

QUALITY OF DIAGNOSTIC STUDIES

Evidence about evidence

B C Reeves

The quality of evaluations of diagnostic test performance

In this issue of the *BJO* (p 261), Siddiqui *et al* review the compliance of researchers with quality standards for evaluations of diagnostic test performance (DTP). "Standards" were originally set by the McMaster evidence based medicine (EBM) group^{1,2} and they have continued to evolve over recent years. Unfortunately, the standards appear to have had little impact since reviews of recent evaluations have shown that they tend to be of poor quality, in medicine generally and in ophthalmology and other specialties.³⁻⁶ The review of Siddiqui *et al* confirms this gloomy picture.

In contrast, during the same period, there has been substantial improvement in the quality and reporting of evaluations of the effectiveness of treatments. Why has research to evaluate DTP not benefited in a similar way from the EBM "movement"? Perhaps improving the quality of research about effectiveness was seen as a priority because it was perceived to be important to patients—the "bit" of health care that makes them better—or because the resources wasted from using treatments that don't work (and not using ones that do) was much easier for the public and media to appreciate. Perhaps the principles of high quality research to evaluate DTP are more difficult to grasp than controlled experiments to assess effectiveness. Or perhaps we can just blame Archie Cochrane!

Whatever the reason, prioritising research about effectiveness might be seen as paradoxical since it is difficult to optimise treatment without first knowing the diagnosis. It is also not clearly justified on an efficiency basis, since substantial (and increasing) amounts of healthcare resources are spent on diagnosis, with new and expensive diagnostic technologies emerging. And the diversity of evidence about DTP is often not appreciated—for example, patients' responses to standard questions when taking a history and standardised observations of clinical signs all constitute diagnostic "test" information, the value of which can be quantified.⁷

The relative neglect of evidence about DTP may, at last, be about to change. The Cochrane Collaboration has long appreciated the importance of such

evidence—a methods groups on the topic was registered in 1995—and, in 2003, the collaboration took the decision to develop a new database of systematic reviews of diagnostic test accuracy. This will be developed in parallel with the existing database of systematic reviews of the effectiveness of healthcare interventions.

This new review of ophthalmic tests might appear to suggest that things are improving compared to the situation during the 1990s.⁵ All evaluations scored some points, with scores ranging from 8–19/25 compared with 0–5/7. However, although all STARD items are important, they are not all *equally* important. Failure to report some item may mislead a reader but does not necessarily invalidate the evidence. In contrast, poor compliance in reporting particular items leads (on average) to biased, optimistic estimates of DTP.⁴ Unfortunately, compliance with these items, about masking/blinding (item 11) and workup bias (item 16), was poorer than for others, with 6/16 and 4/15 papers respectively judged to be compliant with the standard.

Reporting indeterminate results (and analysing them correctly) is also crucial, since decisions still need to be made about patients who give such results. Failure to comply will almost always cause researchers to overestimate DTP. This item was poorly reported as well (item 22: 5/16).

The lack of evidence about diagnostic test performance represents an opportunity for medical researchers to make a significant contribution

Reviews of evidence about DTP suggest that researchers, and journal editors, compartmentalise their knowledge. At last, the message about confidence intervals seems to have been learnt with respect to estimates of effect. Why, then, are estimates of DTP perceived to be immune (item 21: 4/16) (Siddiqui *et al*)?^{5,8}

The STARD items illustrate the distinction between the quality of reporting and the quality of the research itself. This distinction is also true for randomised controlled trials (RCTs) (*cf* CONSORT quality standards⁹) but is less

important, perhaps, because the design principles of RCTs and measures to protect against bias are now well known, relatively simple and, hence, straightforward for readers to appraise. This is not yet the case for evidence about DTP. Note the STARD item that requires researchers to describe how the study population was selected. This leaves the reader to judge the appropriateness of the population for the research question/context of interest, which is the key issue in determining the relevance of the evidence.¹⁰ The STARD initiative is a very important step forward but users of evidence of DTP need to remain vigilant and hone their appraisal skills.

Although requirements for a good evaluation (study design features to protect against bias, and analysis) are not widely appreciated, in other respects such evaluations are often relatively easy to conduct. Evaluations are typically based on cross sectional studies, often without any need for prolonged follow up. Studies often investigate tests for diagnosing rare conditions, which can cause difficulties in recruiting a representative population that includes sufficient individuals with the condition(s) of interest (also true for evaluations of screening accuracy). However, high quality evidence for common conditions, and very simple "tests" (see above), is often lacking. The lack of evidence about DTP represents an opportunity for medical researchers to make a significant contribution (www.carestudy.com).

Methodology for evaluating DTP is an evolving area. In a recent critique,¹¹ the limitations of the current framework were laid bare and challenges for the future set out. The UK National Health Service recently prioritised the commissioning of a review of evidence about methods for evaluation of DTP when there is no gold standard, a problem that is not uncommon (www.publichealth.bham.ac.uk/nccrm/Invitations_to_tender.htm). This decision highlights the importance of DTP evidence for healthcare services.

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Correspondence to: Dr Barney C Reeves, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK; barney.reeves@lshtm.ac.uk

REFERENCES

- 1 Jaeschke A, Guyatt GH, Sackett DL, for the Evidence-based Working Group. Users' Guides to The Medical Literature, III. How to use an article about a diagnostic test. A. Are the results of the study valid? *JAMA* 1994;**271**:389–91.
- 2 Jaeschke A, Guyatt GH, Sackett DL, for the Evidence-based Working Group. Users' Guides to the Medical Literature, IV. How to use an article about a diagnostic test. B. What are the results

- and will they help me in caring for my patients? *JAMA* 1994;**271**:703-7.
- 3 Reid MC, Lachs MS, Feinstein AR. Use of methodological standards in diagnostic test research. Getting better but still not good. *JAMA* 1995;**274**:645-51.
 - 4 Lijmer JG, Mol BW, Heisterkamp S, et al. Empirical evidence of design-related bias in studies of diagnostic tests. *JAMA* 1999;**282**:1061-6.
 - 5 Harper R, Reeves B. Compliance with methodological standards when evaluating ophthalmic diagnostic tests. *Invest Ophthalmol Vis Sci* 1999;**40**:1650-7.
 - 6 Patel HRH, Garcia-Montes F, Christopher N, et al. Diagnostic accuracy of flow rate testing in urology. *BJU Int* 2003;**92**:58-63.
 - 7 McAlister FA, Straus SE, Sackett DL. Why we need large, simple studies of the clinical examination: the problem and a proposed solution. *Lancet* 1999;**354**:1721-4.
 - 8 Harper R, Reeves B. Reporting of precision of estimates for diagnostic accuracy: a review. *BMJ* 1999;**318**:1322-3.
 - 9 The CONSORT Statement. Revised recommendations for improving the quality of reports of parallel group randomized trials. *JAMA* 2001;**285**:1987-91.
 - 10 Harper RA, Henson D, Reeves BC. Appraising evaluations of screening/diagnostic tests: the importance of the study populations. *Br J Ophthalmol* 2000;**84**:1198-202.
 - 11 Feinstein AR. Misguided efforts and future challenges for research on "diagnostic tests". *J Epidemiol Community Health* 2002;**56**:330-2.

DIABETIC KERATOPATHY

Prevention of diabetic keratopathy

Y Kaji

The condition is not thought to represent a serious clinical or pathological entity and hence has been overlooked by both physician and scientist alike

Patient morbidity related to diabetic induced ocular complications has increased year on year commensurate with the worldwide increase in the incidence of diabetes. These complications include retinopathy, neovascular glaucoma, optic neuropathy, keratopathy, and dry eye. Diabetic retinopathy, because of its clinical importance as a leading cause of blindness, has attracted the major thrust of both clinical and basic research. Clinical ophthalmological management of this condition now routinely includes photocoagulation and vitreoretinal surgery. Various systemic and local medications are now also being extensively examined both through basic research and clinical trials to determine their clinical efficacy in managing the complications of diabetic retinopathy.

Diabetic keratopathy has featured as the "poor relation" with regard to both clinical and research interest. The condition is not thought to represent a serious clinical or pathological entity and hence has been overlooked by both physician and scientist alike. Yet with only cursory investigation it is obvious that many patients have visual loss secondary to diabetic keratopathy. Diabetic keratopathy comprises several symptomatic corneal conditions inducing superficial punctate keratopathy and persistent corneal epithelial erosion.¹ The latter can be encountered especially after vitreoretinal surgery, where oedematous and cloudy corneal epithelium, often manually removed to restore clarity, results postoperatively in a poorly healing corneal epithelial surface. De novo epithelial erosion in diabetic patients can often be resistant

to routine clinical management of corneal erosions including topical medication and bandage contact lenses. These poorly healing epithelial surfaces have compromised defences against general microbial attack, predisposing these patients to bacterial and fungal infective keratopathies.

Keratopathy in the presence of diabetes should be considered as a potential sight threatening condition and thence must be given appropriate clinical attention and increased research interest. For this reason, it is important to attempt to analyse the mechanism of diabetic keratopathy and from this, hopefully establish improved techniques to prevent and treat the condition. Before symptomatic diabetic corneal complications, subclinical abnormalities can develop in diabetic corneas; these include a decrease in epithelial barrier function,²⁻⁴ abnormalities in shape of epithelial and endothelial cells,⁵⁻⁹ basement membrane thickening,^{10,11} and decreased corneal sensation.¹²⁻¹⁵ These subclinical abnormalities, however, have often a close temporal relation to the development of symptomatic corneal conditions in diabetes. Several molecular mechanisms are thought to exist, which are related to and may underpin the development of diabetic keratopathy.

It may now be possible to use this simple organ, the cornea, with all its inherent advantages of accessibility, clarity, ease of observation, and lack of cellular complexity to investigate diabetic pathology secondary to increases in polyol pathway and deposition of AGEs

Firstly, an increase in the polyol metabolism in the corneal epithelial cells is reported as a mechanism of diabetic keratopathy.^{16,17} There is a strong similarity in the spatial distribution of aldose reductase, an enzyme entry into polyol pathway and the target organs affected by typical diabetic pathology including kidney and blood vessels.^{16,17} Akagi *et al* reported the accumulation of polyol and the expression of aldose reductase in the corneal epithelium and endothelium.¹⁶ These data are consistent with the clinical findings that the corneal epithelium and endothelium are targets of diabetic complications. The association between diabetes and the polyol pathway inducing corneal changes are further demonstrated using a galactose fed animal model where significant increases in polyol accumulation were noted within the corneal epithelium and endothelium.¹⁷⁻¹⁹ Furthermore, inhibition of aldose reductase activity using aldose reductase inhibitor (ARI) ameliorates corneal changes in both diabetic and galactose fed animals models. In these models, ARI was effective in inhibiting the loss of corneal sensation,¹² delaying corneal epithelial wound healing,²⁰ enlargement of epithelial and endothelial cell size,^{6,7,21} breakdown of corneal epithelial barrier function,⁴ and accumulation of polyol.¹⁹

Although there are a lot of anti-diabetic drugs effective in diabetic animal experiments, few of them have proved efficacy in human studies. ARI treatment, however, has been shown (although only in uncontrolled case studies) to ameliorate corneal changes in diabetic patients.^{8,20,22} In a controlled study using topical ARI treatment Hosotani *et al* have demonstrated an ameliorative effect upon the enlargement of the corneal epithelial cells in diabetic patients.⁹ The study in this issue of the *BJO* by Nakahara *et al* (p 266) is now the second controlled study dealing with the effect of ARI treatment on diabetic keratopathy. In this issue, the authors have shown that topical ARI treatment was effective in the restoration of corneal epithelial barrier function, but not in the prevention of superficial punctate keratopathy. These

results appear to indicate that there may be different mechanisms implicated in the breakdown of the corneal epithelial barrier function and the development of superficial punctate keratopathy.

Decrease in the corneal sensation²³ and loss of nerve derived trophic factor have been postulated as causative factors in the development of diabetic keratopathy. Nakamura *et al* have revealed that insulin-like growth factor 1 (IGF-1) and substance P, a neuropeptide present in sensory nerves, accelerate corneal epithelial wound healing.²⁴ In addition, the authors showed that topical application of substance P and IGF-1 accelerated the corneal epithelial wound healing process in diabetic animals. These studies help to strengthen the potential pathogenic link between decreased corneal sensation and diabetic keratopathy.

Other putative causes of diabetic keratopathy, in addition to enzymatic and neural dysregulations, include structural abnormalities in the corneal epithelium basement membrane.^{10 25-27} Kenyon *et al* were the first to highlight the abnormal interaction of the corneal epithelium and basement membrane.²⁷ They showed that corneal epithelial basement membrane in addition to corneal epithelium was removed with manual epithelial removal during vitreoretinal surgery. For this reason, they speculated that bare corneal stroma, without basement membrane, after corneal epithelial abrasion was the reason for a delay in corneal epithelial wound healing.²⁷ Histologically, thickening and multilamination of the basement membrane²⁵ and a decrease in the penetration of anchoring fibrils (type VII collagen)¹⁰ were noted in diabetic corneas. These structural changes of the basement membrane in diabetic cornea may account for the loose attachment of corneal epithelial cells.

Advanced glycation end products (AGEs) have been implicated in the development of diabetic keratopathy and maybe at least partly explain some of the structural changes noted.^{26 28} AGEs are known to deposit in the basement membrane of the corneal epithelial cells of diabetic patients.²⁶ When this happens the molecular structure of basement membrane components changes and they lose adhesive property. In this way, the corneal epithelial cells lose a clue for the attachment on the basement membrane. In addition, aminoguanidine, an antioxidant, was effective in inhibiting AGE formation and thus ameliorated the attachment of corneal epithelial cells to the basement membrane.²⁶ However, the *in vivo* effect of aminoguanidine on diabetic keratopathy remains unknown.

This review has alluded to several common molecular mechanisms previously

implicated in the pathogenesis of systemic diabetic complications, and now also implicated in the pathogenesis of diabetic keratopathy. Potentially, diabetic keratopathy provides a pathogenic mechanistic model to shed light upon complications within other more complex organs. The value of using such a simple model as the cornea to shed light on complications within structurally much more complex organs, has previously already been elegantly demonstrated by investigators such as Gimbrone *et al*.²⁹ It may now be possible to use this simple organ, the cornea, with all its inherent advantages of accessibility, clarity, ease of observation, and lack of cellular complexity to investigate diabetic pathology secondary to increases in polyol pathway and deposition of AGEs.

I think that the potential value of diabetic keratopathy as a simplistic model of diabetic complications cannot be overstated. For this reason, I postulate that the model should be considered for adoption throughout diabetic research laboratories and within institutions performing double blinded clinical studies determining the effect of novel treatments upon systemic diabetic complications.

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Correspondence to: Yuichi Kajii, MD, PhD, Department of Ophthalmology, University of Tsukuba, Institute of Clinical Medicine, Tennoudai 1-1-1, Tsukuba, Ibaraki, 305-8575, Japan; sanken-ky@umin.ac.jp

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REFERENCES

- Schultz RO, Van Horn DL, Peters MA, *et al*. Diabetic keratopathy. *Trans Am Ophthalmol Soc* 1981;**79**:180-99.
- Gekka M, Miyata K, Nagai Y, *et al*. Corneal epithelial barrier function in diabetic patients. *Cornea* 2004;**23**:35-7.
- Gobbels M, Spitznas M, Oldendoerf J. Impairment of corneal epithelial barrier function in diabetics. *Graefes Arch Clin Exp Ophthalmol* 1989;**27**:142-4.
- Yokoi N, Niya A, Komuro A, *et al*. Effects of aldose reductase inhibitor CT-112 on the corneal epithelial barrier of galactose-fed rats. *Curr Eye Res* 1997;**16**:595-9.
- Tsubota K, Yamada M. The effect of aldose reductase inhibitor on the corneal epithelium. *Cornea* 1993;**12**:161-2.
- Meyer LA, Ubels JL, Edelhauser HF. Corneal endothelial morphology in the rat. Effects of aging, diabetes, and topical aldose reductase inhibitor treatment. *Invest Ophthalmol Vis Sci* 1988;**29**:940-8.
- Matsuda M, Awata T, Ohashi Y, *et al*. The effects of aldose reductase inhibitor on the corneal

- endothelial morphology in diabetic rats. *Curr Eye Res* 1987;**6**:391-7.
- Oguro N, Matsuda M, Ohashi Y, *et al*. Topical aldose reductase inhibitor for correcting corneal endothelial changes in diabetic patients. *Br J Ophthalmol* 1995;**79**:1074-7.
- Hosotani H, Ohashi Y, Yamada M, *et al*. Reversal of abnormal corneal epithelial cell morphologic characteristics and reduced corneal sensitivity in diabetic patients by aldose reductase inhibitor, CT-112. *Am J Ophthalmol* 1995;**119**:288-94.
- Azar DT, Spurr-Michaud SJ, Tisdale AS, *et al*. Decreased penetration of anchoring fibrils into the diabetic stroma. A morphometric analysis. *Arch Ophthalmol* 1989;**107**:1520-3.
- Azar DT, Spurr-Michaud SJ, Tisdale AS, *et al*. Altered epithelial-basement membrane interactions in diabetic corneas. *Arch Ophthalmol* 1992;**110**:537-40.
- Hosotani H, Ohashi Y, Kinoshita S, *et al*. Effects of topical aldose reductase inhibitor CT-112 on corneal sensitivity of diabetic rats. *Curr Eye Res* 1996;**15**:1005-7.
- Fujishima H, Shimazaki J, Yagi Y, *et al*. Improvement of corneal sensation and tear dynamics in diabetic patients by oral aldose reductase inhibitor, ONO-2235: a preliminary study. *Cornea* 1996;**15**:368-75.
- Schultz RO, Peters MA, Sobocinski K, *et al*. Diabetic keratopathy as a manifestation of peripheral neuropathy. *Am J Ophthalmol* 1983;**96**:368-71.
- Daubs JG. Diabetes screening with corneal aesthesiometer. *Am J Optom Physiol Opt* 1975;**52**:31-5.
- Akagi Y, Yajima Y, Kador PF, *et al*. Localization of aldose reductase in the human eye. *Diabetes* 1984;**33**:562-6.
- Kinoshita JH, Fukushi S, Kador P, *et al*. Aldose reductase in diabetic complications of the eye. *Metabolism* 1979;**28**:462-9.
- Kubo E, Nakamura S, Tsuzuki S, *et al*. Inhibitory effect of orally administered aldose reductase inhibitor SNK-860 on corneal polyol accumulation in galactose-fed rats. *Graefes Arch Clin Exp Ophthalmol* 1999;**237**:758-62.
- Awata T, Sogo S, Yamamoto Y. Effects of aldose reductase inhibitor, CT-112, on sugar alcohol accumulation in corneal epithelium of galactose-fed rats. *Jpn J Ophthalmol* 1986;**30**:245-50.
- Awata T, Sogo S, Yamagami Y, *et al*. Effect of an aldose reductase inhibitor, CT-112, on healing of the corneal epithelium in galactose-fed rats. *J Ocul Pharmacol* 1988;**4**:195-201.
- Dafiles MB, Kador PF, Kashima K, *et al*. The effects of sorbinil, an aldose reductase inhibitor, on the corneal endothelium in galactosemic dogs. *Invest Ophthalmol Vis Sci* 1990;**31**:2201-4.
- Fujishima H, Tsubota K. Improvement of corneal fluorescein staining in post-cataract surgery of diabetic patients by an oral aldose reductase inhibitor, ONO-2235. *Br J Ophthalmol* 2002;**86**:860-3.
- Saito J, Enoki M, Hara M, *et al*. Correlation of corneal sensation, but not of basal or reflex tear secretion, with the stage of diabetic retinopathy. *Cornea* 2003;**22**:15-18.
- Nakamura M, Kawahara M, Morishige N, *et al*. Promotion of corneal epithelial wound healing in diabetic rats by the combination of a substance P-derived peptide (FGIM-NH2) and insulin-like growth factor-1. *Diabetologia* 2003;**46**:839-42.
- Taylor HR, Kimsey RA. Corneal epithelial basement membrane changes in diabetes. *Invest Ophthalmol Vis Sci* 1981;**20**:548-53.
- Kajii Y, Usui T, Oshika T, *et al*. Advanced glycation end products in diabetic corneas. *Invest Ophthalmol Vis Sci* 2000;**41**:362-8.
- Kenyon K, Wafai Z, Michels R, *et al*. Corneal basement membrane abnormality in diabetes mellitus. *Invest Ophthalmol Vis Sci* 1978;**17**(Suppl):245.
- Kajii Y, Amano S, Usui T, *et al*. Expression and function of receptors for advanced glycation end products in bovine corneal endothelial cells. *Invest Ophthalmol Vis Sci* 2003;**44**:521-8.
- Gimbrone MA Jr, Cotran RS, Leapman SB, *et al*. Tumor growth and neovascularization: an experimental model using the rabbit cornea. *J Natl Cancer Inst* 1974;**52**:413-27.