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Low Serum Folate is Associated with Increased Risk of Chronic Kidney Disease Independently of Oxidative Stress and Antioxidant Capacities

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Abstract

Hyperhomocysteinemia, increased oxidative stress and decreased antioxidant defense function have been shown to be associated with the risk of chronic kidney disease (CKD) and may cause later developments of vascular disease and cancer in CKD patients. Folate involves in homocysteine metabolism and DNA synthesis and its deficiency may cause hyperhomocysteinemia and cancer development. The purpose of this study was to determine the associations of folate with homocysteine, oxidative stress indicators and antioxidant capacities in patients with CKD of stage 2-3, and to further analyze their relationships with respect to risk for CKD. 97 CKD patients and 135 healthy subjects were recruited. Patients with CKD had significantly higher levels of malondialdehyde and total antioxidant capacities, but had significantly lower activities of glutathione peroxidase, glutathione *S*-transferase and superoxide dismutase when compared to healthy subjects. Serum folate was significantly negatively associated with plasma homocysteine in the case group with and without adjusting confounders. However, there were no any significant associations of folate with oxidative stress indicators and antioxidant capacities in CKD patients and healthy subjects. Subjects with lower serum folate concentration exhibited significantly increased risk of CKD without or with (OR, 0.94; 95% CI, 0.88 – 1.00) adjustment for homocysteine, indicators of oxidative stress and antioxidant capacities. Decreased folate was strongly associated with the risk of CKD independently of homocysteine, oxidative stress indicators and antioxidant capacities.

Introduction

Hyperhomocysteinemia is often seen in patients with CKD, and is associated with the later development of vascular disease in CKD patients. Deficient folate may cause hyperhomocysteinemia which has been shown to be a new potential oxidative stress indicator via its impact on folate status. Increased oxidative stress and decreased antioxidant capacities have also been shown to be associated with the risk of CKD and may cause later cancer development in CKD patients. Folate not only plays an important role in homocysteine metabolism, but also involves in DNA synthesis and its deficiency may cause DNA damage and further lead to cancer development. Although deficient folate might be associated with hyperhomocysteinemia and possibly increased oxidative stress in patients with CKD, it is unclear whether folate, homocysteine and oxidative stress are independently related to risk for CKD or whether they mediate the risk of CKD in connection with each other.

Purpose

To determine the associations of folate with homocysteine, oxidative stress indicators and antioxidant capacities in patients with CKD of stage 2-3, and to further analyze their relationships with respect to risk for CKD.

Subjects & Methods

Subjects

Case group: Consecutive patients were recruited at the outpatient clinic of the division of nephrology of Taichung Veterans General Hospital, Taiwan if they were in stage 2 (eGFR: 60-89 mL/min/1.73m^2] or stage 3 (eGFR: 30 – 59 mL/min/1.73m^2) of CKD. Patients' diagnosis and CKD staging were confirmed by the nephrologist. Patients were excluded if their ages were less than 20 y or greater than 80 y, clinical unstable, pregnant, lactating, had history of cardiovascular disease, cancer or alcoholism, or were taking any medication which could influence folate status.

Healthy group: Healthy subjects who exhibited normal blood biochemical values were recruited from the health management center of Taichung Veterans General Hospital, Taiwan. Subjects were excluded when their ages were less than 20 y or greater than 80 y, had history of gastrointestinal disorder, cardiovascular diseases, liver or renal diseases, diabetes, cancer, alcoholism, or other metabolic diseases.

Experimental protocol

Demographic data: Subjects' age, gender, smoking and drinking habits, family history and medication uses were recorded. The body mass index was calculated from height and weight measurements. Blood pressure was measured. Fasting venous blood samples were collected as required estimating hematological entities and biochemical measurements.

Biochemical measurement: Fasting serum albumin, creatinine, high sensitivity C-reactive protein, total serum cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, plasma homocysteine, serum folate, malondialdehyde, antioxidant enzyme activities were measured.

Results

Table 1. Characteristics of healthy subjects and subjects with CKD[1]

Characteristics	Case group (n = 97)	Control group (n = 135)
Age (y)	53.25 ± 15.17	51.73 ± 8.47
Gender (Male / Female)	66 / 31	89 /46
Body mass index (kg/m^2)	24.03 ± 3.45	24.73 ± 3.57
Blood pressure (mmHg)		
Systolic	129.27 ± 13.24[a]	121.02 ± 15.81[b]
Diastolic	77.08 ± 9.14	77.67 ± 10.87
Serum albumin (g/dL)	4.40 ± 0.32[a]	4.49 ± 0.24[b]
Serum creatinine (mg/dL)	1.41 ± 0.34[a]	0.85 ± 0.20[b]
Serum hs-CRP (mg/dL)	0.14 ± 0.27	0.17 ± 0.36
Lipid profiles		
Triglycerides (mg/dL)	138.11 ± 81.72	151.23 ± 117.81
Total cholesterol (mg/dL)	180.13 ± 35.13[a]	203.16 ± 38.03[b]
High-density lipoprotein (mg/dL)	56.68 ± 16.42	55.12 ± 15.58
Low-density lipoprotein (mg/dL)	109.68 ± 30.56[a]	117.80 ± 31.84[b]
CKD Stage at diagnosis (n, %)		
Stage II	33 (34.02%)	–
Stage III	64 (65.98%)	–
Current smoking habit[1] (n, %)		
Yes	9 (9.28%)	31 (22.96%)
No	88 (90.72%)	100 (74.07%)
Current drinking habit[2](n, %)		
Yes	15 (15.46%)	41 (30.99%)
No	82 (84.54%)	90 (66.67%)

Values are means ± standard deviation. Hs-CRP, high sensitivity C-reactive protein; CKD, chronic kidney disease. Values with different superscript letter are significantly different between two groups; $p < 0.05$. [1]There are four missing data in the control group. [2]There are four missing data in the control group.

Table 2. Homocysteine, folate, oxidative stress and antioxidant capacities in healthy controls and patients with CKD.

	Case group (n = 97)	Control group (n = 135)
Homocysteine (μmol/L)	14.86 ± 4.17[a]	12.18 ± 4.89[b]
≥ 14 μmol/L (n, %)	56, 56.57%	34, 25.19%
Folate (ng/mL)	12.28 ± 7.01[a]	15.71 ± 8.62[b]
< 3 ng/mL (n, %)	1, 1.01%	0
Oxidative stress indicators		
Malondialdehyde (μmol/L)	1.09 ± 0.33[a]	0.91 ± 0.22[b]
Antioxidant capacities		
Total antioxidant capacity (μmol/L)	4433.58 ± 550.85[a]	4320.34 ± 431.79[b]
Glutathione peroxidase (nmol/mL/min)	132.86 ± 59.39[a]	146.85 ± 34.89[b]
Glutathione S-transferase (nmol/mL/min)	34.06 ± 19.62[a]	43.77 ± 31.15[b]
Superoxide dismutase (U/mL)	7.87 ± 5.41[a]	12.20 ± 3.44[b]

Values are means ± standard deviation.
Values with different superscript letter are significantly different between two groups; $p < 0.05$

Table 3. The odds ratios (ORs) for the risk of CKD

	Factors adjusted for[1]			Factors adjusted for[2]			Factors adjusted for[3]		
	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*
Homocysteine (μmol/L)	1.17	1.07 – 1.27	< 0.01	1.12	1.01 – 1.24	0.03	1.08	0.98 – 1.19	0.14
Folate (ng/mL)	0.92	0.88 – 0.97	< 0.01	0.93	0.88 – 0.99	0.02	0.94	0.88 – 1.00	0.04
Serum folate (ng/mL)									
≤ 8.88	1			1			1		
8.89 – 11.83	0.55	0.22 – 1.33	0.18	0.85	0.29 – 2.50	0.76	0.88	0.29 – 2.62	0.81
11.84 – 16.45	0.22	0.09 – 0.62	< 0.01	0.27	0.08 – 0.92	0.04	0.29	0.09 – 1.00	0.05
> 16.45	0.15	0.06 – 0.43	< 0.01	0.17	0.05 – 0.62	0.01	0.19	0.05 – 0.69	0.01

[1]Adjusted for age, gender, body mass index, systolic blood pressure, serum albumin, smoking and drinking habits (model 1).
[2]Adjusted for model 1 and additionally adjusted for malondialdehyde, activities of glutathione *S*-transferase, glutathione peroxidase and superoxide dismutase (Model 2).
[3]Adjusted for model 2 and additionally adjusted for homocysteine and folate.

Conclusion

Low serum folate concentration significantly increased the risk of CKD regardless of plasma homocysteine, oxidative stress and antioxidant capacities. Adequate serum folate status (> 16.45 ng/mL) seems to be an important factor to reduce the risk of stage 2-3 CKD.