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Association between betel-nut chewing and chronic kidney disease in men

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Abstract

Background: Betel-nut use is associated with metabolic syndrome and obesity. However, the association between betel-nut chewing and risk for chronic kidney disease (CKD) is unknown. The present study was conducted to determine the association between betel-nut chewing and CKD in men.

Methods: We retrospectively reviewed health-check records of 3264 men in a hospital-based cross-sectional screening programme from 2003 to 2006. CKD was defined as estimated glomerular filtration rate less than 60 ml/min/1·73 m^2 calculated by the Modification of Diet in Renal Disease formula. Risk factors for CKD including diabetes, hypertension, BMI, smoking, alcohol consumption and age were also considered.

Results: A total of 677 (20·7 %) men were found to have CKD and 427 (13·1 %) participants reported a history of betel-nut use. The prevalence (24·8 %) of CKD in betel-nut users was significantly higher than that (11·3 %) of participants without betel-nut use ($P = 0·026$). In multivariate logistic regression analysis with adjustments for age, hypertension, diabetes and hyperlipidaemia, betel-nut use was independently associated with CKD ($P < 0·001$). The adjusted odds ratio for betel-nut use was 2·572 (95 % CI 1·917, 3·451).

Conclusions: Betel-nut use is associated with CKD in men. The association between betel-nut use and CKD is independent of age, BMI, smoking, alcohol consumption, hypertension, diabetes and hyperlipidaemia.

Keywords
Betel nut
Body mass index
Chronic kidney disease
Diabetes
Hypertension
Men
Metabolic syndrome

The incidence of end-stage renal disease (ESRD) is high and growing rapidly in adults younger than 65 years of age in Taiwan[1]. Outcomes of ESRD treatment tend to be poor; however, the cost of treatment is relatively high[2,3]. Early detection of possible risk factors and early treatment of chronic kidney disease (CKD) may not only slow the decline of renal function, but also prevent the development of severe cardiovascular complications[4]. Apart from well-known risk factors for CKD including age, hypertension, diabetes, obesity and metabolic syndrome, the identification of other possible risk factors associated with CKD is a key for early detection and treatment as well. The prevalence of betel-nut use is about 10 %, with about 600 million users all over the world[5,6], and most betel-nut chewers in Taiwan are male. The prevalence of betel-nut use is rising gradually in Taiwan, especially in rural areas[5]. Evidence has shown that betel-nut chewing is associated with oral cancer[7], hyperglycaemia, obesity, metabolic syndrome[8] and increase in urinary albumin excretion[9]. Betel-nut chewing may be a risk factor for CKD. However, the association between betel-nut chewing and CKD is unknown. We conducted the present cross-sectional retrospective study to determine the association between betel-nut chewing and CKD in Taiwanese men.

Methods

A total of 8027 (3264 men and 4763 women) records in a general health-check programme in China Medical University Beigang Hospital, Yunlin County, Taiwan, were reviewed from 2003 to 2006. The prevalence of betel-nut use (as chews of fresh *Areca catechu* nuts with *Piper betle* leaves and lime) was 13·8 % in men and 0·8 % in women. In view of the lower prevalence of betel-nut use in women, data analysis was limited to 3264 men. CKD was

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defined as estimated glomerular filtration rate (eGFR) of less than 60 ml/min/1·73 m^2 calculated by the Modification of Diet in Renal Disease formula[4]. Basic data on the participants included age, body height, body weight, systolic blood pressure (SBP) and diastolic blood pressure (DBP). Hb, platelet count, blood urea nitrogen (BUN), creatinine, uric acid, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, globulin, cholesterol, TAG and fasting blood sugar were measured standard automated technology. Participants fasted for 12 h overnight before blood sampling in the morning. Data on lifestyle factors and habits were obtained using a questionnaire based on the National Health Institute of Taiwan standard health-check format[10]. Hypertension was defined as blood pressure of at least 140/90 mmHg or the use of antihypertensive medication[11]. Diabetes mellitus was defined as fasting blood glucose level of 140 mg/dl, non-fasting glucose of 200 mg/dl or a history of treatment for diabetes[12]. Smoking was defined as a history of smoking for more than 2 pack-years[13]. Alcohol consumption was defined in those people drinking at least one drink daily[14]. Hyperlipidaemia was defined as serum cholesterol level ≥200 mg/dl, serum TAG ≥200 mg/dl or if lipid-lowering agents were being used. Betel chewing was categorized as never, sometimes or frequently in the last 6 months.

Statistical analyses

Data are reported as mean and standard deviation or frequency and percentage, as appropriate. Baseline characteristics and anthropometric factors were compared between patients with CKD and those without by Student's *t* test or the Mann–Whitney *U* test (as appropriate) for continuous variables and by the χ^2 test for categorical variables. Logistic regression models were used to estimate the odds ratios for CKD. To determine associations between betel-nut use and CKD, a multivariate logistic regression model with adjustments for age, sex, hypertension and diabetes was used. $P < 0·05$ was considered statistically significant. All calculations were carried out using the SPSS for Windows statistical software package version 12 (SPSS Inc., Chicago, IL, USA).

Results

A total of 677 (20·7 %) participants were found to have CKD and 427 (13·1 %) participants had a history of

Table 1 Demographic and biochemical data of study participants by chronic kidney disease (CKD) status: retrospective review of health-check records of 3264 men in a hospital-based cross-sectional screening programme, Yunlin County, Taiwan, 2003 to 2006

	Overall		CKD(−) (*n* 2587)		CKD(+) (*n* 677)	
	Mean	SD	Mean	SD	Mean	SD
Age (years)	64·5	11·6	62·7	11·6	71·7*	8·3
eGFR (ml/min/1·73 m^2)	74·5	19·6	81·0	16·0	49·0*	11·0
BMI (kg/m^2)	24·8	3·3	24·8	3·4	24·5*	3·2
Height (cm)	164·1	6·4	164·2	6·5	163·9	5·9
Weight (kg)	66·8	10·4	67·0	10·4	66·0*	10·0
SBP (mmHg)	134	23	132	22	141*	24
DBP (mmHg)	78	13	78	12	79	14
Hb (g/dl)	14·6	1·4	14·7	1·3	14·0*	1·7
Platelets (10^3/μl)	199	56	200	56	191	55
AST (IU/l)	34	29	34	31	33	22
ALT (IU/l)	35	49	36	53	32*	33
BUN (mg/dl)	18	7	17	5	24*	10
Creatinine (mg/dl)	1·1	0·4	1·0	0·1	1·6*	0·7
Uric acid (mg/dl)	6·5	1·5	6·3	1·4	7·4*	1·6
Albumin (g/dl)	4·0	0·3	4·0	0·3	3·9*	0·4
Globulin (g/dl)	3·2	0·5	3·2	0·5	3·3	0·5
Cholesterol (mg/dl)	194	39	194	40	195	40
TAG (mg/dl)	129	138	129	143	129	82
Fasting blood glucose (mg/dl)	113	46	113	46	111	45
	n	%	*n*	%	*n*	%
Co-morbidity						
Hypertension	749	22·9	501	19·4	248	36·6*
Diabetes	406	12·4	304	11·5	102	15·1*
Hyperlipidaemia	127	3·9	101	3·9	26	3·8
Lifestyle						
Smoking	855	26·2	792	30·6	166	24·5*
Alcohol consumption	958	29·4	746	28·8	109	16·1*
Betel-nut use	427	13·1	321	12·4	106	15·7*

eGFR, estimated glomerular filtration rate by Modification of Diet in Renal Disease formula; SBP, systolic blood pressure; DBP, diastolic blood pressure; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen.
*$P < 0·05$ *v.* CKD(–) in independent *t* test, Mann–Whitney *U* test or χ^2 test.

Table 2 Demographic and biochemical data of participants by history of betel-nut use: retrospective review of health-check records of 3264 men in a hospital-based cross-sectional screening programme, Yunlin County, Taiwan, 2003 to 2006

	Betel nut(−) (*n* 2837)		Betel nut(+) (*n* 427)	
	Mean	SD	Mean	SD
Age (years)	65·2	11·3	59·8*	12·2
eGFR (ml/min/1·73 m^2)	75·0	19·0	74·0	21·0
BMI (kg/m^2)	24·7	3·3	25·3*	3·2
Height (cm)	164·0	6·0	165·0	6·0
Weight (kg)	66·5	10·3	68·8*	10·4
SBP (mmHg)	134	23	131*	22
DBP (mmHg)	78	13	78	13
Hb (g/dl)	14·6	1·4	14·7	1·5
Platelets (10^3/μl)	198	55	201	59
AST (IU/l)	33	30	37*	27
ALT (IU/l)	35	52	38	34
BUN (mg/dl)	18	6	19	9
Creatinine (mg/dl)	1·1	0·4	1·1	0·7
Uric acid (mg/dl)	6·5	1·5	6·4	1·5
Albumin (g/dl)	4·0	0·3	4·0	0·4
Globulin (g/dl)	3·2	0·5	3·2	0·5
Cholesterol (mg/dl)	194	39	191	41
TAG (mg/dl)	123	99	166*	259
Fasting blood glucose (mg/dl)	112	45	118*	43
	n	%	*n*	%
Chronic kidney disease	321	11·3	106	24·8*
Co-morbidity				
Hypertension	664	23·4	85	19·9
Diabetes	356	12·5	50	11·7
Hyperlipidaemia	113	4·0	14	3·1
Lifestyle				
Smoking	661	23·3	297	69·6*
Alcohol consumption	624	22·0	231	54·1*

eGFR, estimated glomerular filtration rate by Modification of Diet in Renal Disease formula; SBP, systolic blood pressure; DBP, diastolic blood pressure; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen.
*$P<0·05$ *v.* betel nut(−) in independent *t* test, Mann–Whitney *U* test or χ^2 test.

betel-nut use. The prevalence of CKD was significantly higher in participants with betel-nut use than in those without (24·8 % *v.* 11·3 %, $P=0·026$). The demographic data and biochemical characteristics of the entire male study group are shown in Table 1. As can be seen, participants with CKD were significantly older and had higher SBP, serum BUN, creatinine and uric acid levels than participants without CKD. The prevalence of hypertension, diabetes and betel-nut chewing was significantly higher in CKD participants than non-CKD participants. Hb, ALT and albumin levels were significantly lower in participants with CKD than in those without.

The prevalence of CKD was 24·8 % (106/427) in betel-nut users, which was significantly higher than that (11·3 %, 321/2837) of non-users. As shown in Table 2, the participants with betel-nut use were younger and had lower SBP than those without. Serum TAG and fasting blood glucose levels were significantly higher in participants with betel-nut use than those without. In addition, participants with betel-nut use also had higher prevalence of smoking and alcohol usage. The unadjusted OR of CKD for traditional risk factors in univariate logistic regression analyses are shown in Table 3. Hypertension and diabetes were associated with increased CKD risk: OR = 2·407 (95 % CI 2·002, 2·894, $P<0·001$) and OR = 1·332 (95 % CI 1·046, 1·697, $P=0·020$), respectively. For the individuals with hypertension and betel-nut use, the OR for CKD increased to 2·766 (95 % CI 1·781, 4·297, $P<0·001$). For participants with diabetes and betel-nut use, the OR for CKD was 1·993 (95 % CI 1·104, 3·601, $P=0·022$). These findings suggest the synergic effect of betel-nut use on CKD risk in patients with diabetes or hypertension.

Table 3 Unadjusted odds ratios and 95 % confidence intervals for association of chronic kidney disease with various risk factors in univariate logistic regression analysis: retrospective review of health-check records of 3264 men in a hospital-based cross-sectional screening programme, Yunlin County, Taiwan, 2003 to 2006

	OR	95 % CI	*P*
Hypertension	2·407	2·002, 2·894	<0·001
Diabetes	1·332	1·046, 1·697	0·020
Smoking	0·736	0·606, 0·894	0·002
Alcohol consumption	0·474	0·379, 0·591	<0·001
Betel-nut use	1·310	1·033, 1·663	0·026
Hypertension + betel-nut use	2·766	1·781, 4·297	<0·001
Diabetes + betel-nut use	1·993	1·104, 3·601	0·022

Table 4 Odds ratios and 95 % confidence intervals for association of chronic kidney disease with various risk factors in multivariate logistic regression analysis after adjustment for age, hypertension and diabetes: retrospective review of health-check records of 3264 men in a hospital-based cross-sectional screening programme, Yunlin County, Taiwan, 2003 to 2006

	OR	95 % CI	*P*
Betel-nut use	2·572	1·917, 3·451	<0·001
BMI*	1·008	0·979, 1·037	0·61
Smoking	1·007	0·799, 1·270	0·950
Hyperlipidaemia	1·055	0·651, 1·709	0·827
Alcohol consumption	0·786	0·609, 1·015	0·064

*OR calculated per 1 kg/m^2 increment.

Risk factors for CKD including smoking, alcohol consumption, BMI and hyperlipidaemia were taken into consideration in multivariate logistic regression analyses with adjustments for age, hypertension and diabetes. As shown in Table 4, betel-nut use, independent of BMI, hyperlipidaemia smoking or alcohol consumption, was significantly associated with CKD ($P<0·001$). The adjusted OR for betel-nut use was 2·572 (95 % CI 1·917, 3·451), suggesting that betel-nut use may be a more important CKD risk factor than alcohol consumption, smoking, BMI or hyperlipidaemia.

Discussion

We found that exposure to betel nut was independently associated with CKD in men based on the data of a hospital-based health-check programme. This postulate was supported by three findings: (i) participants with a history of betel-nut use had a higher prevalence of CKD than those without; (ii) betel-nut use was independently associated with a 2·6-fold increased risk of CKD after adjustment for age, hypertension and diabetes, and the association was independent of BMI, smoking, alcohol consumption and hyperlipidaemia; and (iii) the use of betel nut increased further the risk for CKD in individuals with diabetes or hypertension.

Betel-nut use, an established risk factor for oropharyngeal malignancy, is associated with hyperglycaemia, obesity and metabolic syndrome[8]. Our finding may be explained by several hypotheses. First, the aqueous extract of betel nut can induce breaks in DNA of kidney cells in an animal model[15]. A decreased eGFR has been reported for a subject who regularly consumed about 40 betel nuts/d[16]. Second, participants with betel-nut use have a high prevalence of smoking[17] and alcohol consumption[18] that are themselves risk factors for CKD. The result of multivariate logistic regression analysis (Table 4) suggested that the influence of betel nut may overpower the influence of smoking and alcohol consumption. Third, betel-nut use is associated with metabolic syndrome and obesity[19,20] which are important risk factors for CKD. It is possible that the use of betel nut is associated with CKD through the influence of metabolic syndrome or obesity[8,21]. Betel-nut users had higher serum TAG and fasting blood sugar (Table 2) than non-users; however, the data on HDL and waist circumferences were not available in our study. In view of the effect of CKD on global health, our finding had an important epidemiological implication.

The prevalence of CKD was 20·7 % in our study (age-corrected prevalence 13·8 %), higher than the previous reported prevalence of CKD among the general population in Taiwan[1,22]. Participants in the present study were older than the general population so they might be more at risk for CKD. Nevertheless, the prevalence of betel-nut chewing in our study is close to previous community-based cohort data[8,21]. In addition, participants with betel-nut use had lower SBP than those without, which may be explained by the peripheral cholinergic effect of betel nut and by the relatively younger age of betel-nut chewers.

In conclusion, our study demonstrates a significant association between betel-nut use and CKD in men and this association is independent of age, hypertension, diabetes, BMI, smoking, alcohol consumption and hyperlipidaemia. More studies are needed to confirm our findings and prospective studies are needed to investigate the effect of cessation of betel-nut use in CKD.

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