Protocol

Incidence, Development, and Prognosis of Diabetic Kidney Disease in China: Design and Methods

Yao-Zheng Yang[1], Jin-Wei Wang[1], Fang Wang[1], Yun-Tao Wu[2], Hai-Yan Zhao[2], Min Chen[1], Lu-Xia Zhang[1], Shou-Ling Wu[2], Ming-Hui Zhao[1]

[1]Renal Division, Department of Medicine, Peking University First Hospital, Peking University Institute of Nephrology, Key Laboratory of Renal Disease, National Health and Family Planning Commission of China, Key Laboratory of Chronic Kidney Disease Prevention and Treatment (Peking University), Ministry of Education, Beijing 100034, China

[2]Department of Cardiology, Kailuan Hospital, Tangshan, Hebei 063000, China

Abstract

Background: Although that glomerulonephritis is the major cause of end-stage renal disease in developing countries such as China, the increasing prevalence of diabetes has contributed to the changing spectrum of predialysis chronic kidney disease. Recent studies have revealed an increased proportion of patients with diabetic kidney disease (DKD) in hemodialysis populations in large cities in China. However, studies regarding the clinical phenotype of DKD in China are extremely limited. The incidence, development, and prognosis of diabetic kidney disease (INDEED) study aims to investigate the incidence, progression, and prognosis of DKD, as well as the associated genetic, behavioral, and environmental factors and biomarkers in patients with DKD in China.

Methods: INDEED study is a prospective cohort study based on all participants with diabetes in the Kailuan study, which is a general population-based cohort study in northern China. Altogether, over 10,000 participants with diabetes will be followed biennially. Questionnaires documenting general characteristics, behavioral and environmental factors, and medical history will be administrated. Anthropometric measurements and a series of laboratory tests will be performed in one central laboratory. The DNA, plasma, and urine samples of every participant will be stored in a biobank for future research.

Conclusions: INDEED study will provide essential information regarding the clinical phenotype and prognosis of patients with DKD in China and will be valuable to identify factors and biomarkers associated with patients with DKD in China.

Key words: Biomarker; China; Diabetic Kidney Disease; Incidence; Progression

Introduction

Chronic kidney disease (CKD) is an important public health problem in China because of its high prevalence and adverse effects on patients' outcomes as well as placing a burden on health-care system.[1] In addition to entering end-stage renal disease (ESRD), patients with CKD are at increased risk of mortality and cardiovascular diseases (CVDs).[2-5] Previously, glomerulonephritis was considered as the leading cause of ESRD in China.[2,6] A recent study[7] has revealed an increased proportion of patients with diabetic kidney disease (DKD) in hemodialysis population in large cities such as Beijing and Shanghai, which is consistent with the substantially escalating incidence of diabetes in China during the past two decades.[8-10] Our recent research showed that DKD has already become the leading cause of CKD in the predialysis CKD population, surpassing glomerulonephritis, and hence, it will inevitably become the major cause accounting for dialysis in the near future.[7] However, studies regarding risk factors, clinical phenotype, progression, treatment, and prognosis of DKD are limited in Chinese populations. This is in part due to the late referral to nephrologists of patients with DKD. The Kailuan study,[11,12] an ongoing longitudinal prospective study based on the general population, provides a unique opportunity to investigate DKD in China.

Therefore, the Renal Division of Peking University First Hospital, in collaboration with the Kailuan study, has

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.198002

Address for correspondence: Prof. Lu-Xia Zhang, Renal Division, Department of Medicine, Peking University First Hospital, 8 Xishiku Street, Xicheng District, Beijing 100034, China
E-Mail: zhanglx@bjmu.edu.cn

Received: 07-09-2016 **Edited by:** Ning-Ning Wang
How to cite this article: Yang YZ, Wang JW, Wang F, Wu YT, Zhao HY, Chen M, Zhang LX, Wu SL, Zha MH. Incidence, Development, and Prognosis of Diabetic Kidney Disease in China: Design and Methods. Chin Med J 2017;130:199-202.

initiated the incidence, development, and prognosis of diabetic kidney disease (INDEED) study, which aims to provide reliable data on the clinical phenotype, the genetic, behavioral, and environmental factors, and biomarkers associated with DKD in China.

Methods

Study design

INDEED study is a prospective cohort study based on all participants with diabetes in the Kailuan study. Detailed information about the Kailuan study was described elsewhere.[11,12] In brief, it is an ongoing longitudinal cohort study based on the general population that began in 2006. Altogether, 101,510 individuals (81,110 men and 20,400 women, aged ≥18 years), who were employees (including the retired) of the Kailuan Group and their family members, were recruited to undergo questionnaire assessments and clinical and laboratory examinations conducted in the 11 hospitals affiliated with the Kailuan community in Tangshan.[11,12] The information collected included demographic characteristics, medical comorbidities (e.g., hypertension, diabetes, and CVDs), and lifestyle behaviors (e.g., smoking status, alcohol consumption, and physical activity). Furthermore, pulse wave velocity and ankle-brachial index were measured among certain subgroups.[12] Then, four repeated follow-up examinations were conducted biennially from 2008 to 2014. For INDEED study, all participants with diabetes in the Kailuan study were included and were prospectively followed with a focus on DKD. The DNA, plasma, and urine samples of every participant will be stored in a biobank for future research. The duration of INDEED study is tentatively fixed at 5 years.

Study organization

INDEED study was initiated by the Renal Division of Peking University First Hospital, collaborating with investigators in the Kailuan study. The Kailuan study investigators took charge of on-site investigation, including enrollment and follow-up of participants, processing and transferring samples, distributing and gathering questionnaires, and data collection. Peking University First Hospital performed the central laboratory tests and constructed the central biobank. In addition, we set up a steering committee to develop policies for ancillary studies, performance standards, publications, and presentations; and a scientific advisory committee to provide professional advice about the study protocol and practice.

The INDEED study was approved by the Ethics Committee of the Peking University First Hospital in compliance with the World's Association *Declaration of Helsinki*. All of the participants gave written informed consent before data collection.

Participants

INDEED study will enroll all patients with diabetes in the Kailuan study based on existing data. The inclusion criteria are self-reported history of diabetes mellitus and/or fasting blood glucose ≥7.0 mmol/L and/or self-reported use of antidiabetic medications.

INDEED study will recruit 11,192 patients with diabetes on the basis of existing data from the 2014 Kailuan study.[13]

Baseline and follow-up visit

The baseline visit for INDEED study began in April 2016. In addition to the questionnaire and original tests performed for the Kailuan study, a set of questionnaires regarding the diagnosis and treatment of diabetes, lifestyle and environmental risk factors, complication of diabetes including DKD, and cognitive function was administrated. Furthermore, biosamples including fasting blood and morning urine samples were transported to the Peking University First Hospital in cold chain of −80 °C. Laboratory tests including plasma creatinine, cystatin C, HbA1C, retinol-binding protein; urinary protein-creatinine ratio, albumin-creatinine ratio, orosomucoid, transferrin, and α-microglobulin were measured in the central laboratory to avoid variations in testing values among laboratories. All participants will be followed biennially using protocols similar to the baseline visit.

Biobank

DNA, plasma, and morning spot urine samples from each participant will be collected at baseline and biennially. All biosamples will be stored at −80 °C for future scientific research. A biobank management system will ensure the quality control of sample management.

Study outcomes

The principal clinical outcomes of INDEED can be categorized as CVD events, renal disease events, and death.

CVD events include myocardial infarction, coronary artery disease such as angina pectoris, congestive heart failure, cardiac arrhythmia (resuscitated cardiac arrest, ventricular fibrillation, ventricular tachycardia, atrial fibrillation or flutter, sever bradycardia or atrioventricular block), cerebrovascular events (such as intraparenchymal hemorrhage, subarachnoid hemorrhage, cerebral infarction, and cardioembolic cerebral infarction), peripheral vascular diseases, and venous thrombosis.[14] All CVD events will be acquired from the health insurance reimbursement record and were ascertained by chart review of medical records.

Renal disease events include entering ESRD or a reduction of estimated glomerular filtration rate (eGFR) by half. ESRD is defined as receiving renal replacement therapy, involving dialysis and kidney transplantation. eGFR will be calculated using the CKD Epidemiology Collaboration (CKD-EPI) equation (see below)[15] based on serum creatinine concentration (Scr) at every visit. ESRD will also be acquired from the health insurance reimbursement record and will be ascertained by chart review of medical records.

CKD-EPI equation:

- $eGFR\ (ml \cdot min^{-1} \cdot 1.73\ m^{-2}) = 144 \times (Scr/0.7)^{-0.3289} \times (0.993)^{Age}$ (if female, Scr ≤0.7 mg/dl)

- eGFR ($ml \cdot min^{-1} \cdot 1.73\ m^{-2}$) = $144 \times (Scr/0.7)^{-1.209} \times (0.993)^{Age}$ (if female, Scr >0.7 mg/dl)
- eGFR ($ml \cdot min^{-1} \cdot 1.73\ m^{-2}$) = $141 \times (Scr/0.9)^{-0.411} \times (0.993)^{Age}$ (if male, Scr ≤0.9 mg/dl)
- eGFR ($ml \cdot min^{-1} \cdot 1.73\ m^{-2}$) = $141 \times (Scr/0.9)^{-1.209} \times (0.993)^{Age}$ (if male, Scr >0.9 mg/dl).

Statistical consideration

The baseline characteristics will be presented with descriptive methods such as summary statistics and frequency tables. We will calculate the incidence or mortality according to the existing data from the Kailuan study, which enrolled more than 100,000 people for the biennial follow-up examinations. Then, Kaplan-Meier curves, log-rank tests, and Cox proportional hazards models will be employed to estimate the survival function from lifetime data, compare the survival distributions of patients in various subgroups, and explore the associations of baseline variables with study outcomes.[16] Standard mixed-effects growth curve models supplemented by generalized estimating equations will be used for variables with repeated measurements such as eGFR. Analyses will also be adjusted for potential confounding factors and stratified by potential effect modifiers. All statistical analyses will be conducted in SAS version 9.3 (SAS Institute, Inc., Cary, NC, USA). Values will be considered statistically significant when $P < 0.05$.

Discussion

Glomerulonephritis in developing countries such as China was traditionally the major cause of CKD.[2,6] However, the rapidly increasing incidence of diabetes has played a key role in the transition of the predialysis CKD spectrum.[7] An increasing proportion of patients with DKD among incident hemodialysis patients in large cities in China has been observed,[7] which is consistent with the continuous growth of diabetes in the past 20 years. Despite the increasing incidence of DKD, as a result of the increasing incidence of diabetes, an unmet need exists in China for information about the incidence and development of DKD. Furthermore, most patients with diabetes are not referred to nephrologists until they have reached ESRD. All of the above-mentioned issues constitute obstacles to the early prevention and treatment of DKD. INDEED study, which was established by both renal division of the Peking University First Hospital and Kailuan study, offers a unique opportunity to explore the clinical phenotype, genetic, behavioral, and environmental factors and biomarkers associated with DKD. The data about diabetes and patients with DKD at a relatively early stage collected in INDEED study will provide valuable information for early identification and interventions for high-risk DKD populations, which is crucial in reducing the burden of CKD in China.

A set of strategies were set up for the sake of quality control of this study. A manual of procedures with detailed instructions about the study protocol has been distributed to all study centers of the Kailuan study. All study investigators and staff members completed a training program that taught the methods and process of the study. Periodic on-site monitoring will be repeated every 3 months.

In addition to describing the clinical phenotype of DKD, we expect that INDEED study can provide more insight into the diagnosis, pathogenesis, and treatment of DKD.

Albuminuria and eGFR were traditionally used as early markers of glomerular damage.[17] However, given that many diabetic patients do not develop albuminuria when they suffer from irreparable renal impairment,[18,19] and not all patients with proteinuria will develop progressive kidney dysfunction,[20] new biomarkers are needed to provide better prediction of incidence and progression of DKD. The establishment of the biobank, together with information about the clinical phenotype, could offer opportunities for discovering novel biomarkers associated with the diagnosis and prediction of DKD, exploring the genetic background of DKD, and searching for new targets for intervention.

In conclusion, the INDEED study is designed to collect longitudinal data and biomaterials from a cohort of general population-based patients with diabetes in China. The aim is to provide essential information regarding the clinical phenotype and prognosis of patients with DKD in China and may be able to identify biomarkers associated with the incidence and progression of DKD. Results from the INDEED study will provide reliable data regarding formulating the prevention and intervention strategies for DKD in China.

Financial support and sponsorship

The study was supported by the grants from National Key Technology R & D Program of the Ministry of Science and Technology (No. 2011BAI10B01, and No. 2013BAI09B14), establishment of early diagnosis pathway and model for evaluating progression of chronic kidney disease (No. D131100004713007) from the Beijing Science and Technology Committee, and the National Natural Science Fund (No. 81425008).

Conflicts of interest

There are no conflicts of interest.

References

1. Zhang L, Wang F, Wang L, Wang W, Liu B, Liu J, *et al.* Prevalence of chronic kidney disease in China: A cross-sectional survey. Lancet 2012;379:815-22. doi: 10.1016/S0140-6736(12)60033-6.
2. Barsoum RS. Chronic kidney disease in the developing world. N Engl J Med 2006;354:997-9. doi: 10.1056/NEJMp058318.
3. Codreanu I, Perico N, Sharma SK, Schieppati A, Remuzzi G. Prevention programmes of progressive renal disease in developing nations. Nephrology (Carlton) 2006;11:321-8. doi: 10.1111/j.1440-1797.2006.00587.x.
4. Chen H, Wang DG, Yuan L, Liu GL, He HJ, Wang J, *et al.* Clinical characteristics of patients with diabetic nephropathy on maintenance hemodialysis: A multicenter cross-sectional survey in Anhui Province, Eastern China. Chin Med J 2016;129:1291-7. doi: 10.4103/0366-6999.182832.
5. Weng JP, Bi Y. Epidemiological status of chronic diabetic complications in China. Chin Med J 2015;128:3267-9. doi: 10.4103/0366-6999.171350.

6. Wang H, Zhang L, Lv J. Prevention of the progression of chronic kidney disease: Practice in China. Kidney Int Suppl 2005;67:S63-7. doi: 10.1111/j.1523-1755.2005.09416.x.
7. Zhang L, Long J, Jiang W, Shi Y, He X, Zhou Z, *et al.* Trends in chronic kidney disease in China. N Engl J Med 2016;375:905-6. doi: 10.1056/NEJMc1602469.
8. Yang W, Lu J, Weng J, Jia W, Ji L, Xiao J, *et al.* Prevalence of diabetes among men and women in China. N Engl J Med 2010;362:1090-101. doi: 10.1056/NEJMoa0908292.
9. Xu Y, Wang L, He J, Bi Y, Li M, Wang T, *et al.* Prevalence and control of diabetes in Chinese adults. JAMA 2013;310:948-59. doi: 10.1001/jama.2013.168118.
10. Pan XR, Yang WY, Li GW, Liu J. Prevalence of diabetes and its risk factors in China, 1994. National Diabetes Prevention and Control Cooperative Group. Diabetes Care 1997;20:1664-9.
11. Zhang Q, Zhou Y, Gao X, Wang C, Zhang S, Wang A, *et al.* Ideal cardiovascular health metrics and the risks of ischemic and intracerebral hemorrhagic stroke. Stroke 2013;44:2451-6. doi: 10.1161/STROKEAHA.113.678839.
12. Wu S, Huang Z, Yang X, Zhou Y, Wang A, Chen L, *et al.* Prevalence of ideal cardiovascular health and its relationship with the 4-year cardiovascular events in a Northern Chinese industrial city. Circ Cardiovasc Qual Outcomes 2012;5:487-93. doi: 10.1161/CIRCOUTCOMES.111.963694.
13. Wu Z, Jin C, Vaidya A, Jin W, Huang Z, Wu S, *et al.* Longitudinal patterns of blood pressure, incident cardiovascular events, and all-cause mortality in normotensive diabetic people. Hypertension 2016;68:71-7. doi: 10.1161/HYPERTENSIONAHA.116.07381.
14. Moran AE, Roth GA, Narula J, Mensah GA. 1990-2010 global cardiovascular disease atlas. Glob Heart 2014;9:3-16. doi: 10.1016/j.gheart.2014.03.1220.
15. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, *et al.* A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604-12.
16. Maldonado G, Greenland S. Simulation study of confounder-selection strategies. Am J Epidemiol 1993;138:923-36.
17. Kamijo-Ikemori A, Sugaya T, Kimura K. Novel urinary biomarkers in early diabetic kidney disease. Curr Diab Rep 2014;14:513. doi: 10.1007/s11892-014-0513-1.
18. Thomas MC, Macisaac RJ, Jerums G, Weekes A, Moran J, Shaw JE, *et al.* Nonalbuminuric renal impairment in type 2 diabetic patients and in the general population (National Evaluation of the Frequency of Renal impairment cO-existing with NIDDM [NEFRON] 11). Diabetes Care 2009;32:1497-502. doi: 10.2337/dc08-2186.
19. Perkins BA, Ficociello LH, Silva KH, Finkelstein DM, Warram JH, Krolewski AS. Regression of microalbuminuria in type 1 diabetes. N Engl J Med 2003;348:2285-93.
20. Jha JC, Jandeleit-Dahm KA, Cooper ME. New insights into the use of biomarkers of diabetic nephropathy. Adv Chronic Kidney Dis 2014;21:318-26. doi: 10.1053/j.ackd.2014.03.008.