Diabetes with early kidney involvement may shorten life expectancy by 16 years

Chi Pang Wen[1,2,10], Chia Hsuin Chang[3,4,10], Min Kuang Tsai[1], June Han Lee[1], Po Jung Lu[1], Shan Pou Tsai[5], Christopher Wen[6], Chien Hua Chen[7], Chih Wen Kao[8], Chwen Keng Tsao[5] and Xifeng Wu[9]

[1]Institue of Population Health Sciences, National Health Research Institutes, Zhunan, Taiwan; [2]China Medical University Hospital, Taichung, Taiwan; [3]Department of Internal Medicine, National Taiwan University Hospital and College of Medicine, Taipei, Taiwan; [4]Institute of Preventive Medicine, College of Public Health, National Taiwan; University, Taipei, Taiwan; [5]MJ Health Management Institution, Taipei, Taiwan; [6]Long Beach VAMC Hospital, University of Irvine Medical Center, Irvine, California, USA; [7]Digestive Disease Center, Show-Chwan Memorial Hospital, Changhua, Taiwan; [8]Taipei Medical University, Taipei, Taiwan; and [9]Department of Epidemiology, University of Texas MD Anderson Cancer Center, Houston, Texas, USA

This study aimed to identify the excess risks associated with diabetic patients with early kidney involvement (early diabetic kidney disease). The mortality risks of early diabetic kidney disease, defined as diabetes in early stages 1-3 chronic kidney disease (CKD), were assessed from a cohort of 512,700 adults in Taiwan participating in a health surveillance program from 1994-2008. Three related groups were identified and compared: diabetes without CKD, early diabetic kidney disease, and early CKD without diabetes. Deaths were ascertained through the National Death Registry. One-third of diabetics had early kidney disease, and approximately two-thirds of patients were classified with early CKD due to proteinuria. Patients with early diabetic kidney disease had more lifestyle risks such as inactivity or obesity, which characteristically amplified excess mortality by up to five times. The three-fold increase in all-cause mortality (hazard ratio 3.16) and a 16-year loss in life expectancy made early diabetic kidney disease a serious and yet often overlooked disease, with most patients unaware of their kidney involvement. Mortality for early diabetic kidney disease was nearly twice as high as that for early CKD (hazard ratio 2.01) or diabetes without CKD (hazard ratio 1.79). The 16-year life span loss is much worse than individually from early CKD (six years) or diabetes (ten years). Thus, identifying early proteinuria among diabetic patients and realizing the importance of reducing lifestyle risks like inactivity is a clinical challenge, but can save lives.

Kidney International (2017) **92,** 388–396; http://dx.doi.org/10.1016/j.kint.2017.01.030

KEYWORDS: chronic kidney diseases; diabetes; life expectancy; mortality

Correspondence: *Chi-Pang Wen, Institute of Population Health Sciences, National Health Research Institutes, 35 Keyan Road, Zhunan, Miaoli County 350, Taiwan. E-mail: cwengood@nhri.org.tw*

[10]Chi Pang Wen and Chia Hsuin Chang contributed equally to this work.

Received 1 June 2016; revised 3 January 2017; accepted 19 January 2017; published online 1 June 2017

Diabetes continues to be an important global health challenge despite increased public awareness, intensive monitoring, and aggressive management. The current number of more than 415 million people with diabetes estimated worldwide may increase to over 642 million by 2040.[1,2] Diabetes is associated with increased mortality and morbidity, particularly for cardiovascular disease, stroke, or renal failure, but also for several types of cancer.[3,4] Our knowledge and efforts in managing diabetes-related complications have brought about a substantial decline in their rate of occurrence in the past 2 decades,[5,6] but a large burden of disease still persists as diabetes prevalence continues to increase. The major challenge, however, is to make these patients aware of the seriousness of the condition so that early intervention is possible.

Diabetic kidney disease (DKD) is, by definition, diabetes with kidney involvement, presenting as albuminuria and/or an impaired glomerular filtration rate (GFR).[7–11] DKD, the most common cause of end-stage renal disease (ESRD), has increased by 34% in the US in the last 20 years, despite increasing use of medications that lower blood sugar or blood pressure.[10] Advanced cases of DKD are irreversible and beyond the opportunity for prevention. On the other hand, early DKD, defined as diabetes with CKD stages 1 to 3, clinically expressed as proteinuria and mild loss of kidney function, has a high chance of being medically controlled or even reversed to normal. For the medical community outside the nephrology specialty, however, there is limited vigilance to detect early DKD because its serious nature is not well-known.

With the availability of a large cohort of half a million individuals,[12] we analyzed the characteristics and mortality outcomes of early DKD. Life expectancy for individuals with DKD was then calculated and compared with that for those with "diabetes without CKD" or "CKD without diabetes." Analysis of CKD subjects from this same cohort has been reported previously.[13–15]

RESULTS

A total of 512,700 subjects were identified; among them, 27,455 (5.4%) had diabetes. One-third of those with diabetes (9067 or 33.3%) had early DKD, whereas two-thirds

Table 1 | Baseline demographics and clinical characteristics of participants by diabetes and chronic kidney disease

	Total participants	Reference population[a]	Diabetes without CKD	Early CKD[b] without diabetes	Early DKD[c]
N	512,700	434,268	18,388	50,977	9,067
Mean age (SD)	41.6 (14.0)	39.7 (12.8)	51.1 (11.8)	50.2 (16.5)	59.3 (11.7)
Age (%)					
20–39	53.1	58.3	12.9	32.4	6.9
40–59	33.2	32.5	52.8	30.9	38.5
≥60	13.8	9.2	34.3	36.7	54.6
Male (%)	49.8	49.3	52.2	52.3	54.1
Lower education level (middle school or below, %)	26.3	22.2	54.6	43.5	66.3
Chronic kidney disease (%)					
Stage 1	1.8	0	0	15.2	14.4
Stage 2	4.5	0	0	38.0	40.0
Stage 3	5.0	0	0	46.8	45.6
Total proteinuria	7.5	0	0	60.8	72.3
Trace (±)	5.6	0	0	48.2	41.1
1+	1.2	0	0	8.5	17.5
≥2+	0.8	0	0	4.1	13.8
Hypertension[d] (%)	18.0	13.7	45.5	35.5	64.6
High serum cholesterol[e] (%)	10.7	9.4	20.1	15.2	27.6
Lifestyle risk factors (anyone of the following, %)	61.8	61.9	62.6	60.5	62.6
Physical inactivity	53.5	53.9	48.5	52.1	50.8
Smoking	23.9	23.5	24.0	27.5	25.9
Drinking[f]	17.4	17.1	19.0	19.7	18.4
Obesity[g]	4.0	3.3	9.9	6.0	12.3
Unawareness of disease status	N/A	N/A	44.4	96.8	98.1

CKD, chronic kidney disease; DKD, diabetic kidney disease; N/A, not applicable.
[a]Participants with neither diabetes nor CKD.
[b]Stages 1 to 3.
[c]Diabetes with CKD stages 1 to 3.
[d]Defined as blood pressure ≥ 140/90 mm Hg, self-reported history of hypertension, or use of antihypertensive drugs.
[e]Defined as total cholesterol ≥ 240 mg/dl.
[f]Defined as regular drinking with ≥ 3 times/wk and 2 drinks/time.
[g]Defined as body mass index > 30.

(18,388 or 66.7%) had no kidney involvement. Approximately 50,977 participants (9.9%) had early CKD without diabetes, and 434,268 participants (84.7%) constituted a reference group with neither diabetes nor CKD. Their baseline characteristics are summarized in Table 1. Early DKD patients were older (mean age: 59.3 years) and 54.1% were men. Two-thirds

Table 2 | Hazard ratios for all causes and cause-specific mortality by diabetes and chronic kidney disease status

	Reference[a] *N* = 434,268		Diabetes without CKD *N* = 18,388			Early CKD without diabetes[b] *N* = 50,977			Early DKD[c] *N* = 9067		
	365.5		616.4			606.2			1182.4		
Adjusted mortality rate[d]	Deaths (n)	HR[e]	Deaths (n)	HR[e]	(95% CI)	Deaths (n)	HR[e]	(95% CI)	Deaths (n)	HR[e]	(95% CI)
All causes	**9440**	**1**	**1600**	**1.76**[d]	**(1.6, 1.9)**	**5186**	**1.58**[d]	**(1.5, 1.7)**	**2037**	**3.16**[d]	**(3.0, 3.4)**
CVD	1645	1	284	1.40[d]	(1.2, 1.7)	1329	1.74[d]	(1.6, 1.9)	431	2.78[d]	(2.4, 3.2)
Stroke	717	1	123	1.26	(0.9, 1.7)	564	1.64[d]	(1.4, 1.9)	182	2.74[d]	(2.2, 3.4)
CHD	394	1	94	1.97[d]	(1.4, 2.7)	356	2.04[d]	(1.7, 2.5)	140	3.86[d]	(3.0, 5.0)
Diabetes	154	1	335	22.8[d]	(17.2, 30.3)	164	1.87[d]	(1.3, 2.7)	533	49.66[d]	(37.6, 65.6)
Kidney diseases	67	1	28	4.69[d]	(2.6, 8.6)	269	9.56[d]	(6.4, 14.4)	121	19.79[d]	(12.4, 31.5)
All cancer	**4292**	**1**	**535**	**1.42**[d]	**(1.3, 1.6)**	**1734**	**1.28**[d]	**(1.2, 1.4)**	**441**	**1.75**[d]	**(1.5, 2.0)**
Lung cancer	948	1	93	1.02	(0.8, 1.3)	365	1.04	(0.9, 1.2)	79	1.39[d]	(1.1, 1.8)
Liver cancer	873	1	148	2.19[d]	(1.7, 2.8)	375	1.74[d]	(1.5, 2.1)	123	3.18[d]	(2.5, 4.0)
Colorectal cancer	406	1	61	1.57[d]	(1.1, 2.2)	172	1.24[d]	(1.0, 1.6)	62	2.28[d]	(1.6, 3.2)
Bladder cancer	44	1	12	1.83	(0.6, 5.4)	50	2.54[d]	(1.3, 4.9)	6	2.55	(0.9, 7.0)
Respiratory system	600	1	69	1.28	(0.9, 1.8)	422	1.42[d]	(1.2, 1.7)	105	2.46[d]	(1.9, 3.2)
Infectious disease	135	1	26	1.58	(0.8, 3.1)	85	1.59[d]	(1.1, 2.4)	24	2.34[d]	(1.2, 4.5)

CI, confidence interval; CHD, coronary heart disease; CKD, chronic kidney disease; CVD, cardiovascular disease; DKD, diabetic kidney disease; HR, hazard ratio.
[a]Participants with neither diabetes nor CKD.
[b]CKD stages 1 to 3.
[c]Diabetes with CKD stages 1 to 3.
[d]Expressed as per 100,000 person-years, with sex and age standardized to the 2009 Taiwanese population.
[e]Adjusted by 11 variables: age, sex, body mass index, education level, systolic blood pressure, cholesterol, smoking, drinking, physical activity, Chinese herbal medicine use, and analgesic use.