Perkins JV. Lack of association between keratoconus, mitral valve prolapse, and joint hypermobility. Ophthalmology 1991; 98(2): 170-6. http://dx.doi.org/10.1016/S0161-6420(91)32320-0 PMID: 2008274

[6] Javadi MA, Seadat H, Jafarinasab MR, *et al.* Association of keratoconus and mitral valve prolapse. Iran J Ophthalmic Res 2007; 2(1): 15-8.

[7] Mohammady M, Solaimani MR, Movahedan H. Keratoconus and congenital degenerative heart diseases. J Rafsanjan Univ Med Sci Health Serv 2001; 1: 37-41.

[8] Devereux RB, Perloff JK, Reichek N, Josephson ME. Mitral valve prolapse. Circulation 1976; 54(1): 3-14. http://dx.doi.org/10.1161/01.CIR.54.1.3 PMID: 776440

[9] Siordia JA. Current discoveries and interventions for Barlow's Disease. Curr Cardiol Rep 2016; 18(8): 73. http://dx.doi.org/10.1007/s11886-016-0754-5 PMID: 27312933

[10] Cannon DJ, Foster CS. Collagen crosslinking in keratoconus. Invest Ophthalmol Vis Sci 1978; 17(1): 63-5. PMID: 621128

[11] Kim JO, Hassard DTR. On the enzymology of the cornea. A new enzyme deficiency in keratoconus. Can J Ophthalmol 1972; 7(2): 176-80. PMID: 4670099

[12] Yue BYJT, Baum JL, Smith BD. Collagen synthesis by cultures of stromal cells from normal human and keratoconus corneas. Biochem Biophys Res Commun 1979; 86(3): 465-72. http://dx.doi.org/10.1016/0006-291X(79)91737-6 PMID: 426795

[13] Belliveau MJ, Liao WN, Brownstein S, *et al.* Myxomatous corneal degeneration: A clinicopathological study of six cases and a review of the literature. Surv Ophthalmol 2012; 57(3): 264-71. http://dx.doi.org/10.1016/j.survophthal.2011.09.006 PMID: 22370508

[14] Fontes BM, Ambrósio R Jr, Velarde GC, Nosé W. Corneal biomechanical evaluation in healthy thin corneas compared with matched keratoconus cases. Arq Bras Oftalmol 2011; 74(1): 13-6. http://dx.doi.org/10.1590/S0004-27492011000100003 PMID: 21670900

[15] Shah S, Laiquzzaman M, Bhojwani R, Mantry S, Cunliffe I. Assessment of the biomechanical properties of the cornea with the ocular response analyzer in normal and keratoconic eyes. Invest Ophthalmol Vis Sci 2007; 48(7): 3026-31. http://dx.doi.org/10.1167/iovs.04-0694 PMID: 17591868

[16] Glass DH, Roberts CJ, Litsky AS, Weber PA. A viscoelastic biomechanical model of the cornea describing the effect of viscosity and elasticity on hysteresis. Invest Ophthalmol Vis Sci 2008; 49(9): 3919-26. http://dx.doi.org/10.1167/iovs.07-1321 PMID: 18539936

[17] Grayson M. Diseases of the cornea. St. Louis: C V Mosby 1979; pp. 257-61.

[18] Dudakova L, Jirsova K. The impairment of lysyl oxidase in keratoconus and in keratoconus-associated disorders. J Neural Transm (Vienna) 2013; 120(6): 977-82. http://dx.doi.org/10.1007/s00702-013-0993-1 PMID: 23653221

[19] Kaufman H, McDonald MB, Barron BA, Waltman SR. The cornea. New York: Churchill Livingstone 1988; pp. 194-5.

[20] Rabinowitz YS. Keratoconus. Surv Ophthalmol 1998; 42(4): 297-319. http://dx.doi.org/10.1016/S0039-6257(97)00119-7 PMID: 9493273

[21] Smith DS. Health care management of adults with Down syndrome. Am Fam Physician 2001; 64(6): 1031-8. PMID: 11578024

[22] Lichter H, Loya N, Sagie A, *et al.* Keratoconus and mitral valve prolapse. Am J Ophthalmol 2000; 129(5): 667-8. http://dx.doi.org/10.1016/S0002-9394(00)00371-8 PMID: 10844063

[23] Javadi MA, Rafati N, Mohebi A, Poursalman MR, Forghani MR. Prevalence of keratoconus in patients with mitral valve prolapse. Bina J Ophthalmol 2005; 11: 40-4.