

# World Journal of *Nephrology*

*World J Nephrol* 2019 February 21; 8(2): 33-43



**ORIGINAL ARTICLE****Observational Study**

- 33 Associations of renal function with diabetic retinopathy and visual impairment in type 2 diabetes: A multicenter nationwide cross-sectional study

*Kaewput W, Thongprayoon C, Rangsin R, Ruangkanchanasetr P, Mao MA, Cheungpasitporn W*

**ABOUT COVER**

Editorial Board Member of *World Journal of Nephrology*, Hernán Trimarchi, FACP, MD, PhD, Professor, Nephrology Service, Hospital Británico de Buenos Aires, Buenos Aires 1280, Argentina

**AIMS AND SCOPE**

*World Journal of Nephrology* (*World J Nephrol*, *WJN*, online ISSN 2220-6124, DOI: 10.5527) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

*WJN* covers topics concerning kidney development, renal regeneration, kidney tumors, therapy of renal disease, hemodialysis, peritoneal dialysis, kidney transplantation, diagnostic imaging, evidence-based medicine, epidemiology and nursing. Priority publication will be given to articles concerning diagnosis and treatment of nephrology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, etc.

We encourage authors to submit their manuscripts to *WJN*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great basic and clinical significance.

**INDEXING/ABSTRACTING**

The *WJN* is now abstracted and indexed in PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

**RESPONSIBLE EDITORS FOR THIS ISSUE**

Responsible Electronic Editor: *Han Song*

Proofing Editorial Office Director: *Jin-Lai Wang*

**NAME OF JOURNAL**

*World Journal of Nephrology*

**ISSN**

ISSN 2220-6124 (online)

**LAUNCH DATE**

February 6, 2012

**FREQUENCY**

Irregular

**EDITORS-IN-CHIEF**

Li Zuo

**EDITORIAL BOARD MEMBERS**

<https://www.wjnet.com/2220-6124/editorialboard.htm>

**EDITORIAL OFFICE**

Jin-Lai Wang, Director

**PUBLICATION DATE**

February 21, 2019

**COPYRIGHT**

© 2019 Baishideng Publishing Group Inc

**INSTRUCTIONS TO AUTHORS**

<https://www.wjnet.com/bpg/gerinfo/204>

**GUIDELINES FOR ETHICS DOCUMENTS**

<https://www.wjnet.com/bpg/GerInfo/287>

**GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH**

<https://www.wjnet.com/bpg/gerinfo/240>

**PUBLICATION MISCONDUCT**

<https://www.wjnet.com/bpg/gerinfo/208>

**ARTICLE PROCESSING CHARGE**

<https://www.wjnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjnet.com/bpg/GerInfo/239>

**ONLINE SUBMISSION**

<https://www.f6publishing.com>

## Observational Study

## Associations of renal function with diabetic retinopathy and visual impairment in type 2 diabetes: A multicenter nationwide cross-sectional study

Wisit Kaewput, Charat Thongprayoon, Ram Rangsins, Prajej Ruangkanchanasetr, Michael A Mao, Wisit Cheungpasitporn

**ORCID number:** Wisit Kaewput (0000-0003-2920-7235); Charat Thongprayoon (0000-0002-8313-3604); Ram Rangsins (0000-0002-7175-0963); Prajej Ruangkanchanasetr (0000-0002-5123-5964); Michael A Mao (0000-0003-1814-7003); Wisit Cheungpasitporn (0000-0001-9954-9711).

**Author contributions:** Kaewput W, Thongprayoon C, and Cheungpasitporn W designed research; Kaewput W and Thongprayoon C performed research and analysis; Rangsins R, Ruangkanchanasetr P, Mao MA, and Cheungpasitporn W supervised this research project; Kaewput W, Thongprayoon C wrote the original manuscript; Rangsins R, Ruangkanchanasetr P, Mao MA, and Cheungpasitporn W reviewed, edited, and revised the final manuscript.

**Institutional review board**

**statement:** This study was approved by both the Institutional Review Board of the Royal Thai Army Medical Department and the Ethical Review Committee for Research in Human Subjects, the Ministry of Public Health of Thailand (IRB# S043h/60Exp). Well-trained research nurses reviewed medical records and collected data into a case record form. Data entry into the case record form was then transferred to the central data management of the Medical Research Network of

**Wisit Kaewput, Ram Rangsins,** Department of Military and Community Medicine, Phramongkutklao College of Medicine, Bangkok 10400, Thailand

**Charat Thongprayoon, Michael A Mao,** Division of Nephrology and Hypertension, Department of Medicine, Mayo Clinic, Rochester, MN 55905, United States

**Prajej Ruangkanchanasetr,** Department of Medicine, Phramongkutklao Hospital and College of Medicine, Bangkok 10400, Thailand

**Wisit Cheungpasitporn,** Division of Nephrology, Department of Medicine, University of Mississippi Medical Center, Jackson, MS 39216, United States

**Corresponding author:** Wisit Kaewput, MD, Assistant Professor, Department of Military and Community Medicine, Phramongkutklao College of Medicine, 315 Ratchawithi Rd, Chang Wat, Bangkok 10400, Thailand. [wisitnephro@gmail.com](mailto:wisitnephro@gmail.com)

**Telephone:** +66-23547600-93613

**Fax:** +66-23547733

## Abstract

**BACKGROUND**

Diabetic retinopathy (DR) separately has been noted as a major public health problem worldwide as well. Currently, many studies have demonstrated an association between diabetic nephropathy and DR in type 1 diabetes mellitus (T1DM) patients, but this association is less strong in T2DM. The evidence for an association between renal function and DR and visual impairment among T2DM patients is limited, particularly in the Asian population.

**AIM**

To assess the association between glomerular filtration rate (GFR) and DR, severe DR, and severe visual impairment among T2DM patients in Thailand.

**METHODS**

We conducted a nationwide cross-sectional study based on the DM/HT study of the Medical Research Network of the Consortium of Thai Medical Schools. This study evaluated adult T2DM patients from 831 public hospitals in Thailand in the year 2013. GFR was categorized into  $\geq 90$ , 60-89, 30-59 and  $< 30$  mL/min/1.73 m<sup>2</sup>. The association between GFR and DR, severe DR, and severe visual impairment



the Consortium of Thai Medical Schools to adjudicate that the process of data collection was compiled according to study protocol. The data management team was responsible for inquiries to study sites to verify data. Site monitoring was randomly performed in approximately 10% of study sites.

**Informed consent statement:**

Patients were all patients were recruited from the outpatient clinic. Written informed consent was obtained from patients before enrolment.

**Conflict-of-interest statement:** The authors deny any conflict of interest.

**Data sharing statement:** No additional data are available.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Manuscript source:** Invited manuscript

**Received:** September 26, 2018

**Peer-review started:** September 26, 2018

**First decision:** October 26, 2018

**Revised:** November 7, 2018

**Accepted:** January 28, 2019

**Article in press:** January 28, 2019

**Published online:** February 21, 2019

were assessed using multivariate logistic regression.

## RESULTS

A total of 13192 T2DM patients with available GFR were included in the analysis. The mean GFR was  $66.9 \pm 25.8$  mL/min/1.73 m<sup>2</sup>. The prevalence of DR, proliferative DR, diabetic macular edema, and severe visual impairment were 12.4%, 1.8%, 0.2%, and 2.1%, respectively. Patients with GFR of 60-89, 30-59 and < 30 mL/min/1.73 m<sup>2</sup> were significantly associated with increased DR and severe DR when compared with patients with GFR of  $\geq 90$  mL/min/1.73 m<sup>2</sup>. In addition, increased severe visual impairment was associated with GFR 30-59 and < 30 mL/min/1.73 m<sup>2</sup>.

## CONCLUSION

Decreased GFR was independently associated with increased DR, severe DR, and severe visual impairment. GFR should be monitored in diabetic patients for DR awareness and prevention.

**Key words:** Diabetic retinopathy; Visual impairment; Glomerular filtration rate; Type 2 diabetes

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Currently, the associations of renal function with diabetic retinopathy (DR), its severity, and severe visual impairment in type 2 diabetes mellitus (DM) are inconclusive, especially in the Asian population. In this study, we conducted a nationwide cross-sectional study based on the DM/HT study of the Medical Research Network of the Consortium of Thai Medical Schools. We demonstrated that decreased glomerular filtration rate (GFR) was independently associated with increased DR, severe DR, and severe visual impairment. GFR should be monitored in diabetic patients for DR awareness and prevention.

**Citation:** Kaewput W, Thongprayoon C, Rangsin R, Ruangkanchanasetr P, Mao MA, Cheungpasitporn W. Associations of renal function with diabetic retinopathy and visual impairment in type 2 diabetes: A multicenter nationwide cross-sectional study. *World J Nephrol* 2019; 8(2): 33-43

**URL:** <https://www.wjgnet.com/2220-6124/full/v8/i2/33.htm>

**DOI:** <https://dx.doi.org/10.5527/wjn.v8.i2.33>

## INTRODUCTION

Type 2 diabetes mellitus (DM) is a common chronic disease worldwide<sup>[1]</sup> that poses a major crisis in the global health system<sup>[2]</sup>. The associated morbidity and mortality can be caused by the disease itself or its complications. Severe and not uncommon complications include chronic kidney disease (CKD) and diabetic retinopathy (DR). DR separately has been noted as a major public health problem worldwide as well<sup>[3,4]</sup>. The associated problems include disability, increased healthcare costs, and socioeconomic burdens<sup>[5-8]</sup>.

Currently, many studies have demonstrated an association between diabetic nephropathy and DR in T1DM patients, but this association is less strong in T2DM<sup>[9,10]</sup>. Hence, currently the associations of renal function with DR, its severity, and severe visual impairment vision in T2DM are inconclusive<sup>[11]</sup>, especially in the Asian population<sup>[12,13]</sup>. If such an association of renal function with DR and visual impairment existed, it would provide further support to the importance for regular monitoring of glomerular filtration rate (GFR) in T2DM patients. Furthermore, it would motivate future research on whether more intensive monitoring of T2DM patients may allow earlier detection and prevention of DR and visual impairment. Visual impairment secondary to DR can be corrected if early sight threatening disease is detected and treated with laser photocoagulation.

This study was thus aimed to determine whether such an association between GFR with DR and visual impairment exists, and if so the prevalence and magnitude of this association.

## MATERIALS AND METHODS

### Study design and population

This was a nationwide, multi-center, cross-sectional study in Thailand *via* secondary analysis of the DM/HT dataset in 2013<sup>[14]</sup>. This dataset was a nationwide survey conducted annually in Thailand to evaluate the status of medical care in T2DM patients who visited the public hospitals of the Thai Ministry of Public Health and the clinics in the Thailand National Health Security Office's program. The inclusion criteria of this DM/HT survey consisted of T2DM patients aged  $\geq 35$  years who received regular medical care in the targeted hospitals and clinics ( $n = 831$ ) for at least 12 mo. Patients who received care at primary care units outside of Bangkok and university hospitals were excluded from the study. A two-stage stratified cluster sampling method was used to select a nationally and provincially representative sample of T2DM patients in Thailand. The first stage of sample collection consisted of the provinces that constituted 77 strata. The second stage of sample collection was the hospitals' levels in each province, which were stratified into 5 strata according to the size of the hospital. These 5 strata were regional ( $> 500$  beds), provincial (200-500 beds), large community (80-120 beds), medium community (60 beds), and small community (10-30 beds) hospitals. All regional ( $n = 25$ ), provincial ( $n = 70$ ), and community ( $n = 736$ ) hospitals were included. Of 736 community hospitals, 10%, 20%, and 70% were large, medium and small community hospitals, respectively. For the objectives of this study to assess the association between GFR and DR and visual impairment, we included only patients with available eye examination data in the analysis.

All patients were recruited from the outpatient clinic. Written informed consent was obtained from patients before enrolment. This study was approved by both the Institutional Review Board of the Royal Thai Army Medical Department and the Ethical Review Committee for Research in Human Subjects, the Ministry of Public Health of Thailand. Well-trained research nurses reviewed medical records and collected data into a case record form. Data entry into the case record form was then transferred to the central data management of the Medical Research Network of the Consortium of Thai Medical Schools to adjudicate that the process of data collection was compiled according to study protocol. The data management team was responsible for inquiries to study sites to verify data. Site monitoring was randomly performed in approximately 10% of study sites. This study was conducted by the Strengthening the Reporting of Observational Studies in Epidemiology<sup>[15]</sup>.

### Data collection

Clinical characteristics, demographic information, medication, and laboratory data were collected using manual data retrieval from the medical record as described above. The laboratory data consisted of the 12 mo results prior to the consent process. GFR was estimated based on age, sex, race and the most recent creatinine using the Chronic Kidney Disease Epidemiology Collaboration equation<sup>[16]</sup>. Primary outcome was the diagnosis of DR. DR was diagnosed by ophthalmologists and was identified by ICD10 codes H36.0x. The technique for eye examination was fundus photography by digital camera with interpretation performed by ophthalmologists. The diagnosis of DR was then stratified into: (1) non-proliferative DR; (2) proliferative DR; (3) diabetic macular edema; and (4) non-specific DR. Non-specific DR were defined as DR without available staging data in the medical record. Severe DR was defined as both proliferative DR and macular edema. Visual impairment was based on visual acuity (VA) exam as documented by physicians. Severe visual impairment was defined as a VA exam that consisted of "counting fingers", "hand motions", "projection of light" and "no light perception".

### Statistical analysis

Continuous variables were presented as mean  $\pm$  SD. Categorical variables were presented as count with percentage. Clinical characteristics and outcomes were compared among different estimated GFR (eGFR) group, using analysis of variance for continuous variables and the chi-square test for categorical variables. eGFR was categorized into 4 groups;  $\geq 90$ , 60-89, 30-59 and  $< 30$  mL/min/1.73 m<sup>2</sup>. GFR of  $\geq 90$  mL/min/1.73 m<sup>2</sup> was selected as the reference group. Univariate and then multivariate logistic regression analysis, adjusting for priori-defined variables, was performed to assess the independent association between GFR and DR, severe DR (proliferative DR and macular edema), and severe visual impairment. Odds ratio (OR) with 95% confidence interval (CI) was reported. The adjusted variables were age, sex, smoking, waist circumference, duration of diabetes, comorbidities and medications. Comorbidities were hypertension, coronary artery disease, stroke, and peripheral artery disease. Medications were metformin, sulfonylurea, insulin, and antiplatelet

medication. A *P*-value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 22 (SPSS, Inc., Chicago, IL, United States).

## RESULTS

### **Baseline characteristics**

A total of 13192 adult T2DM patients with available GFR and eye examination data from Thailand public hospitals were included in this analysis. The clinical characteristics are summarized in [Table 1](#). The mean age was  $60.7 \pm 10.3$  years, and 30.4% were male. The mean diabetic duration was  $7.4 \pm 4.8$  years. The mean eGFR was  $67.4 \pm 25.7$  mL/min/1.73 m<sup>2</sup>. Patients with lower GFR were significantly older, female, had longer diabetic duration, higher prevalence of hypertension, coronary artery disease, stroke, peripheral artery disease; and higher medication use of antiplatelets and insulin compared to patients with higher GFR. Lower GFR was additionally associated with lower smoking rates, waist circumference and medication use of metformin and sulfonylureas ([Table 1](#)).

The prevalence of all DR, non-proliferative DR, proliferative DR, diabetic macular edema, and severe visual impairment were 12.4%, 10.0%, 1.8%, 0.2%, and 2.1%, respectively ([Table 2](#)).

### **The association between GFR and DR**

The prevalence of DR was 9.5%, 11.0%, 14.1%, and 20.9% in patients with GFR of  $\geq 90$ , 60-89, 30-59 and < 30 mL/min/1.73 m<sup>2</sup>, respectively (*P* < 0.001) ([Table 2](#)). In adjusted analysis, GFR of 60-89, 30-59 and < 30 mL/min/1.73 m<sup>2</sup> were associated with an increased OR of 1.36 (95%CI: 1.12-1.65), 2.08 (95%CI: 1.70-2.55), and 2.38 (95%CI: 1.79-3.18), respectively, for DR ([Table 3](#)).

### **The association between GFR and severe DR**

The prevalence of proliferative DR was 1.1%, 1.3%, 2.2%, and 5.2% in patients with GFR of  $\geq 90$ , 60-89, 30-59 and < 30 mL/min/1.73 m<sup>2</sup>, respectively (*P* < 0.001) ([Table 2](#)). The prevalence of diabetic macular edema was 0.0%, 0.2%, 0.2%, and 0.4% in patients with GFR of  $\geq 90$ , 60-89, 30-59 and < 30 mL/min/1.73 m<sup>2</sup>, respectively (*P* < 0.06) ([Table 2](#)). The prevalence of severe DR defined as proliferative DR with severe macular edema was 1.1%, 1.4%, 2.3%, and 5.5% in patients with GFR of  $\geq 90$ , 60-89, 30-59 and < 30 mL/min/1.73 m<sup>2</sup>, respectively (*P* < 0.001) ([Table 2](#)). In adjusted analysis, GFR of 60-89, 30-59 and < 30 mL/min/1.73 m<sup>2</sup> was associated with an increased OR of 1.95 (95%CI: 1.14-3.33), 2.82 (95%CI: 1.61-4.93), and 4.89 (95%CI: 2.47-9.67), respectively for severe DR ([Table 4](#)).

### **The association between GFR and severe visual impairment**

The prevalence of severe visual impairment was 0.8%, 1.5%, 3.2%, and 4.8% in patients with GFR of  $\geq 90$ , 60-89, 30-59 and < 30 mL/min/1.73 m<sup>2</sup>, respectively (*P* < 0.001) ([Table 2](#)). In adjusted analysis, GFR of 30-59 and < 30 mL/min/1.73 m<sup>2</sup> was associated with an increased OR of 2.06 (95%CI: 1.22-3.46), and 2.50 (95%CI: 1.31-4.76), respectively for severe visual impairment ([Table 4](#)).

## DISCUSSION

Analysis of the baseline patient characteristics showed that a lower GFR was associated with lower smoking rates, waist circumference and medication use of metformin and sulfonylureas. This finding could be explained by medical providers' intervention to slow the GFR decline in Thailand by recommending smoking cessation and weight reduction in the obese, or perhaps by the anorexia and associated reduced caloric intake in patients with advanced CKD and uremia. The decrease in metformin and sulfonylureas usage may reflect discontinuation of the medication as age progresses or from concerns for increased risk with renal impairment.

### **Prevalence of DR, severe DR (proliferative DR and macular edema) and severe visual impairment**

Available prior studies have reported an overall prevalence of DR in Thailand ranging between 13.6%-31.2%<sup>[17,18]</sup>, and they mostly involved non-proliferative DR. The previous results varied slightly according to the study setting and diagnostic criteria. Among the studies that used clinical funduscopy, the prevalence of DR ranged from

**Table 1** Baseline characteristics *n* (%)

Characteristics	All	eGFR (mL/min/1.73 m <sup>2</sup> )				P-value
		≥ 90	60-89	30-59	< 30	
N	13192	2979 (22.6)	4870 (36.9)	4397 (33.3)	946 (7.2)	
Age (yr), mean ± SD	60.7 ± 10.3	54.1 ± 8.5	59.4 ± 9.6	65.4 ± 9.2	66.0 ± 10.0	< 0.001
Male	4012 (30.4)	860 (28.9)	1587 (32.6)	1303 (29.6)	262 (27.7)	< 0.001
Duration of diabetes (yr), mean ± SD	7.4 ± 4.8	6.1 ± 4.1	7.0 ± 4.5	8.3 ± 5.1	9.1 ± 5.4	< 0.001
Waist circumference (cm), mean ± SD	88.6 ± 10.4	88.9 ± 10.6	88.7 ± 10.3	88.5 ± 10.3	87.4 ± 101.6	< 0.01
Hypertension	9741 (73.8)	1935 (65.0)	3466 (71.2)	3575 (81.3)	765 (80.9)	< 0.001
Smoking	467 (3.5)	127 (4.3)	203 (4.2)	117 (2.7)	20 (2.1)	< 0.001
CAD	621 (4.7)	76 (2.6)	205 (4.2)	269 (6.1)	71 (7.5)	< 0.001
CVD	273 (2.1)	42 (1.4)	94 (1.9)	104 (2.4)	33 (3.5)	< 0.001
PAD	24 (0.2)	5 (0.2)	5 (0.1)	8 (0.2)	6 (0.6)	< 0.01
Antiplatelets	8067 (61.4)	1569 (52.9)	2974 (61.3)	2923 (66.8)	601 (64.0)	< 0.001
Metformin	9756 (74.0)	2592 (87.0)	4066 (83.5)	2894 (65.8)	204 (21.6)	< 0.001
Sulfonylurea	8751 (66.3)	2070 (69.5)	3460 (71.0)	2882 (65.5)	339 (35.8)	< 0.001
Insulin	2866 (21.7)	493 (16.5)	765 (15.7)	1050 (23.9)	558 (59.0)	< 0.001

eGFR: Estimated glomerular filtration rate; CAD: Coronary artery diseases; CVD: Cerebrovascular diseases; PAD: Peripheral artery disease.

12.2%-37%<sup>[19,20]</sup>. Among the studies that used fundus photography, the prevalence of DR ranged from 10.1%-48.1%<sup>[21-24]</sup>. In newly diagnosed diabetes, the prevalence of DR ranged from 1.5%-28.6%<sup>[25]</sup>. Generally, the prevalence of DR at diagnosis of T1DM is reported low between 0-3% while those with newly diagnosed T2DM have a higher prevalence of DR 6.7%-30.2%<sup>[26]</sup>. In this study, the lower prevalence of DR, severe DR and severe visual impairment in Thailand found may be due to multiple reasons: limited access to ophthalmologists, inclusion of earlier diabetic cases, use of different diagnostic criteria, limitations in the technique of eye examination (such as the images produced were two-dimensional unlike the three-dimensional from indirect binocular ophthalmoscopy or the lower magnification and image clarity compared to indirect ophthalmoscopy), and exclusion of primary care units and university hospitals patients. The care for patients in university hospitals might be different from other public hospitals as these patients' medical conditions were likely more complicated. The tertiary and university hospitals may also possess greater availability of medical experts that allow a more comprehensive diagnosis and thus capture of these patients of interest. In public hospitals, this may have led to underdiagnosis of DR patients, resulting in the lower prevalence described.

#### **The association between GFR and DR, severe DR and severe visual impairment**

The present study showed that eGFR by using the CKD-EPI formula is independently associated with DR in adult T2DM patients. This study's results are similar to previous reports from non-Asian ethnicity; Penno *et al*<sup>[27]</sup> and Grunwald *et al*<sup>[28]</sup> studies, which found an independent inverse correlation between eGFR and DR. We found that patients with impaired renal function also were associated with an increased likelihood of DR compared to patients with normal renal function. The pathogenesis of DR and nephropathy is due to microvascular disease. Prior studies have demonstrated that DR and DN have a common pathological basis<sup>[29]</sup> and a similar course of elucidation. Hyperglycemia causes glomerular hyper perfusion leading to an increase in GFR during the early stages of T2DM<sup>[30]</sup>. The accumulation of advanced glycation end products (AGEs) due to hyperglycemia also promotes mesangial proliferation and basement membrane thickening in the glomerulus. Furthermore, multiple pathways such as the activation of the polyol, the protein kinase C, the pentose phosphate<sup>[31]</sup>, oxidative stress, and various cytokines can cause a range of kidney pathology, which includes capillary obstruction, reduction of podocyte proliferation, podocyte death, and urinary protein loss. These can lead to a subsequent decline in renal function. The pathophysiology is similar to those observed in the retina. Hyperglycemia produces deleterious effects on the retina, such as apoptosis of Muller cells, ganglion cells<sup>[32]</sup>, and pericytes; thickening of the capillary basement membrane, and proliferation of endothelial cells in the retina. These effects lead to the pathological changes in DR and threaten a patient's vision. Therefore, GFR not only may be an important clinical marker for DN, but could be correlated with



**Table 2** Prevalence and severity of diabetic retinopathy stratified by estimated glomerular filtration rate level (mL/min/1.73 m<sup>2</sup>) n (%)

Outcomes	All	eGFR (mL/min/1.73 m <sup>2</sup> )				P-value
		≥ 90	60-89	30-59	< 30	
DR	1636 (12.4)	284 (9.5)	534 (11.0)	620 (14.1)	198 (20.9)	< 0.001
Non-proliferative DR	1313 (10.0)	242 (8.1)	438 (9.0)	498 (11.3)	135 (14.3)	< 0.001
Proliferative DR	240 (1.8)	33 (1.1)	63 (1.3)	95 (2.2)	49 (5.2)	< 0.001
Diabetic macular edema	21 (0.2)	1 (0.0)	8 (0.2)	8 (0.2)	4 (0.4)	0.06
Non-specific DR	84 (0.6)	9 (0.3)	33 (0.7)	27 (0.6)	15 (1.6)	< 0.001
Severe DR	258 (2.0)	34 (1.1)	70 (1.4)	102 (2.3)	52 (5.5)	< 0.001
Severe visual impairment	281 (2.1)	24 (0.8)	72 (1.5)	140 (3.2)	45 (4.8)	< 0.001
Counting finger	138 (1.0)	7 (0.2)	43 (0.9)	72 (1.6)	16 (1.7)	< 0.001
Hand movement	77 (0.6)	10 (0.3)	17 (0.3)	35 (0.8)	15 (1.6)	< 0.001
Projection of light	14 (0.1)	0 (0)	5 (0.1)	6 (0.1)	3 (0.3)	0.06
No light perception	56 (0.4)	7 (0.2)	8 (0.2)	30 (0.7)	11 (1.2)	< 0.001

DR: Diabetic retinopathy; eGFR: Estimated glomerular filtration rate.

DR<sup>[33]</sup>. It is worth noting that the prior studies that demonstrated a lack of significant independent association between eGFR and DR in T2DM (Chen *et al*<sup>[12]</sup> and Sabanayagam *et al*<sup>[13]</sup>) were conducted among participants of Asian ethnicity. Contrarily, Penno *et al*<sup>[27]</sup> and Grunwald *et al*<sup>[28]</sup> studies had reported an “inverse correlation between eGFR and DR” in a study population of non-Asian ethnicity. Our study is the first study that has shown a significant independent inverse correlation between eGFR and DR in Asian patients, and thus opposes the possibility of ethnic differences as previously suggested in the prior available literature<sup>[11,34]</sup>.

This current study showed an association of GFR with severe stages of DR. Moreover, even patients with mild to moderate impaired renal function were more likely to have severe stages of DR compared to patients with normal renal function. This study's results are similar to Man *et al*<sup>[11]</sup>, Pugliese *et al*<sup>[35]</sup> and Penno *et al*<sup>[27]</sup> studies which demonstrated an association of GFR with severe DR. This association is potentially due to a shared common pathogenesis as described above. These phenomena further confirm a likely causative relationship as strength of association and biologic gradient. The current study also showed the association of GFR by using CKD-EPI formula and severe visual impairment in T2DM patients. Moreover, patients with CKD also were more likely to have severe visual impairment compared to patients with normal renal function. The likelihood of severe visual impairment was higher with increasing severity of CKD in diabetic patients. The current study's results are similar to Wong *et al*<sup>[36]</sup>. This could also be explained by shared common risk factors for ocular and kidney disease [T2DM, age, smoking, hypertension (HTN), dyslipidemia and obesity] and shared common pathogenic mechanisms of sight-threatening conditions (any retinopathy and cataract) that are also present in persons with diabetes and CKD such as accumulation of AGEs<sup>[37-40]</sup>, vitamin D deficiency<sup>[41]</sup>, and vascular endothelial growth factor driven angiogenesis<sup>[42,43]</sup>.

### Strengths

The present study provides information from a large nationwide multicenter study consisting of adult T2DM Thailand patients. The study measures severe visual impairment by using a semi-quantitative clinical scale composed of bedside testing, which is easy to perform in the community setting. Our analysis for an association between eGFR and DR utilized a multiple logistic regression model that included several possible confounders such as age, gender, smoking, waist circumference, duration of diabetes, comorbidities and medications. Comorbidities consisted of HTN, coronary artery diseases, cerebrovascular diseases and peripheral artery disease. In the final model adjustment, medications adjusted for included sulfonylurea, metformin, insulin, and antiplatelets. Lastly, use of the CKD-EPI eGFR formula is applicable to real-world practice for renal function evaluation in Thailand. The CKD-EPI creatinine equation is also arguably superior to the Cockcroft-Gault formula<sup>[44]</sup> and the Modification of Diet in Renal Disease Study equation<sup>[45]</sup> and could replace them for routine clinical use.

### Limitations

**Table 3 Association of estimated glomerular filtration rate level and diabetic retinopathy**

eGFR (mL/min/1.73m <sup>2</sup> )	Crude OR	95%CI	P-value	Adjusted OR <sup>1</sup>	95%CI	P-value
≥ 90		1 (reference)		1 (reference)		
60-89	1.17	1.01-1.36	0.04	1.36	1.12-1.65	< 0.01
30-59	1.56	1.34-1.81	< 0.001	2.08	1.70-2.55	< 0.001
< 30	2.51	2.06-3.06	< 0.001	2.38	1.79-3.18	< 0.001

<sup>1</sup>Adjusted for age, gender, duration of diabetes, waist circumference, hypertension, smoking, coronary artery diseases, cerebrovascular diseases, peripheral artery disease, antiplatelet, metformin, sulfonylurea, and insulin. eGFR: Estimated glomerular filtration rate.

The limitations of this study include the following. First, the study population does not include patients from university hospitals. Consequently, the prevalence of DR may be significantly underestimated as noted above. Second, data collection was performed using a retrospective medical record review; therefore, incomplete data records with missing diagnoses cannot be verified. Third, this study measured severe visual impairment by using the semi-quantitative clinical scale. Variations in the technique for eye examinations may be confounding factors. Fourth, this study did not classify causes of visual impairment such as cataract, glaucoma and age-related macular degeneration<sup>[42,46]</sup>. Finally, urine albumin values from the parent dataset were assessed in markedly different laboratory methods, such as urine dipstick, 24 h urine protein measurement, and timed urine protein collection. Furthermore, some urine albumin values were missing. Accordingly, we did not include this variable in the analytic model. Several reports have demonstrated however that urine albumin is an independent association with DR in diabetic patients<sup>[12]</sup>.

### Implication

The eGFR by using CKD-EPI formula should be additionally utilized for monitoring risk for DR, severe DR and severe visual impairment in T2DM patients. The importance of timely and frequent eye screening in T2DM and CKD patients cannot be over-emphasized. The early intervention to preserve renal function and adequate control of diabetes is keys to the reduction of ocular disease and prevent irreversible visual loss.

In conclusion, renal function was independently associated with DR, severe DR and severe visual impairment in T2DM patients. Renal function by eGFR should be closely monitored in T2DM patients as it may provide the clinician an additional risk marker to earlier detect, prevent and treat DR. Further studies are needed to demonstrate whether this will translate to improved clinical outcomes.

**Table 4 Subgroup analysis comparing the association of estimated glomerular filtration rate level with severe diabetic retinopathy and severe visual impairment**

eGFR (mL/min/1.73 m <sup>2</sup> )	Crude OR	95%CI	P-value	Adjusted OR <sup>1</sup>	95%CI	P-value
Proliferative diabetic retinopathy and macular edema						
≥ 90		1 (reference)			1 (reference)	
60-89	1.26	0.84-1.91	0.27	1.95	1.14-3.33	0.02
30-59	2.06	1.39-3.04	< 0.001	2.82	1.61-4.93	< 0.001
< 30	5.04	3.25-7.81	< 0.001	4.89	2.47-9.67	< 0.001
Severe visual impairment						
≥ 90		1 (reference)			1 (reference)	
60-89	1.85	1.16-2.94	0.01	1.07	0.62-1.82	0.81
30-59	4.05	2.62-6.26	< 0.001	2.06	1.22-3.46	< 0.01
< 30	6.15	3.73-10.15	< 0.001	2.50	1.31-4.76	< 0.01

<sup>1</sup>Adjusted for age, gender, duration of diabetes, waist circumference, hypertension, smoking, coronary artery diseases, cerebrovascular diseases, peripheral artery disease, antiplatelet, metformin, sulfonlurea, and insulin. eGFR: Estimated glomerular filtration rate.

## ARTICLE HIGHLIGHTS

### Research background

The evidence for an association of renal function with diabetic retinopathy (DR) and visual impairment among type 2 diabetes mellitus (T2DM) patients is limited, particularly in the Asian population. Currently, many studies have demonstrated an association between diabetic nephropathy and DR in T1DM patients, but this association is less strong in T2DM. This study aimed to assess the association between glomerular filtration rate (GFR) and DR, severe DR, and severe visual impairment among T2DM patients in Thailand.

### Research motivation

If such an association of renal function with DR and visual impairment existed, it would provide further support to the importance for regular monitoring of GFR in T2DM patients. Furthermore, it would motivate future research on whether more intensive monitoring of T2DM patients may allow earlier detection and prevention of DR and visual impairment. Visual impairment secondary to DR can be corrected if early sight threatening disease is detected and treated with laser photocoagulation. To further investigate the association between GFR and DR, severe DR, and severe visual impairment were assessed using multivariate logistic regression, the authors conducted a nationwide cross-sectional study based on the DM/HT study of the Medical Research Network of the Consortium of Thai Medical Schools.

### Research objectives

We conducted this study to determine whether such an association between GFR with DR and visual impairment exists, and if so the prevalence and magnitude of this association.

### Research methods

We conducted a nationwide cross-sectional study based on the DM/HT study of the Medical Research Network of the Consortium of Thai Medical Schools. This study evaluated adult T2DM patients from 831 public hospitals in Thailand in the year 2013. GFR was categorized into ≥ 90, 60-89, 30-59 and < 30 mL/min/1.73 m<sup>2</sup>. The association between GFR and DR, severe DR, and severe visual impairment were assessed using multivariate logistic regression.

### Research results

In this study, a total of 13192 T2DM patients with available GFR were included in the analysis. The mean GFR was 66.9 ± 25.8 mL/min/1.73 m<sup>2</sup>. The prevalence of DR, proliferative DR, diabetic macular edema, and severe visual impairment were 12.4%, 1.8%, 0.2%, and 2.1%, respectively. Patients with GFR of 60-89, 30-59 and < 30 mL/min/1.73 m<sup>2</sup> were significantly associated with increased DR and severe DR when compared with patients with GFR of ≥ 90 mL/min/1.73 m<sup>2</sup>. In addition, increased severe visual impairment was associated with GFR 30-59 and < 30 mL/min/1.73 m<sup>2</sup>.

### Research conclusions

We found that decreased GFR was independently associated with increased DR, severe DR, and severe visual impairment. GFR should be monitored in diabetic patients for DR awareness and prevention.

### Research perspectives

This study demonstrated significantly associations of decreased GFR with increased DR, severe DR, and severe visual impairment among diabetic patients. This finding suggests the importance

of timely and frequent eye screening in T2DM and CKD patients cannot be over-emphasized. The early intervention to preserve renal function and adequate control of diabetes is keys to the reduction of ocular disease and prevent irreversible visual loss.

## ACKNOWLEDGEMENTS

The authors wish to thank the Medical Research Network of the Consortium of Thai Medical Schools (MedResNet) Thailand which granted access to the diabetes and hypertension dataset in the DAMUS website.

DAMUS website: <http://www.damus.in.th/damus/index.php>

## REFERENCES

- 1 **Ogurtsova K**, da Rocha Fernandes JD, Huang Y, Linnenkamp U, Guariguata L, Cho NH, Cavan D, Shaw JE, Makaroff LE. IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. *Diabetes Res Clin Pract* 2017; **128**: 40-50 [PMID: [28437734](#) DOI: [10.1016/j.diabres.2017.03.024](#)]
- 2 **Wild S**, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004; **27**: 1047-1053 [PMID: [15111519](#) DOI: [10.2337/diacare.27.5.1047](#)]
- 3 **Yau JW**, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T, Chen SJ, Dekker JM, Fletcher A, Grauslund J, Haffner S, Hamman RF, Ikram MK, Kayama T, Klein BE, Klein R, Krishniah S, Mayurasakorn K, O'Hare JP, Orchard TJ, Porta M, Rema M, Roy MS, Sharma T, Shaw J, Taylor H, Tielsch JM, Varma R, Wang JJ, Wang N, West S, Xu L, Yasuda M, Zhang X, Mitchell P, Wong TY; Meta-Analysis for Eye Disease (META-EYE) Study Group. Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care* 2012; **35**: 556-564 [PMID: [22301125](#) DOI: [10.2337/dc11-1909](#)]
- 4 **Sivaprasad S**, Gupta B, Crosby-Nwaobi R, Evans J. Prevalence of diabetic retinopathy in various ethnic groups: a worldwide perspective. *Surv Ophthalmol* 2012; **57**: 347-370 [PMID: [22542913](#) DOI: [10.1016/j.survophthal.2012.01.004](#)]
- 5 **Kapur A**, Harries AD. The double burden of diabetes and tuberculosis - public health implications. *Diabetes Res Clin Pract* 2013; **101**: 10-19 [PMID: [23305899](#) DOI: [10.1016/j.diabres.2012.12.001](#)]
- 6 **Corriere M**, Rooparinesingh N, Kalyani RR. Epidemiology of diabetes and diabetes complications in the elderly: an emerging public health burden. *Curr Diab Rep* 2013; **13**: 805-813 [PMID: [24018732](#) DOI: [10.1007/s11892-013-0425-5](#)]
- 7 **Laxy M**, Hunger M, Stark R, Meisinger C, Kirchberger I, Heier M, von Scheidt W, Holle R. The Burden of Diabetes Mellitus in Patients with Coronary Heart Disease: A Methodological Approach to Assess Quality-Adjusted Life-Years Based on Individual-Level Longitudinal Survey Data. *Value Health* 2015; **18**: 969-976 [PMID: [26686780](#) DOI: [10.1016/j.jval.2015.07.003](#)]
- 8 **Costa AF**, Flor LS, Campos MR, Oliveira AF, Costa MF, Silva RS, Lobato LC, Schramm JM. Burden of type 2 diabetes mellitus in Brazil. *Cad Saude Publica* 2017; **33**: e00197915 [PMID: [28380131](#) DOI: [10.1590/0102-311X00197915](#)]
- 9 **Pedro RA**, Ramon SA, Marc BB, Juan FB, Isabel MM. Prevalence and relationship between diabetic retinopathy and nephropathy, and its risk factors in the North-East of Spain, a population-based study. *Ophthalmic Epidemiol* 2010; **17**: 251-265 [PMID: [20642348](#) DOI: [10.3109/09286586.2010.498661](#)]
- 10 **Wolf G**, Müller N, Mandecka A, Müller UA. Association of diabetic retinopathy and renal function in patients with types 1 and 2 diabetes mellitus. *Clin Nephrol* 2007; **68**: 81-86 [PMID: [17722706](#) DOI: [10.5414/CNP68081](#)]
- 11 **Man RE**, Sasongko MB, Wang JJ, MacIsaac R, Wong TY, Sabanayagam C, Lamoureux EL. The Association of Estimated Glomerular Filtration Rate With Diabetic Retinopathy and Macular Edema. *Invest Ophthalmol Vis Sci* 2015; **56**: 4810-4816 [PMID: [26218909](#) DOI: [10.1167/iov.15-16987](#)]
- 12 **Chen YH**, Chen HS, Tarng DC. More impact of microalbuminuria on retinopathy than moderately reduced GFR among type 2 diabetic patients. *Diabetes Care* 2012; **35**: 803-808 [PMID: [22338100](#) DOI: [10.2337/dc11-1955](#)]
- 13 **Sabanayagam C**, Foo VH, Ikram MK, Huang H, Lim SC, Lamoureux EL, Tai ES, Wong TY. Is chronic kidney disease associated with diabetic retinopathy in Asian adults? *J Diabetes* 2014; **6**: 556-563 [PMID: [24636277](#) DOI: [10.1111/1753-0407.12148](#)]
- 14 **Medical Research Network of the Consortium of Thai Medical Schools: MedResNet (Thailand)**. Data Archival for Maximum Utilization System (DAMUS). DM/HT study (NHSO Research Project). 2013; Available from: URL: <http://www.damus.in.th/damus/index.php>
- 15 **von Elm E**, Altman DG, Egger M, Pocock SJ, Göttsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *PLoS Med* 2007; **4**: e296 [PMID: [17941714](#) DOI: [10.1371/journal.pmed.0040296](#)]
- 16 **Levey AS**, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; **150**: 604-612 [PMID: [19414839](#) DOI: [10.7326/0003-4819-150-9-200905050-00006](#)]
- 17 **Reutrakul S**, Deerochanawong C. Diabetes in Thailand: Status and Policy. *Curr Diab Rep* 2016; **16**: 28 [PMID: [26894266](#) DOI: [10.1007/s11892-016-0725-7](#)]
- 18 **Nitiyanant W**, Chetthakul T, Sang-A-kad P, Therakiatkumjorn C, Kunsuikmengrai K, Yeo JP. A survey study on diabetes management and complication status in primary care setting in Thailand. *J Med Assoc Thai* 2007; **90**: 65-71 [PMID: [17621735](#) DOI: [10.1186/1744-8603-9-11](#)]
- 19 **Namperumalsamy P**, Kim R, Vignesh TP, Nithya N, Royes J, Gijo T, Thulasiraj RD, Vijayakumar V. Prevalence and risk factors for diabetic retinopathy: a population-based assessment from Theni District, south India. *Br J Ophthalmol* 2009; **93**: 429-434 [PMID: [19091856](#) DOI: [10.1136/bjo.2008.147934](#)]
- 20 **Javadi MA**, Katibeh M, Rafati N, Dehghan MH, Zayeri F, Yaseri M, Sehat M, Ahmadi H. Prevalence of diabetic retinopathy in Tehran province: a population-based study. *BMC Ophthalmol* 2009; **9**: 12



- [PMID: 19835608 DOI: 10.1186/1471-2415-9-12]
- 21 **Bursell SE**, Fonda SJ, Lewis DG, Horton MB. Prevalence of diabetic retinopathy and diabetic macular edema in a primary care-based teleophthalmology program for American Indians and Alaskan Natives. *PLoS One* 2018; **13**: e0198551 [PMID: 29924846 DOI: 10.1371/journal.pone.0198551]
  - 22 **Hapnes R**, Bergrem H. Diabetic eye complications in a medium sized municipality in southwest Norway. *Acta Ophthalmol Scand* 1996; **74**: 497-500 [PMID: 8950402 DOI: 10.1111/j.1600-0420.1996.tb00607.x]
  - 23 **Varma R**, Macias GL, Torres M, Klein R, Peña FY, Azen SP; Los Angeles Latino Eye Study Group. Biologic risk factors associated with diabetic retinopathy: the Los Angeles Latino Eye Study. *Ophthalmology* 2007; **114**: 1332-1340 [PMID: 17306879 DOI: 10.1016/j.ophtha.2006.10.023]
  - 24 **Zhang G**, Chen H, Chen W, Zhang M. Prevalence and risk factors for diabetic retinopathy in China: a multi-hospital-based cross-sectional study. *Br J Ophthalmol* 2017; **101**: 1591-1595 [PMID: 28855195 DOI: 10.1136/bjophthalmol-2017-310316]
  - 25 **Ruta LM**, Magliano DJ, Lemesurier R, Taylor HR, Zimmet PZ, Shaw JE. Prevalence of diabetic retinopathy in Type 2 diabetes in developing and developed countries. *Diabet Med* 2013; **30**: 387-398 [PMID: 23331210 DOI: 10.1111/dme.12119]
  - 26 **Williams R**, Airey M, Baxter H, Forrester J, Kennedy-Martin T, Girach A. Epidemiology of diabetic retinopathy and macular oedema: a systematic review. *Eye (Lond)* 2004; **18**: 963-983 [PMID: 15232600 DOI: 10.1038/sj.eye.6701476]
  - 27 **Penno G**, Solini A, Zoppini G, Orsi E, Zerbini G, Trevisan R, Gruden G, Cavalot F, Laviola L, Morano S, Nicolucci A, Pugliese G; Renal Insufficiency And Cardiovascular Events (RIACE) Study Group. Rate and determinants of association between advanced retinopathy and chronic kidney disease in patients with type 2 diabetes: the Renal Insufficiency And Cardiovascular Events (RIACE) Italian multicenter study. *Diabetes Care* 2012; **35**: 2317-2323 [PMID: 23093684 DOI: 10.2337/dc12-0628]
  - 28 **Grunwald JE**, Alexander J, Ying GS, Maguire M, Daniel E, Whittock-Martin R, Parker C, McWilliams K, Lo JC, Go A, Townsend R, Gadegbeku CA, Lash JP, Fink JC, Rahman M, Feldman H, Kusek JW, Xie D, Jaar BG; CRIC Study Group. Retinopathy and chronic kidney disease in the Chronic Renal Insufficiency Cohort (CRIC) study. *Arch Ophthalmol* 2012; **130**: 1136-1144 [PMID: 22965589 DOI: 10.1001/archophthalmol.2012.1800]
  - 29 **Manaviat MR**, Afkhami M, Shoja MR. Retinopathy and microalbuminuria in type II diabetic patients. *BMC Ophthalmol* 2004; **4**: 9 [PMID: 15228626 DOI: 10.1186/1471-2415-4-9]
  - 30 **Silveiro SP**, Friedman R, de Azevedo MJ, Canani LH, Gross JL. Five-year prospective study of glomerular filtration rate and albumin excretion rate in normofiltering and hyperfiltering normoalbuminuric NIDDM patients. *Diabetes Care* 1996; **19**: 171-174 [PMID: 8718441 DOI: 10.2337/diacare.19.2.171]
  - 31 **Goldberg HJ**, Scholey J, Fantus IG. Glucosamine activates the plasminogen activator inhibitor 1 gene promoter through Sp1 DNA binding sites in glomerular mesangial cells. *Diabetes* 2000; **49**: 863-871 [PMID: 10905498 DOI: 10.2337/diabetes.49.5.863]
  - 32 **Hammes HP**, Federoff HJ, Brownlee M. Nerve growth factor prevents both neuroretinal programmed cell death and capillary pathology in experimental diabetes. *Mol Med* 1995; **1**: 527-534 [PMID: 8529118 DOI: 10.1007/BF03401589]
  - 33 **He F**, Xia X, Wu XF, Yu XQ, Huang FX. Diabetic retinopathy in predicting diabetic nephropathy in patients with type 2 diabetes and renal disease: a meta-analysis. *Diabetologia* 2013; **56**: 457-466 [PMID: 23232641 DOI: 10.1007/s00125-012-2796-6]
  - 34 **Mottl AK**, Kwon KS, Garg S, Mayer-Davis EJ, Klein R, Kshirsagar AV. The association of retinopathy and low GFR in type 2 diabetes. *Diabetes Res Clin Pract* 2012; **98**: 487-493 [PMID: 23068959 DOI: 10.1016/j.diabres.2012.09.041]
  - 35 **Pugliese G**, Solini A, Zoppini G, Fondelli C, Zerbini G, Vedovato M, Cavalot F, Lamacchia O, Buzzetti R, Morano S, Nicolucci A, Penno G; Renal Insufficiency and Cardiovascular Events (RIACE) Study Group. High prevalence of advanced retinopathy in patients with type 2 diabetes from the Renal Insufficiency And Cardiovascular Events (RIACE) Italian Multicenter Study. *Diabetes Res Clin Pract* 2012; **98**: 329-337 [PMID: 23020932 DOI: 10.1016/j.diabres.2012.09.006]
  - 36 **Wong CW**, Lamoureux EL, Cheng CY, Cheung GC, Tai ES, Wong TY, Sabanayagam C. Increased Burden of Vision Impairment and Eye Diseases in Persons with Chronic Kidney Disease - A Population-Based Study. *EBioMedicine* 2016; **5**: 193-197 [PMID: 27077127 DOI: 10.1016/j.ebiom.2016.01.023]
  - 37 **Busch M**, Franke S, Rüster C, Wolf G. Advanced glycation end-products and the kidney. *Eur J Clin Invest* 2010; **40**: 742-755 [PMID: 20649640 DOI: 10.1111/j.1365-2362.2010.02317.x]
  - 38 **Ortwerth BJ**, Chemoganskiy V, Mossine VV, Olesen PR. The effect of UVA light on the anaerobic oxidation of ascorbic acid and the glycation of lens proteins. *Invest Ophthalmol Vis Sci* 2003; **44**: 3094-3102 [PMID: 12824256 DOI: 10.1167/iovs.02-0857]
  - 39 **Stitt AW**. AGEs and diabetic retinopathy. *Invest Ophthalmol Vis Sci* 2010; **51**: 4867-4874 [PMID: 20876889 DOI: 10.1167/iovs.10-5881]
  - 40 **Canning P**, Glenn JV, Hsu DK, Liu FT, Gardiner TA, Stitt AW. Inhibition of advanced glycation and absence of galectin-3 prevent blood-retinal barrier dysfunction during short-term diabetes. *Exp Diabetes Res* 2007; **2007**: 51837 [PMID: 17641742 DOI: 10.1155/2007/51837]
  - 41 **Payne JF**, Ray R, Watson DG, Delille C, Rimler E, Cleveland J, Lynn MJ, Tangpricha V, Srivastava SK. Vitamin D insufficiency in diabetic retinopathy. *Endocr Pract* 2012; **18**: 185-193 [PMID: 21940279 DOI: 10.4158/EP11147.OR]
  - 42 **Wong CW**, Wong TY, Cheng CY, Sabanayagam C. Kidney and eye diseases: common risk factors, etiological mechanisms, and pathways. *Kidney Int* 2014; **85**: 1290-1302 [PMID: 24336029 DOI: 10.1038/ki.2013.491]
  - 43 **Wong CW**, Teo BW, Lamoureux E, Ikram MK, Wang JJ, Tai ES, Sethi S, Wong TY, Sabanayagam C. Serum Cystatin C, Markers of Chronic Kidney Disease, and Retinopathy in Persons with Diabetes. *J Diabetes Res* 2015; **2015**: 404280 [PMID: 26576434 DOI: 10.1155/2015/404280]
  - 44 **Michels WM**, Grootendorst DC, Verduijn M, Elliott EG, Dekker FW, Krediet RT. Performance of the Cockcroft-Gault, MDRD, and new CKD-EPI formulas in relation to GFR, age, and body size. *Clin J Am Soc Nephrol* 2010; **5**: 1003-1009 [PMID: 20299365 DOI: 10.2215/CJN.06870909]
  - 45 **Matsushita K**, Mahmoodi BK, Woodward M, Emberson JR, Jafar TH, Jee SH, Polkinghorne KR, Shankar A, Smith DH, Tonelli M, Warnock DG, Wen CP, Coresh J, Gansevoort RT, Hemmelgarn BR, Levey AS; Chronic Kidney Disease Prognosis Consortium. Comparison of risk prediction using the CKD-EPI equation and the MDRD study equation for estimated glomerular filtration rate. *JAMA* 2012; **307**: 1941-1951 [PMID: 22570462 DOI: 10.1001/jama.2012.3954]

- 46 **Grunwald JE**, Alexander J, Maguire M, Whittock R, Parker C, McWilliams K, Lo JC, Townsend R, Gadegbeku CA, Lash JP, Fink JC, Rahman M, Feldman H, Kusek J, Ojo A; CRIC Study Group. Prevalence of ocular fundus pathology in patients with chronic kidney disease. *Clin J Am Soc Nephrol* 2010; 5: 867-873 [PMID: [20299372](#) DOI: [10.2215/CJN.08271109](#)]

**P- Reviewer:** Dinc M, Pedersen EB

**S- Editor:** Dou Y **L- Editor:** A **E- Editor:** Song H





Published By Baishideng Publishing Group Inc  
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA  
Telephone: +1-925-2238242  
Fax: +1-925-2238243  
E-mail: [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)  
Help Desk: <https://www.f6publishing.com/helpdesk>  
<https://www.wjgnet.com>

