A correlation study between metabolic syndrome and chronic kidney disease among populations older than 40 years

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Abstract: Aim: This study aimed to investigate epidemiological features of chronic kidney disease (CKD) and explore the correlation between CKD and metabolic syndrome (MS) among individuals ≥ 40 years old in urban populations of Henan Province, China. The broad purpose of the study was to improve the prophylaxis and treatment of CKD, reduce and defer the occurrence of end-stage renal disease, and provide evidence to support national public health and medical insurance strategies. **Methods:** This field epidemiology cross-sectional study followed a multistage stratified cluster random sampling strategy. The sampling frame consisted of urban residents ≥ 40 years old, who resided in the cities of Zhengzhou, Jiaozuo, and Pingdingshan in Henan Province, China. Epidemiological data pertaining to CKD were collected by questionnaires, physical examinations, kidney damage tests, blood glucose and lipid measurements for all subjects and were analyzed by statistical methods. **Results:** A total of 4156 adults took part in the investigation and 3981 (95.7%; 40-89 years old) valid samples were obtained, including 2178 males and 1803 females (the male to female ratio was 1.21:1). The overall prevalence of hypertension and diabetes in the 3981 subjects was 15.04% and 5.76%, respectively. Participants with MS had higher prevalence of albuminuria and decreased estimated glomerular filtration rate (eGFR) than those without MS. Participants with hypertension had higher prevalence of albuminuria and prevalence of decreased eGFR than those without. Participants with abnormally high triglyceride (TG) levels had a higher prevalence of decreased eGFR than those without. Participants with abnormal carbohydrate metabolism had a higher prevalence of albuminuria than those without. Of those subjects who exhibited signs of individual MS components, i.e. hypertension, low high-density lipoprotein cholesterol (HDL-C), high TG, fasting blood glucose ≥ 5.6 mmol/L, and abnormally large waist circumference, the prevalence of CKD was 18.27%, 11.49%, 15.89%, 31.03% and 12.24%, respectively. In addition, participants with hypertension, high TG, or fasting blood glucose ≥5.6 mmol/L had higher CKD prevalence than those without. The prevalence of CKD increased as the number of MS components increased. **Conclusions:**,MS is a basic risk factor for CKD, and the risk of acquiring CKD increases with the increase of the number of MS components.

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1.Introduction

Chronic kidney disease (CKD) and end-stage renal disease (ESRD) arising from CKD have become significant public health problems worldwide due to their high incidence, poor prognosis and high costs of treatment. According to the 2007 annual report of the United States Renal Data System, about 85,000 people die from ESRD annually and kidney disease is the ninth leading cause of death in the United States (Miniño et al., 2007). In Asia, an epidemiological report showed that the CKD prevalence among adults older than 40 years in Beijing was 9.4%, and the associated risk factors were similar to the pattern observed in western countries(Zhang et al., 2007) .

The contribution of diabetes and hypertension to the development of CKD was early recognized (Bomback et al., 2010; Fakhrzadeh et al., 2009). Recent studies have provided evidence that metabolic syndrome (MS) and its abnormal components, including obesity, hyperlipidemia and hyperuricemia, affect the generation and progression of CKD (Bomback et al., 2010; Fakhrzadeh et al., 2009).

The present study followed a multistage stratified cluster random sampling strategy. The sampling frame consisted of urban residents aged 40 years or older, who resided in the cities of Zhengzhou, Jiaozuo, Pingdingshan and Kaifeng, all in Henan Province. Epidemiological data obtained by questionnaires, physical examinations, kidney damage tests, blood glucose and lipid measurements for all subjects were analyzed by statistical methods. The prevalence, awareness rate and associated risk factors of CKD were obtained in order to design future strategies aimed at national prevention and control of pandemic of CKD.

2.Subjects and methods

Study population

The target population consisted of urban residents ≥ 40 years old, of Zhengzhou, Jiaozuo, Pingdingshan and Kaifeng in Henan Province from May 2007 to October 2009. Informed consent was obtained from all participants. The required statistical sample size (n) was calculated using following equation (HU,2006):

$$n = \left[\frac{57.3t_{\alpha}}{Sin^{-1}\left(\delta\sqrt{P(1-P)}\right)}\right]^2$$

in which, the test standard, α = 0.05, tα = 1.96;the allowable error, δ = 2%;P = 15.0%, as the estimated prevalence rate of CKD,according to literature analysis and the general population CKD prevalence rate (10.1% ~ 11.3%). Following the formula ,sample size should be 4156 adults, of those 3981 the effective cases. For each participant, demographic characteristics and health history was collected using a questionnaire and an overall physical examination and laboratory tests were performed.

Physical examination

The physical examination included measurements of height, weight (in light clothing without coat, hat and shoes), and blood pressure (BP; using calibrated electronic and mercury sphygmomanometers). BP was first measured by an electronic sphygmomanometer. If the two measurements were higher than the diagnostic criteria, the mercury sphygmomanometer was used after 15 minutes of rest with the participant in a seated position. The body mass index (BMI) was calculated as weight (in kilograms) divided by height squared (in square meters).

Laboratory tests

After an overnight fast, venous blood samples were collected to determine the levels of blood glucose, total cholesterol, triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), using oxidase tests and colorimetry.

Quality assurance

A repeat survey was performed on 5% of the study population; the results were used to verify the representativeness and reliability of samples. The microbiological examination conformed to the laboratory quality control standard.

Diagnostic criteria for MS

MS was defined according to the diagnostic criteria of the International Diabetes Federation (IDF) (Motta et al., 2009) as central obesity (waist circumference ≥ 90 cm in men and ≥ 80 cm in women), together with the presence of two or more of the following risk factors: fasting TG ≥ 1.7 mmol/L or under relevant medical treatment; fasting HDL-C < 0.9 mmol/L in men or < 1.1 mmol/L in women or under relevant medical treatment; systolic BP ≥ 130 mmHg (1 mmHg = 0.133 kPa) or diastolic BP ≥ 85 mmHg or under relevant medical treatment; fasting blood glucose level ≥ 5.6 mmol/L or under relevant medical treatment.

Diagnostic criteria for CKD

CKD was defined according to the definition and classification recommended by Kidney Disease Quality Outcome Initiative (K/DOQI)(Levey et al,2005) as any of the following: (1) albuminuria, defined as urinary albumin-to-creatinine ratio (ACR) ≥ 30 mg/g in urine specimens, including microalbuminuria (ACR = 30-299 mg/g) and macroalbuminuria (ACR ≥ 300 mg/g); (2) hematuria. Urinary specimens with red blood cells of 1+ or greater were centrifuged and the urinary sediment was microscopically examined. Three or more red blood cells by high power field were considered positive (excluding contamination and women during menstruation); (3) decreased glomerular filtration rate (GFR), defined as estimated GFR (eGFR) < 60 mL/min/1.73 m^2. The eGFR was calculated from the Modification of Diet in Renal Disease Study equation calibrated with Chinese CKD patient data(Ma et al., 2006).

Statistical methods

Data entry was performed using EpiData 3.0 software (EpiData Association, Odense, Denmark) by professional data entry clerks and repeated twice to assure accuracy. All statistical analyses and calculations were performed using Statistical Package for the Social Sciences (SPSS) 10.0 software (SPSS Inc., Chicago, IL). Prevalence rates were standardized according to demographic data of the Henan Province Fifth Census (http://www.stats.gov.cn/tjgb/rkpcgb/). Measurement data are presented as mean ± standard deviation. Differences between groups were compared using Student's t-test, one-way analysis of variance, and the Mann-Whitney rank sum test. Categorical data were compared using the chi-square (χ^2) and chi-square for trend tests. P<0.05 was considered statistically significant.

3. Results

Basic information of study population

A total of 4156 residents took part in the investigation and 3981 (95.7%; 40-89 years old) were included in this study, including 2178 males and 1803 females (the male to female ratio was 1.21:1). The prevalence of hypertension and diabetes were 15.12% (602/3981) and 5.83% (232/3981), respectively. The prevalence of hypertension and diabetes standardized according to the demographic data of Henan Province Fifth Census were 15.04% and 5.76%, respectively. The diabetes prevalence in women was higher than that in men (7.38% vs. 4.55%, χ^2 = 14.407, p < 0.01). Compared with men, the levels of urea nitrogen, serum creatinine and serum uric acid in women were lower (p < 0.01), and the levels of TC, HDL-C and LDL-C were higher (p < 0.05), as shown in Table 1.

Table 1. Basic information of study population

Item	Male (n = 2178)	Female (n = 1803)	*t* value	*p* value
Age (year)	50.28 ± 16.41	53.39 ± 13.28	0.965	0.341
BP				
Systolic BP (mmHg)	131.65 ± 15.42	129.47 ± 17.56	1.602	0.116
Diastolic BP (mmHg)	83.45 ± 9.18	80.43 ± 11.26	1.818	0.231
Hypertension	317 (14.55%)	285 (15.81%)	1.205	0.272
Body mass index (kg/m^2)	23.87 ± 4.25	22.65 ± 5.15	1.048	0.301
Blood lipid				
Total cholesterol (mmol/L)	4.75 ± 0.66	5.21 ± 1.03	6.712	< 0.001▽
Triglyceride (mmol/L)	1.88 ± 1.24	1.80 ± 1.16	1.619	0.108
HDL-C (mmol/L)	1.16 ± 0.23	1.33 ± 0.28	12.886	< 0.001▽
LDL-C (mmol/L)	2.75 ± 0.72	2.91 ± 0.89	3.391	0.001▽
Blood glucose (mmol/L)	5.04 ± 1.15	5.12 ± 1.29	1.029	0.302
Diabetes	99 (4.55%)	133 (7.38%)	14.407	< 0.001▽
Kidney examination				
Urea nitrogen (mmol/L)	5.76 ± 1.54	5.09 ± 1.36	8.912	< 0.001▽
Serum creatinine (μmol/L)	73.86 ± 14.49	57.50 ± 10.66	20.653	< 0.001▽
Serum uric acid (μmol/L)	368.87 ± 82.18	299.30 ± 65.42	16.612	< 0.001▽

▼$p < 0.05$; ▽$p < 0.01$ compared to the female.

Indicators of kidney damage and prevalence of CKD among patients with MS

Prevalence of albuminuria, hematuria and decreased eGFR among patients with MS

A total of 565 patients met the MS diagnostic criteria of IDF. Participants with MS had a higher prevalence of albuminuria and decreased eGFR compared to those without MS (6.90% vs. 4.65%, $\chi^2 = 5.184$, $p < 0.01$ and 5.00% vs. 0.97%, $\chi^2 = 51.148$, $p < 0.01$, respectively; Table 2).

Table 2. Prevalence of albuminuria, hematuria and decreased eGFR among participants with and without MS

Participants	n	Albuminuria	Hematuria	Decreased eGFR
With MS	565	39 (6.90%)▽	35 (6.19%)	28 (5.00%)▽
Without MS	3416	159 (4.65%)	217 (6.35%)	33 (0.97%)
Total	3981	198 (4.97%)	252 (6.33%)	61 (1.53%)

▼$p < 0.05$; ▽$p < 0.01$ compared to participant without MS.

Table 3. Prevalence of albuminuria and decreased eGFR among participants with MS components

	Albuminuria				eGFR		
	Case	Prevalence	Statistic	*p*-value	Prevalence	χ^2 value	*p*-value
BP ≥ 140/90 mmHg							
Yes	602	42 (6.98%)	$\chi^2 = 6.021$	$p = 0.014$▼	16 (2.66%)	$\chi^2 = 5.955$	$p = 0.015$▼
No	3379	156 (4.62%)			45 (1.33%)		
HDL-C (< 0.9 mmol/L in men , < 1.1 mmol/L in women)							
Yes	766	30 (3.92%)	$\chi^2 = 2.243$	$p = 0.134$	17 (2.22%)	$\chi^2 = 2.967$	$p = 0.085$
No	3215	168 (5.23%)			44 (1.37%)		
Triglyceride ≥ 1.70 mmol/L							
Yes	862	51 (5.92%)	$\chi^2 = 2.069$	$p = 0.150$	20 (2.32%)	$\chi^2 = 4.527$	$p = 0.033$▼
No	3119	147 (4.71%)			41 (1.31%)		
Fasting blood glucose ≥ 5.6 mmol/L							
Yes	232	35 (15.09%)	$\chi^2 = 53.305$	$p < 0.001$▽	6 (2.59%)	$\chi^2 = 1.814$	$p = 0.178$
No	3749	163 (4.35%)			55 (1.47%)		
Waist circumference (≥ 90 cm in men, ≥ 80 cm in women)							
Yes	956	56 (5.86%)	$\chi^2 = 2.081$	$p = 0.149$	18 (1.88%)	$\chi^2 = 1.025$	$p = 0.311$
No	3025	142 (4.69%)			43 (1.42%)		

▼$p < 0.05$; ▽$p < 0.01$ compared between participants with and without MS components.

Prevalence of albuminuria and decreased eGFR among participants with MS components

Among participants with MS components (i.e. hypertension, low HDL-C, high TG, fasting blood glucose ≥ 5.6 mmol/L, and abnormally large waist circumference), the prevalence of albuminuria and decreased eGFR was higher in those with abnormally high BP compared to those with normal BP (6.98% vs. 4.62%, $\chi^2 = 6.021$, $p = 0.014$ and 2.66% vs. 1.33%, $\chi^2 = 5.955$, $p = 0.015$, respectively). There was no statistical difference in the prevalence of albuminuria or decreased eGFR between those with abnormally low HDL-C or waist circumference and those without. Participants with abnormally high TG had higher prevalence of decreased eGFR than those with normal TG (2.32% vs. 1.31%, $\chi^2 = 4.527$, $p = 0.033$). There

was no statistical difference in the prevalence of albuminuria between those with and without normal TG. Participants with abnormal carbohydrate metabolism had higher prevalence of albuminuria than those without (15.09% vs. 4.35%, χ^2 = 53.305, p < 0.001), while there was no statistical difference in decreased eGFR between these two groups, as shown in Table 3 and Figure 1A and 1B.

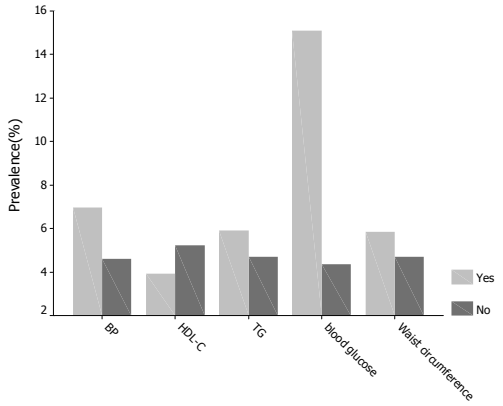

Figure 1-A. Prevalence of albuminuria among participants with MS components

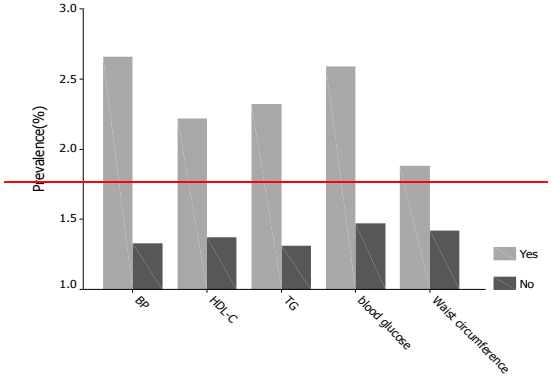

Figure 1-B. Prevalence of decreased eGFR among participants with MS components

Prevalence of CKD among participants with MS components

Of those subjects who exhibited signs of hypertension, low HDL-C, high TG, fasting blood glucose ≥ 5.6 mmol/L, and abnormally large waist circumference, the prevalence of CKD was 18.27%, 11.49%, 15.89%, 31.03% and 12.24%, respectively. In addition, participants with hypertension, high TG, or fasting blood glucose ≥ 5.6 mmol/L had a higher CKD prevalence than those without (18.27% vs. 9.20%, χ^2 = 44.434, p < 0.001; 15.89% vs. 9.11%, χ^2 = 32.903, p < 0.001; and 31.03% vs. 9.31%, χ^2 = 109.043, p < 0.001, respectively), as shown in Table 4 and Figure 2.

Number of MS components and prevalence of CKD Of 1824 participants with MS components, 35.20% (642/1824), 22.15% (404/1824), 30.97% (565/1824), 7.62% (139/1824) and 4.06% (42/966) had 1, 2, 3, 4, and 5 MS components.

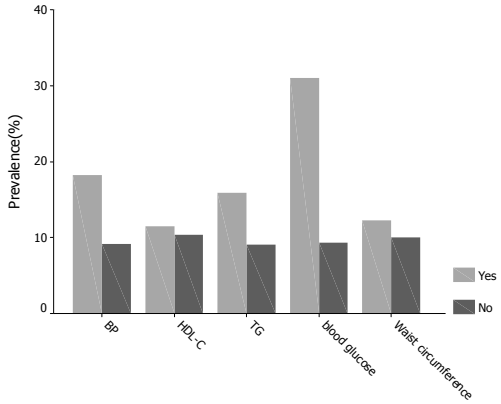

Figure 2. The prevalence of CKD among participants with MS components

The prevalence of CKD among participants who had more than one MS component was higher compared to those without MS components (p < 0.01). According to the chi-square for trend test, the prevalence of CKD increased as the number of MS components increased (χ^2 = 211.638, p < 0.0l), as shown in Table 5 and Figure 3.

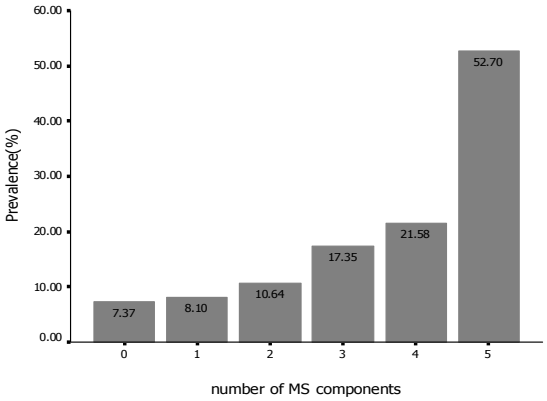

Figure 3. The prevalence of CKD among participants with varying number of MS components

4. Discussion

MS, also known as insulin resistance metabolic syndrome (IRMS), often includes obesity, hypertension, high blood glucose and dyslipidemia. Obesity, hypertension and high BP are often treated as independent risk factors for CKD (Kramer et al., 2009; Snyder et al., 2009; Muntner et al., 2010). In China, epidemiological data showed that since the 1950s, the prevalence of hypertension had increased from 5.11% to 18.8% (Zhai et al., 2010). An investigation by WHO in the year 2000 showed that the prevalence of diabetes mellitus was 5.2% among men and 5.3% among women in China (Yang et al., 2010).

Table 4. The prevalence of CKD among participants with MS components

	CKD			
	Case	Prevalence	χ^2 value	*p* value
BP ≥ 140/90 mmHg				
Yes	602	110 (18.27%)	$\chi^2 = 44.434$	$p < 0.001$▽
No	3379	311 (9.20%)		
HDL-C (< 0.9 mmol/L in men , < 1.1 mmol/L in women)				
Yes	766	88 (11.49%)	$\chi^2 = 0.836$	$p = 0.361$
No	3215	333 (10.36%)		
Triglyceride ≥ 1.70 mmol/L				
Yes	862	137 (15.89%)	$\chi^2 = 32.903$	$p < 0.001$▽
No	3119	284 (9.11%)		
Fasting blood glucose ≥ 5.6 mmol/L				
Yes	232	72 (31.03%)	$\chi^2 = 109.043$	$p < 0.001$▽
No	3749	349 (9.31%)		
Waist circumference (≥ 90 cm in men, ≥ 80 cm in women)				
Yes	956	117 (12.24%)	$\chi^2 = 3.680$	$p = 0.055$
No	3025	304 (10.05%)		

▼$p < 0.05$; ▽$p < 0.01$ compared between participants with and without MS components.

Table 5. The prevalence of CKD among participants with varying number of MS components

Number of MS components	Case	CKD		
		Prevalence	χ^2 value	*p* value
0	2157	159 (7.37%)	—	
1	642	52 (8.10%)	$\chi^2 = 0.377$	$p = 0.539$
2	404	43 (10.64%)	$\chi^2 = 5.015$	$p = 0.025$▼
3	565	98 (17.35%)	$\chi^2 = 52.090$	$p < 0.001$▽
4	139	30 (21.58%)	$\chi^2 = 34.913$	$p < 0.001$▽
5	74	39 (52.70%)	$\chi^2 = 181.793$	$p < 0.001$▽

▼$p < 0.05$; ▽$p < 0.01$ compared to participants with no MS component.

Our previous epidemiological study among residents aged 40 years or older in Henan Province showed that the prevalence rates of hypertension and diabetes were 15.04% and 5.76% respectively, the crude and standardized prevalence rates of CKD were 10.58% and 10.49% respectively (Shan et al., 2010). This is comparable to the prevalence of CKD among adults in the United States, which was about 11% (Stevens et al., 2010). The increase of hypertension and diabetes prevalence in China may have effects on the spectrum of CKD disease, making the risk factors of CKD similar to that of the developed countries. In 2005, Kurella et al(2005)reported a cohort study in which the subjects were Americans with GFR ≥ 60 mL/min per 1.73 m^2 at baseline. After 9 years of follow-up, it was found that 7% of the participants had developed CKD (GFR < 60 mL/min per·1.73m^2). The odds ratio (OR) of developing CKD in participants with MS was 1.43. Compared with participants with no MS component, those with one, two, three, four, and five components had OR for developing CKD of 1.13, 1.53, 1.75, 1.84, and 2.45, respectively. The results showed that MS was a risk factor for the development of CKD, the increased number of MS components was associated with the increased risk of CKD.

In our study, we found that persons with MS disease had greater prevalence of albuminuria and decreased eGFR than persons without. The prevalence of CKD increased with the number of MS components. Persons with hypertension, abnormal TG, or fasting blood glucose ≥ 5.6 mmol/L had greater prevalence of CKD than those without (p < 0.01). We guessed there were diversified pathogenesis responsible for CKD. The kidney damage caused by hypertension is mainly manifested as injury of renal blood vessel and parenchyma induced by hemodynamics changes and other factors (e.g. increase of reactive oxygen species, metabolic disorder) (Griffin et al., 2006). Animal examinations and clinical research have confirmed that dyslipidemia can induce kidney damage, including glomerular fat deposition, glomerulosclerosis, damage of epithelial cells, increase of mesangial cells, accumulation of extracellular matrix and damage of renal interstitium(Muntner et al., 2000). High blood glucose induces advanced glycation end products and hence damages the kidney; increase of polylol pathway activation leads to dysfunction of kidney cells; glomerulus hemodynamics changes cause high filtration, high infusion and increase of protein kinase C activity in kidney, and eventually lead to increase and accumulation of extracellular matrix of glomerulus(Indridason et al., 2007; Moin et al., 2008). Furthermore,it was reported that obesity induced renal hemodynamics changes, hyperplasia and hypertrophy of mesangial cells, fat deposition and hyperleptinemia, and hence led to renal damage(Iseki et al., 2004); patients with uric acid nephrolithiasis were insulin resistant and prone to have low urinary ammonium and

pH, which could result in increased risk of uric acid precipitation, producing or aggravating chronic urate nephropathy(Abate et al., 2004).

Although the prevalence of CKD has a tendency to increase each year, it has not aroused many people's attention. A survey taken in the United States showed that the awareness rate of CKD among patients with GFR at 15-59 mL/min per 1.73 m^2 and albuminuria was only 24.3%, and the awareness rate of CKD among patients with GFR ≥ 90 ml/min per 1.73 m^2 and no microalbuminuria was even lower(Coresh et al., 2005). Investigative data from the U.S. National Health and Nutrition Examination Survey showed that for noninstitutionalized adults with CKD stages 1-5, the awareness rates were 40.5%, 29.3%, 22.0%, 44.5% and 100%, respectively (Zhai et al., 2010). In our study, the CKD awareness and treatment rates were even lower, at 9.5% and 8.31%, respectively. Such low awareness may be because: (1) the onset of CKD is not accompanied by readily detectable symptoms, making it difficult to ascertain; (2) the public is not educated regarding CKD; (3) physicians fail to make precise diagnosis of CKD; and (4) there are insufficient medical and public health services and resources.

In conclusion, MS is a basic risk factor for the development of CKD, and the risk of acquiring CKD increases as the number of MS components increase. Clinical physicians must attach more importance to efforts to control MS components, improve diagnosis and treatment of CKD, and prevent CKD from developing into ESRD.

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