

Uric Acid, Metabolic Risk Factors,
and Chronic Kidney Disease: Clinical
Investigation in a Female Elderly
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Abstract

Purpose: To explore the prevalence and associated factors for Chronic Kidney Disease (CKD) among female elderly fishing and agricultural population in Taipei, Taiwan.**Methods:** Females (n=1,606) aged 65 years and over voluntarily admitted to a teaching hospital for a physical check-up were collected in 2010.**Results:** The prevalence of CKD was 8.2%. Age, hyperuricemia, and hyperglycemia were statistical significantly related to CKD. The sensitivity and specificity of serum uric acid and fasting blood glucose concentration as a marker of CKD were estimated 76.5%, 70.9% and 51.5%, 53.5%, respectively.**Conclusion:** Hyperuricemia and hyperglycemia independently affect the prevalent CKD in this sub-population.

Introduction

Chronic Kidney Disease (CKD) has become a global public health challenge because of its higher prevalence and the concomitant increase in risk of End-Stage Renal Disease (ESRD), Cardiovascular Disease (CVD), and premature death [1-4]. Patients with early-stage CKD had no symptoms and the majority of individuals in early stage of CKD had gone undiagnosed even in developed countries [5]. In addition, previous study showed that a vast number of patients with moderate CKD die before they develop more advanced CKD [6]. The early detection of this disorder by routine screening followed by appropriate clinical intervention would offer a practical means for the prevention of condition-associated severe kidney abnormalities.

During the past decade in Taiwan, which also has undergone a dramatic socioeconomic change and a succession of unhealthy lifestyles to let an increased burden in chronic diseases? Several studies have published information on the prevalence of CKD in different Chinese populations [1,7-9]. To the best of our knowledge, however, few clinical evidence-based studies attempted to determine the prevalence and possible etiology of CKD for the female elderly agricultural and fishing population of Taiwan, which also faced to the burden of this disorder. In order to identify the prevalence of and associated risk factors for CKD, the present study was conducted to explore the potential for condition-related factors, because it was considered to know underscore important implications for the understanding of the overall pathogenesis of CKD in this sub-elderly population. As above, the purpose of this study is to investigate the context of prevalence of and cardiovascular risk factors for CKD amongst the female elderly agricultural and fishing population, as determined by the application of a healthy volunteer subjects screening program health examination in Taipei, Taiwan.

Methods

Study population

This cross-sectional study was conducted with a total of 1,606 female elder healthy occupational adults with agricultural and fishing professional fields voluntarily admitted to one teaching hospital in Northern Taiwan for an annual physical check-up between January, 1, 2010 and December, 31, 2010. All procedures were performed in accordance with the guidelines of our institutional ethics committee and adhered to the tenets of the Declaration of Helsinki. All patients' information was anonymous. Informed consent was obtained from all participants before the screening.

Data collection

The medical histories and measurements of the participants were obtained by well-trained nurses. Personal and family histories of hypertension, type 2 diabetes, cardiovascular diseases, and other chronic diseases were obtained by a structured questionnaire. The participants were asked to take off the shoes and any other belongings that could possibly add extra weight when they were weighed. Heights and weights were evaluated based on Body Mass Index (BMI). The waist circumference was measured at the level of the iliac processes and the umbilicus with a soft tape measure to evaluate abdominal obesity. Blood pressures were measured twice in the sitting position with an interval of 15 min between the measurements, by means of standard sphygmomanometers of appropriate width, after a rest period for 30 min. Those taking antihypertensive therapy were considered to be hypertensive. Fasting blood samples were drawn via venipuncture from study participants by clinical nurses. Overnight-fasting serum and plasma samples (from whole blood preserved with EDTA and NaF) were kept frozen (-20°C) until ready for analysis.

Estimated glomerular filtration rate (eGFR)

The Estimated Glomerular Filtration Rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) equation, which was modified for data from Chinese CKD patients [7,10]. The reduced renal function was defined as an eGFR < 60 mL/min/1.73m²: eGFR (mL/min/1.73m²) = 175 x Calibrated Serum creatinine (mg/dL) - 1.234 x age (year) - 0.179 [female x 0.79].

Metabolic risk factors

Definitions of the following diseases / conditions were obesity: a BMI ≥ 25Kg/m² and hyperuricemia (≥ 6mg/dL). Serum ALT level ≥ 40U/L was classified as elevated [11]. Metabolic syndrome was

defined using the modified criteria recommended in the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III guidelines. At least 3 of the following 5 parameters should be present: abdominal obesity (waist circumference > 90 cm for males), hypertension (SBP > 130 mm Hg and/or DBP > 85 mm Hg) or history of antihypertensive usage, hyper-triglyceridemia (≥ 150 mg/dl) or presence of treatment for this disorder, low HDL-C (< 40 mg/dl in males) or presence of treatment for this disorder, and high fasting plasma glucose (> 100 mg/dl) or presence of diagnosis of type 2 diabetes [12,13].

Statistical analysis

Statistical analysis was performed using SPSS for Windows, (SPSS version 18.0; Chicago, IL, USA). The two-sample independent t-test and one-way ANOVA method were adopted to assess differences in the mean value of continuous variables. The χ^2 -trend test was used to determine significant differences in proportions among categorical variables. Mantel-Haenszel statistics are used in the analysis of stratified categorical data. Multiple logistic regressions were also performed to investigate the independence of factors associated with the prevalence of CKD. Receiver Operating Characteristic (ROC) curves were used to explore the characteristics of a diagnostic test by graphing the false positive rate (1-specificity) on the horizontal axis and the true-positive rate (sensitivity) on the vertical axis for various cutoff values. A p-value of < 0.05 was considered to represent a statistically significant difference among test populations.

Results

As figure 1 show, the overall prevalence of CKD for the female elderly study participants was 8.2% (95%CI: 6.9-9.5%). From the Cochran-Armitage trend test, the prevalence of each type of CKD showed an increase with age (p < 0.0001). Subjects aged 85 years and over (25.0%, 95CI: 17.5-32.5%) had a more than 6-fold risk for CKD compared with the subjects aged 65-74 years (3.9%, 95%CI: 2.6-5.2%).

Table 1 shows the demographic characteristics of the participants who were and were not diagnosed with CKD. In addition to DBP, waist circumference, total cholesterol, serum uric acid, ALT and serum creatinine were significant difference in age subgroups. Using the two-sample independent t-test, the associated factors that were significantly related to CKD included age, metabolic components, serum uric acid, ALT, and serum creatinine.

The relationship proportion of Chinese elderly female with CKD and individual components are shown in Table 2. Hyperglycemia (p < 0.001), hypertriglyceridemia (p = 0.002), and low HDL-C (p = 0.04) were statistically significantly associated with an increased age-specific prevalence of CKD. There was a significant relationship between the metabolic syndrome and the prevalence of CKD (p = 0.003).

The effect of independent associated risk factors upon CKD was examined using the multiple logistic regression models. As is depicted in Table 3, subsequent to adjustment for confounding factors, age (OR = 1.12, 95%CI: 1.09-1.15), hyperuricemia (yes vs. no, OR = 7.94, 95%CI: 5.07-12.42), and hyperglycemia (yes vs. no, OR = 1.67, 95%CI: 1.08-2.56).

The sensitivity and specificity of fasting blood glucose and serum uric acid concentration for the diagnosis of CKD are shown in Figure 2. For fasting blood glucose, the estimated Area under Curve (AUC)

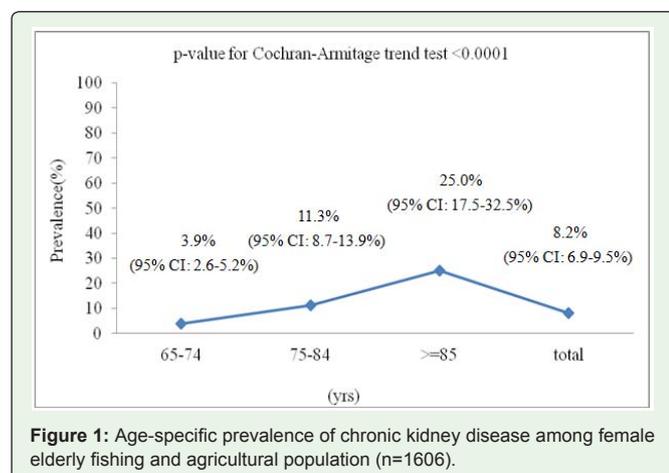


Figure 1: Age-specific prevalence of chronic kidney disease among female elderly fishing and agricultural population (n=1606).

Table 1: Demographic characteristic of participants with and without chronic kidney disease (n=1606).

Variables	General	Age			p-value for F-test	Chronic kidney disease		p-value for t-test
	(n = 1606) mean + SD	65-74 (n = 903) mean + SD	75-84 (n = 575) mean + SD	≥85 (n = 128) mean + SD		Yes (n = 132) mean + SD	No (n = 1474) mean + SD	
Age	74.4±6.7	-	-	-	-	79.9±6.8	73.9±6.4	<0.001
SBP (mm Hg)	139.1±37.6	137.5±45.4	140.4±24.2	143.7±22.6	0.12	141.3±25.4	138.9±38.5	0.47
DBP (mm Hg)	79.4±23.6	81.0±29.5	77.7±11.9	75.8±13.5	0.007	75.9±12.2	79.7±24.4	0.08
BMI (kg/m ²)	25.7±4.2	25.9±4.1	25.5±4.1	25.3±4.8	0.1	25.4±3.8	25.7±4.2	0.45
Waist circumference (cm)	83.4±9.7	82.7±9.5	84.5±9.5	83.2±11.4	0.003	84.3±9.9	83.3±9.7	0.29
Fasting blood glucose (mg/dl)	102.1±28.5	102.3±29.9	101.8±26.9	102.3±26.1	0.95	112.81±39.6	101.2±27.1	<0.001
Triglycerides (mg/dl)	135.7±76.9	133.6±73.1	138.6±81.3	137.0±82.9	0.48	157.6±94.7	133.7±74.8	0.001
Total cholesterol (mg/dl)	210.0±37.5	212.2±37.6	208.4±36.7	201.66±38.9	0.005	204.6±39.8	210.5±37.2	0.08
HDL-C (mg/dl)	58.1±15.2	58.5±14.8	58.0±15.9	56.3±15.2	0.32	56.7±16.9	58.3±15.1	0.27
Uric acid(mg/dl)	5.5±1.5	5.4±1.3	5.4±1.3	5.9±1.6	<0.001	7.2±1.8	5.4±1.4	<0.001
ALT (U/L)	29.9±16.5	31.0±17.0	29.1±16.2	26.3±14.2	0.003	27.1±15.6	30.2±16.6	0.04
Serum Creatinine(mg/dl)	0.81±0.48	0.76±0.45	0.86±0.51	0.97±0.49	<0.001	1.69±1.35	0.74±0.12	<0.001

Table 2: The relationship between metabolic components and chronic kidney disease in the study participants (n=1606).

	65-74 yrs	75-84 yrs	≥85 yrs	Total	p-value for Mantel-Haenszel
	CKD Prevalence (95% CI)	χ ² test			
Metabolic components					
Elevated blood pressure	4.9 (3.1-6.7)	11.6 (8.5-14.8)	21.9 (13.6-30.2)	8.9 (7.2-10.6)	0.42
Central obesity	5.4 (2.3-8.5)	12.6 (7.6-17.6)	18.2 (5.0-31.4)	9.4 (6.6-12.2)	0.53
Hyperglycemia	9.3 (5.1-13.5)	12.4 (6.5-18.3)	40.0 (22.5-57.5)	13.2 (9.6-16.8)	<0.001
Hyper triglyceridemia	6.6 (3.7-9.5)	15.0 (9.8-20.2)	28.6 (14.9-42.3)	11.4 (8.6-14.2)	0.002
Low HDL - C	8.6 (2.0-15.2)	16.9 (8.2-25.6)	25.0 (14.7-56.7)	14.3(8.9-19.7)	0.04
Metabolic syndrome					
No	2.7 (1.5-3.9)	10.7 (3.1-7.1)	22.7 (14.4-31.0)	7.0 (5.6-8.4)	
Yes	9.1 (4.7-13.5)	13.4 (7.3-19.5)	32.3 (15.8-48.8)	13.0 (9.3-16.7)	0.003

Table 3: Multiple logistic regression on the risk factors associated with the chronic kidney disease among female elderly fishing and agricultural population (n=1,606).

Variables	CKD vs. non-CKD		
	Odds Ratio	95% Confidence Interval	p-value
Age (year)	1.12	1.09-1.15	<0.001
Hyperuricemia (yes vs. no)	7.94	5.07-12.42	<0.001
Central obesity (yes vs. no)	1.07	0.62-1.62	0.81
Elevated blood pressure (yes vs. no)	1.03	0.66-1.61	0.88
Hyperglycemia (yes vs. no)	1.67	1.08-2.56	0.02
Hyper triglyceridemia (yes vs. no)	1.24	0.81-1.91	0.33
Lower HDL-C (yes vs. no)	1.13	0.65-1.98	0.67

was 0.57 (95%CI: 0.51-0.62) for diagnosis of CKD and cut-off value estimated as 94.5 mg/dl with 51.5% sensitivity and 53.5% specificity. The AUC for serum uric acid concentration in the identification of CKD was 0.79 (95%CI: 0.75-0.84) and the cut-off value, sensitivity, and specificity were 5.95 mg/dl, 76.5%, and 70.9%, respectively.

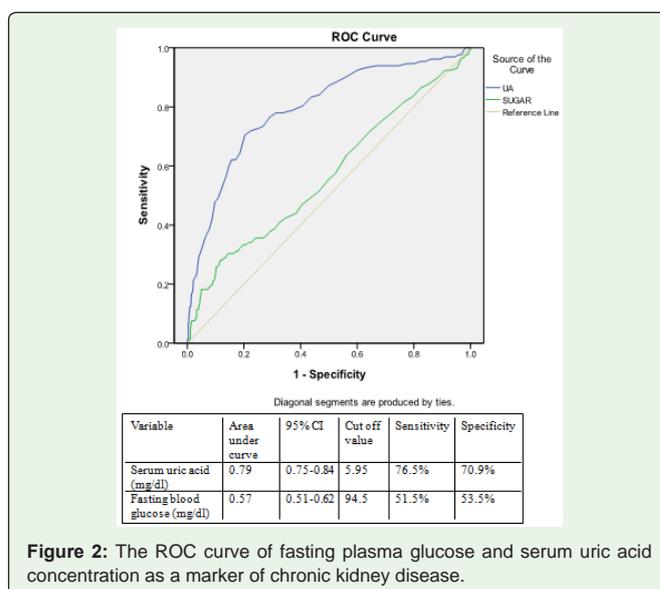


Figure 2: The ROC curve of fasting plasma glucose and serum uric acid concentration as a marker of chronic kidney disease.

Discussion

Clinical-epidemiological aspects for the development of chronic kidney disease

In the present CKD screening for the female elderly, the results provide an opportunity to elucidate the associations between putative factors and the clinical diagnosed CKD. The significant associated factors in our study are congruent with the biological plausibility that cardiovascular risk factors may affect the development or progression of CKD. From the evidenced-based medicine viewpoint, Cardiovascular Disease (CVD) accounts for premature death in about 50% of dialysis patients [2]. The strong association between mild CKD and CVD has been shown and mild to moderate CKD is strongly associated with an increase in cardiovascular mortality [2,14].

Older age represented significant risk factors related to the likelihood of a CKD after adjustment for confounding factors in this study. Previous study also indicated that the prevalence of CKD increased sharply in participants after 60 years of age [15]. Renal functions deteriorate in the aged population for various reasons. The subjects might have had a renal disease, such as nephrosclerosis or ischemic kidney disease partly explain the higher prevalence of CKD in the older population [15]. Early detection of CKD could be beneficial if accompanied by early intervention and suppress the pathways for renal injury.

Consistent with previous studies [7,16], our results show that the not only hyperuricemia is strongly associated with CKD, but also this association is independent of metabolic components. This may imply that the higher uric acid is an indicator for the deterioration of CKD. Hyperuricemia is usually caused by inadequate renal excretion of uric acid and has been found to accelerate renal disease in the remnant kidney models and to accelerate experimental cyclosporine nephropathy [16,17]. Although some studies indicated that hyperuricemia may be a direct pathogenic factor in CKD, the effect of hyperuricemia on progression of kidney disease in humans remains unclear [7,18].

Recent studies indicated that metabolic syndrome also increases susceptibility [1,2,9,12,16]. There are multiple mechanisms of CKD among metabolic components, and these are not yet well delineated [18,19]. The greater the number of metabolic components indicated the greater the prevalence and incidence of CKD [20]. However, when the modified NCEP criteria was used, the numbers of subjects classified as having metabolic syndrome increased, the magnitude of risk for CKD tended to decrease [21]. This study suggests that the prevalence of CKD among elderly females is only significantly higher in subjects with, as opposed to without, hyperglycemia, and is independent of other confounding factors. Diabetes mellitus-induced renal damage is high in Asian subjects [22]. In many parts of Asia, diabetes has emerged as the leading cause of ESRD [15,21]. In addition, several lines of evidence suggest that both hypertension and dyslipidemia may be important factors for the development and progression of CKD [23,24]. We also show a positive trend for association with CKD for elevated blood pressure, hypertriglyceridemia, and lower HDL-C with similar magnitude of adjusted risk although not statistically significant.

The importance of obesity in the development and progression of CKD has been suggested by animal studies and by the development of focal segmental glomerulosclerosis in some obese human subjects [22,24]. Epidemiologic studies also examined the association between obesity and risk of CKD and reported inconsistent results [1,25,26]. In our study, when risk factors were considered individually after adjustments for confounding factors, obesity and central obesity were not associated with increased adjusted risk of prevalence of CKD. Even in the US population, the direct role of obesity as a risk factor for new CKD might be marginal [27]. The apparent lack of effect of obesity could be ascribed to the lower number of obese subjects and the lower degree of obesity rather than the lack of effects of obesity on CKD development per se [22].

It is noticing that we used ROC curve to find the cut-off value of serum uric acid and fasting blood glucose of a diagnostic test for CKD. The cut-off value of serum uric acid was estimated 5.95 mg/dl and implied that a serum uric acid higher than 5.95 mg/dl but below the 6.0 mg/dl for hyperuricemia should be considered medium risk for CKD. In addition, potential public health action point of fasting blood glucose (94.5mg/dl) should be targeted and health interventions stepwise were proposed for female elderly population to prevent the CKD. However, further studies are needed to more accurately identify the sensitivity and specificity of clinical markers in the context of CKD diagnosis such a health screening.

Methodological consideration

A major limitation in this study was the potential self-selection bias due to the hospital-based study design, which resulted in a sample that was not representative of the general population in Taiwan. However, we believe that our findings are still useful as background data for future studies of the epidemiology of CKD based on relative larger sample sizes. Secondly, this study only included subjects who were aged ≥ 65 years and may have different characteristics compared with whole female population. Nevertheless, this sub-population was more susceptible to have CKD and easily to know the trend happened in Taiwan and take early prevention strategies. Finally, our measurements were conducted at only a single point in time and, therefore, may not reflect long-term exposure to important demographic or biochemical factors. The solution to such a quandary would be to conduct a number of prospective longitudinal analogous studies to see if they would complement the population-based (cross-sectional) findings of this study.

Conclusion

The prevalence of CKD is related to older age, hyperuricemia, and hyperglycemia in this study. Further studies are needed to elucidate the temporal sequence of events that typically lead to CKD among elderly population. In order to prevent the CKD, promoting this female sub-population with controlled glycemic, uric acid, and health improvement for kidney function are essential.

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Authors' Contribution

Yi-Chun Hu, Yu-Fen Chen, Hsi-Che Shen, and Tao-Hsin Tung carried out the study and drafted the manuscript. Ya-Ting Liang participated in the design of the study and performed the statistical analysis. Hsi-Che Shen and Tao-Hsin Tung conceived of the study, and participated in its design and coordination. All authors read and approved the final manuscript.

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