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Micronutrients and lifestyles in Taiwanese patients with stage 3 to 5 chronic kidney disease

Shou-Shan Chiang, M.D.[a], Cheng-Wei Tai, M.S.[b], Chi-Jung Chung, M.S.[b], Horng-Sheng Shiue, M.D.[c], Jin-Bor Chen, M.D.[d], Chien-Tien Su, M.D.[e], and Yu-Mei Hsueh, Ph.D.[f,*]

[a]*Department of Internal Medicine/Nephrology, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan*
[b]*School of Public Health, Taipei Medical University, Taipei, Taiwan*
[c]*Department of Chinese Medicine, Chang Gung Memorial Hospital, and Graduate Institute of Medical Sciences, College of Medicine, Taipei Medical University, Taipei, Taiwan*
[d]*Nephrology Division, Chang Gung Memorial Hospital-Kaohsiung Medical Center, Chang Gung University College of Medicine, Kaohsiung, Taiwan*
[e]*Department of Family Medicine, Taipei Medical University Hospital, Taipei, Taiwan*
[f]*Department of Public Health, School of Medicine, Taipei Medical University, Taipei, Taiwan*

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Abstract

Objective: Lycopene is an antioxidant that reduces oxidative stress. Analgesics are commonly used and may impair kidney function. However, the associations among plasma lycopene, analgesic use, and chronic kidney disease (CKD) are unknown. A hospital-based, case–control study was conducted to determine the association among plasma lycopene, analgesic use, and CKD.

Methods: Two hundred one patients with CKD and 313 controls were recruited, and CKD was defined as an estimated glomerular filtration rate <60 mL/min per 1.73 m^2, as calculated by the Modification of Diet in Renal Disease formula. Plasma antioxidants were measured by high-performance liquid chromatography.

Results: This study showed that the higher the plasma lycopene was, the lower the CKD risk. Specifically, in subjects with a plasma lycopene level ≥17.97 or 7.72–17.97 μg/dL, the adjusted odds ratio of CKD was 0.32 (95% confidence interval 0.18–0.58) or 0.49 (95% confidence interval 0.29–0.83), respectively, compared with subjects with a plasma lycopene level <7.72 μg/dL, independent of age, gender, level of education, paternal and maternal ethnicities, cigarette smoking, analgesic use, hypertension, and diabetes history. In contrast, the higher the plasma retinol level, the higher the risk of CKD. A significantly higher risk was demonstrated in analgesic users than in non-users (odds ratio 3.83, 95% confidence interval 1.75–8.40), but a significantly lower risk was shown in subjects who used analgesics on an as-needed basis than in non-users. Plasma lycopene tended to interact additively with analgesic consumption in modifying the CKD risk; however, the interactions were statistically insignificant.

Conclusion: This is the first study showing that a low plasma lycopene level is associated with CKD risk.

Keywords: Micronutrients; Lycopene; Analgesics; Chronic kidney disease

Introduction

Much epidemiologic and clinical evidence has shown a link between several factors and the initiation and progression of chronic kidney disease (CKD). Apart from well-known risk factors for CKD, including age [1], genetic [2] or familial predisposition [3], hypertension [4], and diabetes, obesity, and metabolic syndrome [5], the identification of other risk factors related to CKD is important for early detection and treatment.

The association between habitual analgesic use and kidney function has been inconsistent [6,7]. One study has found that the metabolic process of analgesics produces oxidative

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*Corresponding author. Tel.: +886-2-2736-1661, ext. 6513; fax: +886-2-2738-4831.

E-mail address: ymhsueh@tmu.edu.tw (Y.-M. Hsueh).

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stress [8]. Oxidative stress plays a role in the pathogenesis and complications of CKD [9]. Recent studies have also indicated that increased adiposity may amplify the oxidative stress and inflammation that accompany moderate to severe CKD [10], although a recent study has reported that lycopene supplementation reduces apoptosis but does not affect oxidant-responsive heme oxygenase-1 in human lymphocytes [11]. However, lycopene and vitamin C from tomato juice have been shown to have an influence on the biomarkers of oxidative stress and inflammation [12]. Plasma water-soluble antioxidants, such as vitamin C, deteriorate within a very short time unless specimens are acid-stabilized and then frozen [13], and in this study frozen plasma specimens were not acid-stabilized before storage. Lycopene is a lipid-soluble antioxidant and has been inversely associated with lipid peroxidation, including low-density lipoprotein oxidation [14] and reduced oxidative stress and inflammation [12]. Low plasma levels of lycopene or analgesic consumption may be a risk factor for CKD. However, the associations among lycopene, analgesic consumption, and CKD are unknown. We conducted the present case–control study to determine the associations among plasma lycopene, analgesic consumption, and CKD in Taiwanese subjects.

Material and methods

Study subjects and questionnaire interview

Two hundred one patients with clinically proven CKD (age range 22–88 y) were recruited from the Department of Internal Medicine/Nephrology of Shin Kong Wu Ho-Su Memorial Hospital in Taipei, Taiwan, from September 2005 to December 2007. The glomerular filtration rate (GFR) is traditionally considered the best overall index of renal function in health and disease. We used the abbreviated equation from the Modification of Diet in Renal Disease Study [15] to estimate the GFR as $186.3 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times (0.742$ for females) and defined five stages of CKD. In this study, subjects with stage 3 to 5 renal disease (GFR <60 mL/min per 1.73 m^2) for 3 mo were diagnosed with CKD. A total of 313 age-matched control subjects with no evidence of CKD (GFR ≥ 60 mL/min per 1.73 m^2) were accrued from a hospital-based pool, including those receiving senior citizen health examinations at Taipei Medical University Hospital and those receiving adult health examinations at Taipei Municipal Wan Fang Hospital.

Well-trained personnel carried out standardized personal interviews based on a structured questionnaire. The information collected included demographic and socioeconomic characteristics, general potential risk factors for CKD (lifestyle, alcohol consumption, and cigarette smoking in quantified detail), exposure to potential occupational and environmental carcinogens (hair dyes and pesticides, long-term medication history, and consumption of conventional and alternative medicines), and personal and family histories of hypertension, diabetes, and CKD. Frequent alcohol drinkers were defined as those who consumed alcohol >3 d/wk for ≥ 6 mo; those who consumed less than this level were classified as occasional drinkers. Pesticide users were farmers who used pesticides for agricultural purposes. The research ethics committee of Taipei Medical University (Taipei, Taiwan) approved the study. All patients provided informed consent forms before sample and data collection. The study was consistent with the World Medical Association Declaration of Helsinki. A 10-mL blood sample was also collected from subjects on recruitment by use of vacuum syringes treated with ethylenediaminetetra-acetic acid and disposable needles. Plasma samples were centrifuged at 3000 rpm for 15 min at room temperature, separated into aliquots, and stored at $-80°C$ until analyzed.

Determination of plasma antioxidant micronutrient levels

The levels of β-carotene, lycopene, α-tocopherol, and retinol of plasma samples were measured by high-performance liquid chromatography according to the procedure described previously [16]. Analysis was carried out using reverse phase high-performance liquid chromatography (Hitachi, Naka, Japan) with the mobile phase of methanol:acetonitrite:chloroform (47:47:6) and multiwave length monitoring. Retinol was detected at 325 nm, α-tocopherol was detected at 280 nm, and lycopene and β-carotene were detected at 466 nm. The plasma samples for each case–control set were thawed from the $-80°C$ refrigerator in dim light at room temperature and assayed on the same day to ensure that temporal variability in the laboratory assays would affect cases and controls equally. All laboratory personnel were unaware of the disease status of the subjects from whom the plasma samples were obtained. The recovery rates for β-carotene, lycopene, α-tocopherol, and retinol were 90% to 100% at the highest concentration and 90% to 107% at the lowest concentration of the standard solution. The precision (coefficient of variance) of β-carotene, lycopene, α-tocopherol, and retinol was 1.0% to 6.0%. We also used α-tocopherol acetate as an internal control to reduce systematic error; the coefficient of variance for α-tocopherol acetate was 2.5%.

Statistical analysis

Continuous variables are expressed as mean $\pm$ standard error. Student's t test was used to compare differences in the plasma antioxidants between case subjects and controls. Multiple logistic regression models were used to estimate the multivariate-adjusted odds ratio (OR) and the 95% confidence interval (CI). Cutoff points for continuous variables were the respective tertiles of the controls. Significance tests for linear trend among ORs across exposure strata were calculated by categorizing exposure variables and treating scored variables as continuous. For the joint-effect analysis,

the cutoff points for the antioxidant micronutrients were the respective medians of the controls. The synergy index proposed by Rothman [17] was computed to assess the additive interaction relation between antioxidant micronutrients and analgesic consumption on CKD risk. An observed synergy index value that departs substantially from the expected additive null, i.e., synergy index not equal to 1, suggests an additive interaction effect. The OR values and the variance–covariance matrix were then used to calculate values for the synergy index and 95% CIs [18].

Results

The sociodemographic characteristics of the cases and controls are presented in Table 1. Subjects who had higher educational levels had a significantly lower risk than those with lower educational levels. Mainland Chinese or aboriginal and Hakka Taiwanese had a significantly lower CKD risk than the Fukien Taiwanese. Subjects with diabetes or hypertension had a significantly higher CKD risk than those without diabetes or who were normotensive (ORs 2.10 and 2.15, 95% CIs 1.38–3.35 and 1.48–3.55, respectively) when adjusted for multiple variables.

Table 2 presents the association among lifestyle, chemical contact, analgesic use, and CKD. Cigarette smokers had a significantly lower CKD risk than non-smokers. Alcohol or coffee consumption, pesticide exposure, and paint or dye use did not affect the risk of CKD. The significantly higher risk was shown in analgesic users than in non-users (OR 3.83, 95% CI 1.75–8.40). In contrast, subjects who used analgesics as needed had a significantly lower risk than non-users (OR 0.29, 95% CI 0.14–0.60) when adjusted for multiple variables.

Figure 1 shows the association between plasma micronutrients and GFR in CKD cases. Plasma retinol was not related to the GFR, but α-tocopherol, lycopene, and β-carotene were significantly related to the GFR.

Based on trend analysis of micronutrient strata in tertiles, with the exception of α-tocopherol and β-carotene, retinol was shown to be significantly associated with CKD risk in a dose–response relation, especially in subjects with a plasma retinol level $\geq$162.96 μg/dL (OR 8.06, 95% CI 4.25–15.17) compared with those with a retinol level $<$107.57 μg/dL. Conversely, higher lycopene levels produced a lower CKD risk after multivariate analysis (Table 3). In subjects with a plasma lycopene level $\geq$17.97 or 7.72–17.97 μg/dL, the OR and 95% CI of CKD was 0.32 (0.18–0.58) or 0.49 (0.29–0.83) compared with those with a level $<$7.72 μg/dL, independent of age, gender, educational level, paternal and maternal ethnicities, cigarette smoking, analgesic use, and hypertension and diabetes history.

Table 1
Sociodemographic characteristics of chronic kidney disease and healthy controls

Variables	Cases (%)	Healthy controls (%)	Odds ratios* (95% CI)	Odds ratio† (95% CI)
Gender				
Male	100 (49.8)	181 (44.4)	1.00	1.00
Female	101 (50.2)	227 (55.6)	0.87 (0.62–1.21)‡	0.47 (0.29–0.74)‖
Age (y), mean ± SD	59.18 ± 13.79	59.73 ± 13.36	1.00 (0.99–1.01)§	0.97 (0.96–1.02)
Educational level				
Illiterate/elementary school	103 (51.2)	104 (25.5)	1.00	1.00
Junior /senior high school	57 (28.4)	134 (32.7)	0.34 (0.22–0.53)¶	0.36 (0.22–0.59)¶
College and above	41 (20.4)	170 (41.3)	0.15 (0.09–0.26)¶	0.18 (0.10–0.34)¶
Paternal ethnicity				
Fukien Taiwanese	178 (88.6)	237 (57.6)	1.00	1.00
Hakka Taiwanese	8 (3.9)	49 (12.5)	0.25 (0.13–0.51)¶	0.27 (0.12–0.60)¶
Mainland Chinese/aboriginal	15 (7.5)	122 (29.9)	0.19 (0.11–0.32)¶	0.28 (0.15–0.52)¶
Maternal ethnicity				
Fukien Taiwanese	180 (89.6)	250 (60.7)	1.00	1.00
Hakka Taiwanese	8 (3.9)	47 (12.0)	0.28 (0.14–0.57)¶	0.29 (0.13–0.66)¶
Mainland Chinese/aboriginal	13 (6.5)	111 (27.3)	0.19 (0.11–0.34)¶	0.26 (0.14–0.51)¶
Diabetes				
No	133 (73.9)	370 (91.8)	1.00	1.00
Yes	47 (26.1)	33 (8.2)	2.37 (1.34–4.18)¶	2.10 (1.38–3.35)‖
Hypertension				
No	104 (57.8)	306 (75.9)	1.00	1.00
Yes	76 (42.2)	97 (24.1)	2.30 (1.48–3.56)¶	2.15 (1.48–3.55)‖

CI, confidence interval

* Adjusted for age and gender.

† Adjusted for age, gender, cigarette smoking, coffee drinking, analgesic usage, educational level, paternal and maternal ethnicities, and hypertension and diabetes histories, except its main variable in the model.

‡ Adjusted for age.

§ Adjusted for gender.

‖ $P < 0.01$.

¶ $P < 0.001$.

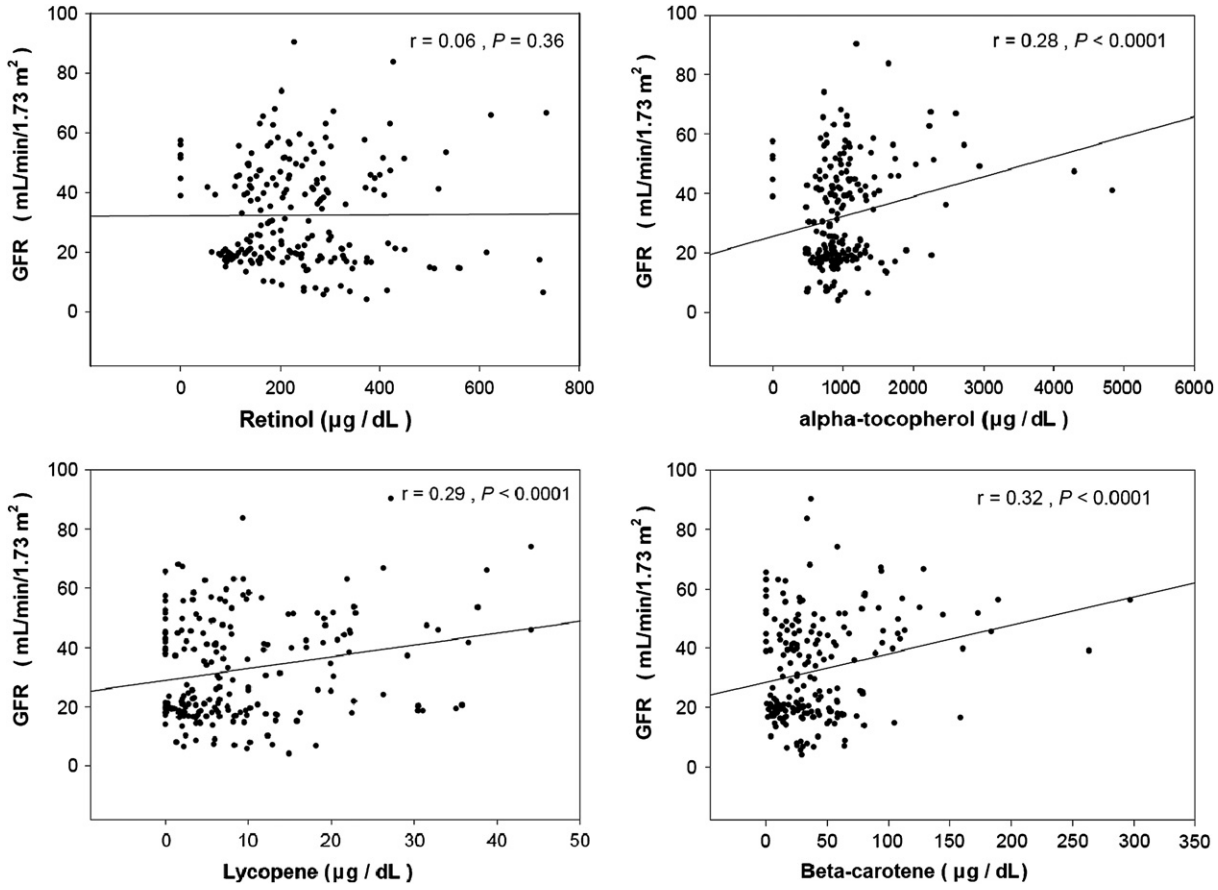

Fig. 1. Association between micronutrients and GFR in patients with chronic kidney disease. GFR, glomerular filtration rate.

Because both micronutrients (retinol and lycopene) and analgesic use affect the CKD risk, further analyses were carried out to assess the joint effects of the two risk factors (Table 4). Trend analysis revealed progressively increased risks through exposure to no risk factors, one of the factors, or both risk factors. Although plasma lycopene or retinol tended to interact additively with analgesic consumption in modifying the CKD risk, the interactions were statistically insignificant, as shown by the absence of a substantial deviation from 1 in the synergy index.

Discussion

Many studies [19,20] have reported that hypertension and diabetes are important risk factors for CKD. We also found two times the CKD risk for patients with hypertension or diabetes compared with those with normal blood pressure and without diabetes in this study. Diabetes and hypertension may activate the renin-angiotensin-aldosterone system, accompanied by a loss of glycemic control [21], or enhance oxidative stress or inflammation [4] with progression to nephropathy. In addition, the present study showed that women had a significantly lower CKD risk than men, in disagreement with a previous study [22]. A recent study has found that moderate wine consumption may enhance kidney antioxidant defense against renal injury [23]; however, alcohol consumption did not affect the risk of CKD in this study. We did not determine why cigarette smokers had a significantly lower risk of CKD in this study compared with non-smokers; perhaps controls are less concerned about their lifestyle because they are healthy; another possible reason may be the prevalent cases were advised to discontinue cigarette smoking. Subjects with a low level of education had a higher CKD risk than those with a high level of education, as reported in another Taiwanese study [24]. Paternal and maternal ethnicities as Hakka Taiwanese or Mainland Chinese or aboriginal had a lower CKD risk than Fukien Taiwanese; this disparity of ethnicity on CKD prevalence remains unexplained, in much the same way that blacks have a higher CKD prevalence than whites in the United States [25].

Results from this study have shown that high plasma lycopene levels were independently and inversely associated with CKD. This postulate was supported by several findings. First, study subjects with a high plasma lycopene level had a lower prevalence of CKD than those with a low plasma lycopene level. Second, the highest or higher plasma lycopene groups were related to a 0.32- or 0.49-fold decreased risk of CKD than those with a low plasma lycopene level, independent of age, gender, level of education, paternal or maternal ethnicity, cigarette smoking, analgesic usage, and hypertension

Table 2
Association among lifestyle, chemical contact, analgesic usage, and chronic kidney disease

Variables	Cases (%)	Controls (%)	Odds ratio* (95% CI)	Odds ratio† (95% CI)
Cigarette smoking				
No	166 (82.6)	305 (74.8)	1.00	1.00
Yes	35 (17.4)	103 (25.2)	0.48 (0.29–0.79)‡	0.40 (0.23–0.70)‡
Alcohol drinking				
No	186 (92.5)	357 (87.5)	1.00	1.00
Yes	15 (7.5)	51 (12.5)	0.61 (0.33–1.14)	1.28 (0.62–2.64)
Coffee dinking				
No	109 (54.2)	191 (46.9)	1.00	1.00
Yes	45 (22.4)	95 (23.4)	1.78 (1.07–2.96)‡	1.48 (0.84–2.61)
Occasional	47 (23.4)	121 (29.7)	1.02 (0.64–1.60)	1.07 (0.65–1.76)
Dye contact				
No	117 (96.7)	403 (99.3)	1.00	1.00
Yes	4 (3.3)	3 (0.7)	1.01 (0.55–1.87)	0.33 (0.21–1.51)
Paint contact				
No	186 (92.5)	381 (93.8)	1.00	1.00
Yes	15 (7.5)	25 (6.2)	1.06 (0.68–1.65)	1.06 (0.52–2.15)
Pesticide contact				
No	197 (98.0)	396 (97.5)	1.00	1.00
Yes	4 (2.0)	10 (2.5)	0.96 (0.50–1.85)	1.14 (0.70–1.85)
Analgesic usage				
No	157 (78.1)	309 (75.1)	1.00	1.00
Yes as usual	24 (11.9)	14 (3.4)	3.25 (1.56–6.76)§	3.83 (1.75–8.40)§
Yes as the need arises	20 (10.0)	83 (20.5)	0.58 (0.34–1.00)	0.29 (0.14–0.60)§

CI, confidence interval
* Adjusted for age and gender.
† Adjusted for age, gender, educational level, paternal and maternal ethnicities, and hypertension and diabetes histories.
‡ $P < 0.05$.
§ $P < 0.01$.

and diabetes history. Third, the subjects with low plasma lycopene levels and habitual analgesic use had a further increased risk for CKD. These findings may be explained by several hypotheses. First, lycopene is a potent antioxidant shown to quench reactive oxygen species in vitro [26] and to diminish oxidative stress biomarkers of serum thiobarbituric acid-reactive substances in vitro [27]. Second, lycopene can attenuate inflammatory cytokine-stimulated endothelial cell adhesion molecule expression [28]. It is possible that high plasma lycopene levels are inversely associated with CKD through lycopene decreasing the oxidative stress and attenuating the inflammation.

In this study, there was no correlation between the plasma retinol level and GFR; however, it was found that study subjects with high plasma retinol had a higher risk of CKD than those with a low plasma retinol. In addition, the OR of CKD was significantly increased to 8.06 or 2.05 for subjects with the highest or higher plasma retinol levels than those with a low retinol level after adjusted multiple risk factors. The elevated plasma retinol in patients with CKD is consistent with a previous study in which it was found that increased plasma retinol and retinol-binding protein (RBP) levels in patients with chronic renal failure [29,30] may be due to reduced vitamin excretion and decreased conversion of retinol to retinoic acid [31]. An animal study also observed an increase of serum retinol in the nephrectomized rats, suggesting the increase in retinol is associated with RBP, coupled with the thyroxine-binding protein, and the upregulation of the hepatic release mechanism in renal disease [32]. It has been suggested that plasma RBP might be a biomarker of nephropathy [33–35], and there is a strong correlation between the plasma retinol and RBP levels [29]. Based on these findings, high plasma retinol may be a biomarker related to the CKD risk. However, we cannot exclude both findings regarding the association between retinol and lycopene levels with low GFR in this study as the result rather than the cause for a low GFR.

The possibility that long-term ingestion of analgesics leads to renal pathology and renal failure is controversial. There is evidence of a relation between the ingestion of phenacetin-containing analgesics and kidney disease [36]. An early study reported that lifetime regular acetaminophen use was related to CKD [37], and another study found that subjects who often take acetaminophen or non-steroidal anti-inflammatory drugs have an increased risk of end-stage renal disease, but not for those who often take aspirin [38]. We cannot explain why subjects who used analgesics on an as-needed basis had a lower CKD risk than never-users; perhaps the appropriate use of analgesics can prevent CKD [39]. In this study we found that analgesic users had a significantly higher CKD risk than non-users. Long-term use of analgesics leads to renal injury through chronic interstitial fibrosis with or without papillary necrosis [40], damage is generally irreversible, and progression to renal failure occurs.

Table 3
Dose–response relation between chronic kidney disease risk and plasma level of antioxidant micronutrients

Variables	Cases/controls	Odds ratio* (95% CI)	Odds ratio† (95% CI)
Retinol (μg/dL)			
< 107.6	21/136	1.00	1.00
107.6–163.0	46/136	2.15 (1.22–3.81)§	2.05 (1.03–4.03)‡
≥ 163.0	134/136	6.35 (3.79–10.67)‖	8.06 (4.25–15.17)‖
P for trend		<0.0001	<0.0001
α-Tocopherol (μg/dL)			
< 818.7	65/136	1.00	1.00
818.7–1153.9	88/136	1.47 (0.98–2.13)	1.60 (0.94–2.52)
≥ 1153.9	48/136	0.81 (0.51–1.27)	1.06 (0.61–1.79)
P for trend		0.40	0.77
Lycopene (μg/dL)			
< 7.7	108/136	1.00	1.00
7.7–18.0	52/136	0.46 (0.29–0.72)‖	0.49 (0.29–0.83)§
≥ 18.0	41/136	0.35 (0.22–0.56)‖	0.32 (0.18–0.58)‖
P for trend		<0.0001	<0.0001
β-Carotene (μg/dL)			
< 17.2	61/136	1.00	1.00
17.2–40.3	66/136	1.14 (0.74–1.75)	1.10 (0.66–1.85)
≥ 40.3	74/136	1.31 (0.85–2.01)	1.29 (0.77–2.15)
P for trend		0.22	0.33

CI, confidence interval
* Adjusted for age and gender.
† Adjusted for age, gender, educational level, paternal and maternal ethnicities, cigarette smoking, coffee drinking, analgesic usage, and hypertension and diabetes histories.
‡ $P < 0.05$.
§ $P < 0.01$.
‖ $P < 0.001$.

Diclofenac-induced non-steroidal anti-inflammatory drug nephrotoxicity involves oxidative stress, which translates into orderly fragmentation of genomic DNA leading to apoptotic death in the kidney [41].

Our study has some important limitations that need to be considered when interpreting our results. First, selection bias was minimized even though cases and controls were recruited from two different hospitals, because these hospitals belonged to medical centers and were located in Taipei. Furthermore, the majority of cases and controls lived in Taipei and were similar to each other with respect to dietary habits. Possible selection bias may have occurred because the recruited controls were more likely women, with less elementary school education, and less often Fukien Taiwanese than the CKD cases. However, in a large-scale screening program, it has been reported that men had a higher rate of CKD than women, and subjects with a low level of education had a higher CKD risk than subjects with a high level of education in Taiwan [24]. Second, we could not validate the self-reported analgesic use because of the lack of independent records for these medications. In addition, we did not collect information on the kind of analgesics and the duration of their use. Therefore, we could not evaluate the different kinds of analgesics and the consumption of certain cumulative amounts of an analgesic for the CKD risk. Many people in Taiwan access traditional Chinese medicine and folk medicine; however, we had no information about herbal remedies in this study, and we cannot exclude the possibility that analgesic-adulterated herbs may have accounted for our findings, at least in part. Third, the accuracy of one-spot evaluation of plasma antioxidants may be in doubt. However, the values might be reliable with no accompanying changes in lifestyle in all subjects. Fourth, because of the small sample, statistical significance should be interpreted with caution.

In conlusion, this is, to our knowledge, the first study showing that a low plasma lycopene level is associated with CKD risk.

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Table 4
Multiple logistical regression analysis effects of combination of antioxidant micronutrient levels and analgesic use status on chronic kidney disease

Variables	Analgesic use status	Cases/controls	Odds ratio* (95% CI)	Synergy index
Retinol (μg/dL)				1.15 (0.41–3.11)
≥ 135.8	No/yes as the need arises	142/193	1.00	
	Yes as usual	21/8	3.46 (1.36–8.04)†	
< 135.8	No/yes as the need arises	34/199	0.22 (0.13–0.36)‡	
	Yes as usual	5/6	1.53 (0.33–7.09)	
P for trend			<0.0001	
Lycopene (μg/dL)				6.09 (0.11–216.01)
≥ 12.7	No/yes as the need arises	49/176	1.00	
	Yes as usual	10/24	4.54 (1.31–15.71)†	
< 12.7	No/yes as the need arises	125/183	2.97 (1.76–5.01)‡	
	Yes as usual	19/23	12.82 (3.71–44.33)‡	
P for trend			<0.0001	

CI, confidence interval
* Adjusted for age, gender, educational level, paternal and maternal ethnicities, cigarette smoking, coffee drinking, and hypertension and diabetes histories.
† $P < 0.05$.
‡ $P < 0.001$.

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