CHAPTER V

DISCUSSION

5.1 The prevalence of diabetic retinopathy

In this study, the prevalence of retinopathy is 42.1%. It is similar to the prevalence of the US (40.3%, The Eye Diseases Prevalence Research group) [58] and Spain (42.4%, Lopez-Bastida) [52]. But these are less than the prevalence in the Wisconsin Epidemiologic Study which is 54%. The difference of prevalence can explain by the different of screening population who are different in race, ethnicity , hospital / non-hospital based population and type of diabetes. The other explanation is the different in method of screening, in the the Wisconsin Epidemiologic Study used the seven-standard field stereoscopic fundus photography which revealed wider viewing angle and this allowed the reader find more abnormalities such as microaneurysms in peripheral field. The WESDR performed in 2,990 primary care DM patients. (include type I DM 40 %) This may increase the number of detected cases.

For sight threatening diabetic retinopathy (include severe NPDR, PDR and CSME), the prevalence is 17.7% in our study. It is higher than the prevalence from The Eye Diseases Prevalence Research group which is 8.2%. Our study revealed higher prevalence because this research performed in the tertiary care center (hospital-based) and this leads to selection bias.

Future projections suggest that diabetic retinopathy will increase as a global public health problem, both with aging of the population and increasing age-specific prevalence of DM over time.

5.2 Test performance

To assess the diagnostic performance we use the accuracy of the test which is its correspondence with the true value and has two separate components (sensitivity and specificity). In this study, we found that fundus images interpreted by most family physicians had a fair sensitivity and fair specificity (65-78% and 79-89% respectively). In contrast to the other 2 family physicians that had a relatively high sensitivity but considerably low specificity (94-95% and 31-41% respectively). At these ranges of sensitivity and specificity, they are not met the minimum requirement for screening method especially in serious condition (diabetic retinopathy for referrals).

This level of accuracy represents an improvement when compared with techniques that are currently used by primary care physicians. Previous studies have shown that primary care physicians using standard direct ophthalmoscopy correctly identify less than 50% of serious retinopathy even when they dilate the eyes [60]. When using standard direct ophthalmoscopy without dilation, even those experienced in ophthalmoscopy have rates for correct assessment of only about 50% [41].

When compare our results with systematic review by Williams GA[47], there were a three level I evidence of studies using single-field fundus photography as a screening tool for diabetic retinopathy. These studies revealed the sensitivity of 61-90 % and specificity of 85-97% which are higher than our study. The reference standard was seven-standard field fundus photography. The referral cut point was at moderate NPDR (2 studies) and severe NPDR (1 study). The sample size of 1 study was comparable with our study (354 vs 363) but the other 2 studies were less than ours. (197, 118) Of these 3 studies, they all using skillful readers for images interpretation. It reflects that experience of interpretation is crucial.

Compare to recent study in Thailand, Ruamviboonsuk P. [51] assessed on sensitivity among a group of ophthalmic care providers, including ophthalmologists, ophthalmic nurses and photographers, the result showed sensitivity range from 0.7 – 1.0 and specificity from 0.61-0.97 . The diagnostic accuracy are slightly better than our study (even exclude of ophthalmologist results). We found many factors that affected the differences in results. First, non-ophthalmologist readers received 2-days intensive training course which longer than our study . Second, referral cut point was set at severe

NPDR or worse that more abnormalities can be easily detected. Third, all non-ophthalmologists have currently worked as ophthalmic care providers, make them have more experience for interpretation.

Consider the study in Spain, Lopez-Bastida [52] studied the sensitivity and specificity of the single field fundus photography used the dilated indirect ophthalmoscopy and slit-lamp biomicroscopy as the reference standard. In this study revealed promising results than our study (100 % sensitivity and 100 % specificity of sight threatening DR, 92 % sensitivity and 96% specificity for any DR) because they used retina specialist in interpreting the digital images. The other explanation is the higher threshold of the cut point which may present more obvious fundus findings than the less severe stages.

There are several causes that must be considered in interpreting the results of this study. First, we evaluated accuracy after only 2 training hours and 2 weeks of practice that may not provide enough knowledge and skill for the non-ophthalmologic personnel as result in varying in diagnostic performance in this study. A comprehensive instruction course including a well-defined syllabus, with more supervision by experts, repeated comparisons of screening results, and regular refresher courses is required. It is likely that the interpretation by family physicians would probably be more accurate after using the tools for a longer period especially to detect small neovascularisation and discriminate between drusen and exudates. Second, poor image quality from many causes. Cataracts and pupil constriction in elderly or diabetic patients are the most common causes of poor quality photography. In our study, there were 42.1% of participants aged more than 60 years and 19.8% of participants with significant cataract. There are a clinically significant number of patients who require mydriasis to achieve gradable images (88/363, 24.4%). To achieve optimal quality of screening in a practical setting, on the basis of our results, mydriasis could be offered either to everyone or targeted to the minority who need it. Digital photography allows an immediate assessment of image quality, and mydriasis could be offered immediately to those who appear to require mydriatics. The risk of precipitating glaucoma is negligible [59].

In diseases in which diagnosis is based mainly on an image, as in DR, skill of photographers also had significant impacts on image interpretation too. The development

of new imaging technologies with larger field of view and stereoscopic view is essential and may solve these problems. Third, family physicians interpreted the images without clinical data such as diabetic duration and visual acuity. Fourth, the standardized patients in this study were not represented typical patients in primary care; they were selected from a tertiary care setting and likely to have higher proportion of severe disease, as well as more complicated eye condition such as cataract.(which is the main cause of poor quality images)

The unusually high proportion of over-refer images judged by the third and fourth family physicians were refined the cause either reflect their lack of confidence in interpretation, misinterpretation (between drusen and exudates, flame shape hemorrhage and neovascularization, massive exudates and severe NPDR, media opacity from cataract and vitreous hemorrhage, asteroid hyalosis and exudates), image ambiguity, or individual background and experience for further study.

A high number of false positive cases lead to low PPV, low specificity and low accuracy in the third and fourth family physicians. This was mainly from lack of confidence and experience in interpretation more than from poor quality photographs. When the poor quality photographs were excluded from the analysis, the sensitivity and specificity had a little change(table 16). A lot of false positive cases lead to increase the health care providers' cost, work load and patient anxiety.

Table 18 The sensitivity, specificity, accuracy after exclusion of poor quality images

Family physician	% sensitivity (previous value)	% specificity (previous value)	% accuracy (previous value)
1	61.5 (63.8)	91.1 (87.9)	81.7 (80.2)
2	77.1 (77.6)	81.8 (79.4)	80.3 (78.8)
3	93.6 (94.0)	32.6 (31.2)	51.9 (51.2)
4	94.5 (94.8)	42.4 (40.9)	58.8 (41.9)
5	67.9 (68.1)	92.8 (89.5)	84.9 (82.6)

When inspecting the false negative cases which is more serious, there were a number of false negative cases (6, 7, 26, 37, 41 cases) which account for 5.2-35.3 % of

true positive cases. In this study, causes of false negatives consist of misinterpretation between drusen and exudates, tractional retinal detachment and ungradable images, underdetection of neovascularisation and limited retinal field.

However, from this study there was a potential reduction of referrals to ophthalmologists from 77 to 221 patients(true negative cases), corresponding to a 21.2 – 60.9 % reduction in referrals, ensuring long-term reduced waiting lists.

We decided to use moderate NPDR to be the referral cut point to preserve for more safety margin. When we try to change referral cut point to any DR and severe NPDR. We found that when we decreased the referral threshold the sensitivity increased but the specificity decreased. When we increased the threshold, the sensitivity varied but specificity increased. The results were show in table 17. Even after changing the cut point, the sensitivity and specificity are still not suitable for a screening test.

Table 19 The sensitivity, specificity of the fundus photographs interpreted by family physicians in DR screening at different cut points value

The cut point	Values	The 1st family physician	The 2nd family physician	The 3rd family physician	The 4th family physician	The 5th family physician
Any DR	sensitivity	73.7	81.7	96.7	98.0	77.8
	specificity	85.2	70.5	13.3	16.2	81.4
Moderate	sensitivity	64.7	77.6	94.0	94.8	68.1
NPDR	specificity	87.9	79.4	31.2	40.9	89.5
Severe NPDR	sensitivity	64.0	56.0	96.0	72.0	76.0
	specificity	88.5	90.8	51.5	81.7	89.9

Another aspect of assessing diagnostic and screening test--the question of whether a test is reliable or repeatable. Clearly, regardless of the sensitivity and specificity of a test, if the test results cannot be reproduced, the value and usefulness of the test are minimal. The factors that contribute to the variation between test results are intra-observer variation and inter-observer variation. In this study, the intra-observer

agreement of the first family physician (who provided the fair sensitivity and specificity) was better than the third family physician. (who provided the high sensitivity and low specificity). The inter-observer agreement were good between the first, second and fifth family physicians.(who provided the fair sensitivity and specificity) But the inter-observer agreement were mostly fair when we assessed the agreement between any family physicians and the third or fourth family physicians. From this point of view reflects that the test results interpreted by the third and fourth family physicians were not reliable and repeatable.

Ruamviboonsuk P. [51] assessed on the agreement among a group of ophthalmic care providers, including retina specialists, ophthalmologists, ophthalmic nurses and photographers using weighted kappa statistics. The result revealed the kappa value were moderate and good among the retina specialists and only fair among other ophthalmic care providers. Even though different methods of reliability assessment were used, the weighted kappa and ICC are comparable. Both methods can be used for assessing agreement of ordinary outcome. The kappa values among ophthalmic care providers other than the retina specialists were less than the ICC of our study in the reliability assessment.(moderate vs fair) The key factor that made better reliability in among retina specialist is experience in interpretation. There are no intra-observer reliability evaluation in Ruamviboonsuk's study.

Despite the limitations, this study shows one promising way to improve screening for diabetic retinopathy. Currently, many diabetic patients do not get screened adequately for retinopathy, partly because screening by primary care physicians is neither accurate nor efficient using currently available techniques. Our study suggests one technique that primary care physicians or family physicians can use to screen for diabetic retinopathy with greater accuracy and efficiency. Using this technique, family physicians can correctly refer most diabetic patients who are likely to have serious retinopathy. This technique will probably not replace the current standard of having all diabetic patients evaluated by an eye specialist, because a high number of false negative cases. (6, 7, 26, 37, 41 cases) might not be acceptable. The technique, however, might at least improve care for those who currently do not regularly see eye specialists; having an abnormality identified by their primary care physician may motivate patients to seek further evaluation

by an ophthalmologist. If the results of this study can be replicated in larger populations, then this technique may be one way for primary care physicians to improve care for their patients with diabetes.

Additionally, most diabetic patients see their primary care physician several times a year; it is likely that the test sensitivity would be higher if multiple examinations are conducted during the course of a year.

The advantages of single-field fundus photography interpreted by trained readers are ease of use (only one photograph is required), convenience, and ability to detect retinopathy. The most important advantage inherent to single-field nonmydriatic digital photographic screening is its facilitation of remote diagnostic interpretation by a trained grader either physician or non-physician. That is likely to improve patient compliance in screening programs. The disadvantage is that reported sensitivity values are less than ideal when compared with 7–standard field photography. When compared with ophthalmoscopy, however, single-field fundus photography has the potential to improve the quality of the evaluation and the numbers of patients evaluated. The use of the nonmydriatic camera for follow-up of patients with early diabetic retinopathy in the physician's office might be considered in situations where dilated eye examination by ophthalmologist cannot be obtained. Patient education also occurs during examinations. Patients know the importance of controlling their blood glucose, blood pressure, and serum lipids, and this importance can be reinforced at a time when patients are particularly aware of the implications of vision loss.

Older people are at higher risk for cataract, glaucoma, age-related macular degeneration, and other potentially blinding disorders that also can be detected by fundus photography. Moreover, hospital diabetes specialists, ophthalmologists, and primary care doctors could readily share the digital retinal images of their patients, which will certainly improve the treatment of the diabetic patient.

This new tool that can enhance the practice and distribution of ophthalmology services. Costs and technical barriers will decrease as technology advances. When that happens, comprehensive teleophthalmology will become a reality, playing a critical role in the lives of patients and physicians. The digital nonmydriatic photography combined with telemedicine offers the potential of increasing the screening rate by doing the screening

in primary health care settings rather than in the ophthalmologist's office. At the same time, telemedicine with 2-ways communication of physicians about their patients make all receive continuing medical education.

The digital format for single-field fundus images can be reliably interpreted for diabetic retinopathy screening, if interpreters have enough experience and expertise. Continuing education is needed to maintain their expertise.

5.3 Limitations

- CSME (Clinically Significant Macular Edema)

All of the techniques non-stereo retinal imaging have limitations in the detection of macular edema. Besides slitlamp biomicroscopy, oral fluorescein could be an alternative, because this screening method has good sensitivity in detecting macular edema. On the other hand, it is much more time-consuming than retinal photography and has a small risk of allergic reaction, which is a drawback when using the technique on a large scale.

We can considered that all eyes with hard exudates <500 um from the fovea had macular edema but this instrument cannot distinguish retinal thickening when without hard exudates. However, because patients with macular edema have important reduction of visual acuity, a combination of eye fundus image and visual acuity assessment would help improve the accuracy of the technique. Moreover, use of the Amsler test would improve detection of macular edema in the context of screening. It is also possible that, in the near future, stereoscopic images may be available to solve this problem.

- Reference standard

In clinical trials, seven-standard field stereoscopic fundus photography graded by more than one independent grader is the most reliable reference standard. However indirect ophthalmoscopy with precorneal lens is the preferred and widely accepted method and more practical when screening for diabetic retinopathy. Thus, it is a logical

reference standard for screening procedure to be evaluated. And it is superior for detecting retinal thickening and neovascularization than seven-standard field stereoscopic fundus photography.

- **Limited retinal field**

Single field nonstereoscopic fundus photography reveals only posterior pole of the retina (less area than seven-standard field fundus photography and indirect ophthalmoscopy).However diabetic retinopathy trends to develop in posterior pole more than in periphery and several studies showed high sensitivity of single field nonmydriatic fundus photography to detect diabetic retinopathy. In this study, there were some cases of false negative caused by limited retinal field. New model of retinal camera with wider field of view will solve this problem.

- Ungradable images

Because our study purpose was to assess accuracy of retinal images interpreted by family physicians as a situation of diabetic retinopathy screening in rural areas where the gold standard is unpractical and ophthalmologists are not readily available. Reports from our study, the ungradable images were mostly caused by media opacity and small pupils. Patients with media opacity also should be referred to the ophthalmologist for ophthalmologic evaluation. In cases of small pupils, use of mydriatic agent may be helpful to improve image quality. But in cases failed after use of mydriatic agent, all of them need to refer for ophthalmologic evaluation.

5.4 clinical implication

If single field nonmydriatic fundus photography interpreted by family physicians is comparable with indirect ophthalmoscopy, we can introduce single field fundus photography interpreted by family physician as an alternative tool for diabetic retinopathy screening. This is useful to screen for majority of patients in rural area. We can give early

treatment and prevent visual loss of diabetic patients. Although to meet an ophthalmologist for annually eye evaluation is the most preferable to get benefit to evaluate DR and detect other eye problems. But in Thailand at present time, we still lack of ophthalmologists, so DR screening with single field fundus photography may be next to the best we can do. When applied in the primary care setting, it can substantially lower the number of ophthalmic referrals.

Further studies will be required to assess the implementation of programs that are based on single-field fundus photography in a real clinical setting with well-define strategy to confirm the clinical effectiveness and cost-effectiveness of these techniques in improving population visual outcomes. Future research also should include establishing standardized protocols and satisfactory performance standards for diabetic retinopathy screening programs.