CHAPTER II

LITERATURE REVIEW

A rationale for screening of diabetic retinopathy is the established efficacy of laser photocoagulation surgery in preventing visual loss. Two large National Institutes of Health (NIH) sponsored trials, the Diabetic Retinopathy Study (DRS) and the Early Treatment Diabetic Retinopathy Study (ETDRS), determined that laser photocoagulation surgery was beneficial in reducing the risk of further visual loss [12-14] but generally not beneficial in reversing already diminished acuity. This preventive effect and the fact that patients with proliferative diabetic retinopathy (PDR) or macular edema may be asymptomatic provide strong support for a screening program to detect diabetic retinopathy.

The American Diabetes Association's position statement [52] titled "Retinopathy in Diabetes" states that dilated indirect ophthalmoscopy, coupled with biomicroscopy and seven-standard field stereoscopic 30 degrees fundus photography is an accepted method for examining diabetic retinopathy. Seven-standard field stereoscopic fundus photography is more sensitive at detecting retinopathy than is clinical examination, but clinical examination is superior for detecting both retinal thickening from macular edema and early neovascularization.

Research regarding diabetic retinopathy has evolved progressively over the last 30 years, producing a vast foundation of knowledge about its risks, natural history, and treatment efficacy. However the optimal for detecting diabetic retinopathy in the large diabetic population is unclear.

Several alternative methods for detecting diabetic retinopathy also have been reported. These included using direct ophthalmoscopy by different healthcare providers. In 1985, Moss SE. [37] had compared between direct ophthalmoscopy performed by ophthalmologist, specially trained optometrist and ophthalmic technician and seven field stereoscopic fundus photography for determining severity of diabetic retinopathy in 2,708 diabetic patients. This study concluded that direct ophthalmoscopy appeared to be a conditionally acceptable alternative to grading a gross classification of diabetic retinopathy. In 2004, Gill JM. [38] also evaluated the use of nonmydriatic

Panoptic direct ophthalmoscopy by 11 family physicians and 1 local ophthalmologist to screen for diabetic retinopathy in 28 patients using clinical examination by the ophthalmologist as a reference standard. The referral threshold was the presence of exudate within 1 disc diameter of macula or 3 or more hemorrhages temporal to macula. The results showed 83-91 percents sensitivity (family physicians) and 81 percents sensitivity (ophthalmologist). But this study performed in a small number of patients (28 patients). However, direct ophthalmoscopy screening method had lost of interest because of its low sensitivity and specificity, need of experience, need of mydriasis and more affected by media opacity.

The other alternative methods in screening for diabetic retinopathy were evaluated. Seven standard field stereoscopic 30 degrees fundus photography has been the standard technique in a number of clinical trials and epidemiologic studies. However, it is uncomfortable to undergo fundus photography because of the light needed to focus and the intense flash involved in taking the pictures. By reducing the number of fields, it may be possible to enhance compliance by reducing discomfort and examination time. A number of studies evaluated the efficacy of this instrument with decreasing number of fields were shown below.

In 1989, Moss SE. [39] had investigated in population-based study of 2,694 diabetic persons to detect diabetic retinopathy compared 2, 3, 4 fields of stereoscopic fundus photography and used seven standard field stereoscopic fundus photography as a reference standard. The result of this study showed that the sensitivity to detect any retinopathy increases with increase number of fields. (87-95 %) Bresnick GH. [40] also studied in the year 2000 using stereoscopic fundus photographic grading data for primary care diabetic retinopathy screening protocol from 3,711 ETDRS patients. The results revealed that assessing retinopathy severity in posterior fundus (field 1, 2, 3) have the potential to identify most diabetic patients with vision threatening retinopathy.

Despite promising results, there are some drawbacks of these studies such as, still time-consuming, need photographer experience, skilled reader and the seven standard field stereoscopic fundus photography is not routinely available world-wide especially outside a research setting.

Nonstereoscopic wider viewing angle, 45 degrees fundus camera recently has been introduced, either mydriatic or nonmydriatic, single field or multiple fields, as an instrument in many diabetic retinopathy screening researches. In 1985 Klein R.[41] evaluated 3 alternative methods to grading of diabetic retinopathy: direct ophthalmoscopy, nondilated and dilated single field nonstereoscopic 45 degrees retinal photography interpreted by trained grader compared to 30 degrees seven-standard field photography (only field 1, 2, 4) in 99 patients. Diabetic retinopathy was classified in 4 levels, no DR, mild NPDR, all other NPDR, PDR. The exact agreement were 54.3%, 82.5% and 86.5% of direct ophthalmoscopy, nondilated and dilated single field nonstereoscopic 45 degrees retinal photography respectively.

In 1993, Peters AL. [42] assessed the efficacy of a single field nonmydriatic polaroid retinal camera interpreted by trained reader as a screening method for serious diabetic retinopathy (pre proliferative, proliferative diabetic retinopathy and macular edema). There were 522 patients recruited in this study. The clinical examination by 2 retina specialists was used as a reference standard and the referral cut point set at any retinopathy levels. The results showed sensitivity of 100% and specificity of 82%.

In 1995, Harding SP. [43] Compared between 2 methods, single field nonmydriatic 45 degrees retinal camera interpreted by trained reader and dilated direct ophthalmoscope by ophthalmologist for community based screening for sight-threatening diabetic retinopathy.(moderate pre-proliferative diabetic retinopathy, circinate maculopathy, exudate in macular area) There were 320 patients included. The reference standard was slit lamp examination by retinal specialist. The sensitivity of fundus photography is higher than direct ophthalmoscopy. (89% VS 69 %)

In 2001, Stellingwerf C. [44] compared between 2-field 45 degrees mydriatic retinal photography interpreted by retinal specialist and clinical examination by ophthalmologist in diabetic retinopathy screening. There were 469 patients participated in this study. The study revealed sensitivity 83%, specificity 88% for any diabetic retinopathy and sensitivity 95%, specificity 99% for sight-threatening diabetic retinopathy (retinopathy grade 3.5 or higher).

Gomez-Ulla F [45] studied in the year 2002 to find the agreement between 4-field fundus photography interpreted by the ophthalmologist and clinical examination by the ophthalmologist. The result showed the k value1.0 in the presence of DR by both techniques, the ICC of 0.92 in gradation and there was disagreement in 8 of 126 eyes.

In 2004, Murgatroyd H. [46] studied to find differences between single field mydriatic, single field nonmydriatic and multiple field mydriatic (temporal, macular, nasal to disc) fundus photography interpreted by 2 trained graders in diabetic retinopathy screening in 398 patients. The reference standard was
slit-lamp examination by ophthalmologist. The results showed sensitivity 77%, 81%, 83%, specificity 95%, 92%, 93% for single field mydriatic, single field nonmydriatic and multiple field mydriatic fundus photography respectively.

The systematic review by Williams GA. et al [47] of single-field fundus photography for diabetic retinopathy screening published in the year 2004 (the review started in the year 1968 to 2003), the panel selected 32 articles for the panel methodologist to review and rate according to the strength of evidence. Three of the 32 reviewed articles were classified as level I evidence, and 4 were classified as level II evidence (the details of level I evidence were shown in table 1). This review concluded that single-field fundus photography is not a substitute for a comprehensive ophthalmic examination, but there is level I evidence that it can serve as a screening tool for diabetic retinopathy, to identify patients with retinopathy for referral for ophthalmic evaluation and management.

Table 1 summary of details of level I evidence articles in systematic review by Williams

Study	N	Reference standard	Referral threshold	Results	Comments
Pugh et al (1993)	352	7standard fields (ETDRS)	Moderate NPDR	Fundus photography reveals higher sensitivity than clinical examination (81 VS 33)	42/50 ungradable images became gradable after dilatation

Table 1 summary of details of level I evidence articles in systematic review by Williams

Study	N	Reference standard	Referral threshold	Results	Comments
Taylor et al (1999)	118	7standard fields (ETDRS)	Sight-threatening DR	Fundus photography demonstrated the sensitivity of 90%	Additional images could be obtained from 20 degree field
Lin et al (2002)	197	7standard fields (ETDRS)	ETDRS >=35	The sensitivity of fundus photography is 78%	

From the results of studies above, this emerging innovation and advances in digital retinal imaging have fostered a spectrum of alternative approaches to evaluate patients for diabetic retinopathy. Single-field fundus photography is more favorable than multiple-field fundus photography because increasing number of field does not significant increase sensitivity and specificity. On the other hand, single field fundus photography interpreted by trained readers or ophthalmologist has many advantages such as ease of use, convenience, ability to detect retinopathy, and telemedicine application. In addition, mydriasis may improve image quality and reduce technical failure rate, but may not increase the sensitivity or specificity of detecting retinopathy.

But there are few studies that reported different results of this method. In 1995, Sui SC. [48] evaluated single field nonmydriatic photography interpreted by ophthalmologist and nondilated direct ophthalmoscopy by physicians in diabetic retinopathy screening using clinical examination by 2 ophthalmologists as a reference standard in 153 patients. The study result showed the sensitivity 64 %, 41% and specificity 90%, 93% for single field nonmydriatic photography and nondilated direct ophthalmoscopy respectively. In 2000, Lim JI.[49] showed different result of 22 diabetic patients. The nonmydriatic digital fundus imaging interpreted by retina specialist for detection of neovascularization, IRMA, hemorrhage, exudate had a low sensitivity rate, high specificity rate and is less clinically useful than dilated 3-field of standard 35 mm

slide [28]. These two studies performed in small sample size, suboptimal reference standard and may be affected by intraobserver reliability.

In Thailand, there are 2 studies evaluated single field 45 degrees nonstereoscopic nonmydriatic color fundus photography interpreted by different health care professionals with various results.

In 2005, Ruamviboonsuk P. [50] evaluated the practicability of single field 45 degrees nonstereoscopic nonmydriatic color fundus photography interpreted by retina specialists in diabetic retinopathy screening in rural area compared with dilated clinical examination by retina specialist. There were 130 patients. The sensitivity was 80 % and specificity was 96 % in detecting any retinopathy. In this study, the reference standard is not a gold standard. It needs to be performed the indirect ophthalmoscopy coupled with slit-lamp biomicroscopy to detect macular edema and small neovascularization. The sample size in this study is too small.

Ruamviboonsuk P. [51] also reported in 2006 to assess the agreement using weighted kappa statistics among a group of ophthalmic care providers, including retina specialists, ophthalmologists, ophthalmic nurses and photographers. There is only fair agreement among all readers. (k=0.34) They also evaluated the sensitivity and specificity using the severe NPDR as the referral cut point. The reference standard was the consensus of 3 retina specialists' interpretation of the single field nonstereoscopic fundus photography. This is not a true gold standard. The single field fundus photography has some limitations such as limitation of field, no stereoscopic view and the quality of images affected by media opacity. The indirect ophthalmoscopy coupled with slit-lamp biomicroscopy is the most preferable reference standard in Thailand.

In 2007, Lopez-Bastida J [52] studied the sensitivity and specificity of digital retinal imaging using dilated indirect ophthalmoscopy with slit-lamp biomicroscopy by a retina specialist as a reference standard. This study performed in type I and type II diabetic patients of 773 cases (30.5 % were type I) in a hospital-based program. The digital images were interpreted by the retina specialists. The results revealed the sensitivity of 92 % and 100 %, specificity of 96% and 100 % at any retinopathy and sight-threatening DR respectively. The population in this study is not representatives of

the true population because it is a hospital-based program and the sample population included more proportion of type I diabetes.

Because most persons with diabetes receive their care in primary care setting, and primary care physicians or family physicians are the main healthcare providers in this setting, the study designed to evaluate that single field digital fundus photography interpreted by family physicians can serve as a screening tool for diabetic retinopathy to identify patients for referral for ophthalmic evaluation and management is needed to conduct.