Original Paper

Association of Circulating Levels of ADMA with Carotid Intima-Media Thickness in Patients with CKD: a Systematic Review and Meta-Analysis

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Key Words

Chronic kidney disease • Asymmetric dimethylarginine • Carotid intima-media thickness • Atherosclerosis • Meta-analysis

Abstract

Background/Aims: The incidence of cardiovascular disease in patients with chronic kidney disease (CKD) is significantly higher than that in the general population. Carotid intima-media thickness (CMT) is considered to be an important predictor of atherosclerosis. Asymmetric dimethylarginine (ADMA) acted as an endogenous nitric oxide synthase inhibitor, which was elevated in patients with CKD, but whether plasma ADMA correlate with the CMT in CKD patients is still not elucidated. **Methods:** We searched the PubMed, Cochrane Library and Embase electronic database. A total of 334 related articles were retrieved, after screened by the inclusion and exclusion criterions, 6 articles were selected. **Results:** After an overall pooled estimate of correlation coefficient (R) within the 6 articles, we found that levels of circulating ADMA were positively related to CMT in the patients with CKD. Furthermore, the partial correlation coefficient (PR) was used to reduce the interference caused by the hybrid factors. After correction of other risk factors, it also turned out that levels of circulating ADMA were positively related to CMT. **Conclusion:** Circulating levels of ADMA in CKD patients were positively related to CMT, which could be a predictor of early-onset atherosclerosis and atherosclerotic disease in patients with CKD.

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Introduction

Cardiovascular disease has become the most common chronic disease in most countries around the world, and is the important burden of global public health [1]. The incidence of cardiovascular disease in patients with chronic kidney disease (CKD) is significantly higher than that in the general population. Early atherosclerosis was known as subclinical atherosclerosis [2], which was manifested as an increase in carotid intima-media thickness (CIMT). Sibal L al [3] confirmed that atherosclerotic lesions occurred earlier in carotid artery than the coronary artery. Therefore, CIMT was considered to be a predictor of atherosclerosis [4].

Endothelial dysfunction was a key factor in the progression of atherosclerotic cardiovascular disease [5]. The integrity of endothelial function was closely related to the stable condition of nitric oxide system [6]. Asymmetric dimethylarginine (ADMA) is one of the products of the protein metabolism process and act as an endogenous nitric oxide synthase (NOS) inhibitor. It is produced by methylation of arginine residues via protein arginine N-methyltransferases in intracellular proteins [7]. Generally, ADMA can competitively inhibit the activity of NOS and reduce the production of nitric oxide in endothelial cells, thus lead to the dysfunction of endothelial cells, which played a significant role in the progression of atherosclerosis [8]. The level of circulating ADMA was confirmed to elevate in patients with CKD [9], some studies also showed that elevated levels of circulating ADMA were associated with myocardial ischemia and stroke in CKD patients [10-13], but whether plasma ADMA can be used as a predictor of cardiovascular disease in the CKD patients is still not elucidated. Accordingly, we performed a systematic review and meta-analysis to investigate the association of circulating levels of ADMA with CIMT in the CKD patients.

Materials and Methods

Literature search

We systematically searched the PubMed, Cochrane Library and Embase electronic database with the strategy of using the keywords '(L-arginine OR ADMA OR asymmetric dimethylarginine), (carotid intima media thickness OR atherosclerosis) AND (CKD OR chronic kidney diseases)'. Relevant studies were identified up to March 29, 2017, and the search was limited to studies using the "English" language.

Study selection

A total of 334 articles were retrieved, all articles searched were screened and extracted by 2 independent authors to identify trials according to the inclusion and exclusion criterions, differences were solved by discussion. Inclusion criterions were studies had investigated the association between ADMA and CKD patients, articles that provided the data of circulating ADMA, CIMT and R value, research type was of prospective or cross-sectional study, the original article. Studies were excluded if (1) they were review articles, guidelines, consensus statements, letters, editorials, and conference abstracts; (2) the data was not yet published, repeated or ongoing research; (3) Studies in which plasma ADMA, CIMT or R level were not measured.

Statistical analysis

Statistical analyses of the enrolled patients were figured up by Stata software (version 12.0). I^2 statistics was used to measure the proportion of total variation due to heterogeneity beyond chance. $P < 0.05$ was considered of statistical significance. Two authors assessed the risk of bias of the included studies based on the criterions in the Cochrane Handbook version 5.0.1. Random-effects model was used when studies were thought to have significant heterogeneity as $I^2 \geq 50\%$ and $P < 0.1$. In contrast, the fixed-effects model was used in case of no significant heterogeneity ($I^2 < 50\%$ and $P \geq 0.1$).

Fig. 1. Flow diagram of the trial selection process.

Results

Search results

A total of 334 related articles were retrieved in a combined search of the PubMed, Cochrane Library and Embase electronic database by following the above search method. 295 articles were excluded by reading the title and abstract. Among the 39 articles retrieved in completed form, 7 were excluded for lack of CIMT level, 15 were excluded for lack of ADMA plasma level, 5 for investigating the correlation between other cardiovascular risk with CIMT and 6 studies for repeated reports. Finally, 6 articles [14-19] including 5 cross-sectional studies and 1 prospective study that involving 616 patients were included in the study (Fig. 1).

Study characteristics

Main features of included studies were provided in Table 1. Among the 616 subjects involved, 358 were males and 258 were females. Data of correlation coefficient (R) was found from 6 studies. Traditional cardiovascular risk factors, such as age, sex, plasma lipids and blood pressure were corrected in these studies. Multiple regression analyses were reported in these 6 studies, in which the relations between circulating ADMA concentration and CIMT were adjusted for possible confounders (Table 2).

Association of ADMA levels with CIMT

We overall pooled estimate of R within the 6 articles by using the statistical software. Then taking into consideration of the I^2 value was larger than 50% ($I^2=73\%$), which may

lead to notably heterogeneity, we used a random effect model, and the result obtained showed that levels of circulating ADMA were positively related to CIMT in the patients with CKD ($R=0.38$; 95%CI: 0.31-0.46, $P=0.002$) (Fig. 2).

In view of the result may be interfered by the hybrid factors, we swotted the partial correlation coefficient, by an overall assessment of PR, random effect model was also selected consider for the heterogeneity ($I^2=62.8\%$). After correction of other risk factors, similar ultimateness turned out that levels of circulating ADMA were positively related to CIMT (PR=0.38; 95%CI: 0.31-0.46, $P=0.03$) (Fig. 3).

The relations between circulating ADMA concentration and CIMT were adjusted for possible confounders were show in Table 2. Multiple regression analyses were reported in all of these 6 studies, the value of correlation coefficient can be found in these articles, funnel plot that use effect size as the abscissa, and sample volume as the ordinate was a commonly adopted method to identify publication bias (Fig. 4).

Table 1. Main features of included studies

Author	Publication	study-design	Enrollment	Age	Male	Population
Zoccali, C, et al	2002	Prospective	90	57.0±13.9	51	CKD(HD patients)
Nanayakkara, et al	2005	Cross-sectional	93	53.0±12.0	53	CKD
Kumagai, H, et al	2006	Cross-sectional	197	56.9±8.6	132	CKD(HD patients)
Zhang, W. R., et al	2006	Cross-sectional	138	52.0	81	CKD
Kocak, H, et al	2008	Cross-sectional	30	42.0±13.0	16	CKD(PD Patients)
Petrica, L, et al	2011	Cross-sectional	68	58.1±7.1	25	CKD (early DN)

Table 2. Effects of correlation coefficient and partial correlation coefficient

Author	Publication	N	Correlation R	coefficient 95%CI	(R) P	Partial PR	correlation 95%CI	Coefficient(PR) P
Zoccali, C, et al	2002	90	0.32	(0.12, 0.49)	0.002	0.28	(0.08,0.46)	0.01
Nanayakkara, et al	2005	93	0.46	(0.28,0.61)	<0.0001	0.45	(0.27,0.60)	<0.0001
Kumagai, H, et al	2006	197	0.32	(0.19,0.44)	0.0009	0.00	(-0.14,0.14)	NS
Zhang, W. R., et al	2006	138	0.4	(0.33,0.59)	0.001	0.33	(0.17,0.47)	<0.001
Kocak, H, et al	2008	30	0.5	(0.18,0.74)	<0.01	0.54	(0.22,0.75)	<0.01
Petrica, L, et al	2011	68	0.2	(0.02,0.47)	<0.001	0.40	(0.18,0.58)	0.001

Fig. 2. Forest plot for the correlation coefficient (R) between circulating levels of ADMA and CIMT. CI, confidence interval.

Fig. 3. Forest plot for the partial correlation coefficient (PR) between circulating levels of ADMA and CIMT adjusted for possible confounders. CI, confidence interval.

Fig. 4. Funnel plot for estimation of the potential publication bias for the association between plasma ADMA and CIMT.

Discussion

The levels of circulating ADMA were confirmed to elevate in CKD patients, but there was still lack of sufficient researches to show whether plasma ADMA can be used as a predictor of cardiovascular disease in these patients. Our meta-analysis included data from 616 patients aimed to confirm the association of circulating levels of ADMA with CIMT in CKD patients. After the comprehensive selection and analysis of these eligible documents, the results showed that the circulating levels of ADMA were positively related to CIMT in CKD patients, indicating that elevated circulating level of ADMA could be a predictor of early-onset atherosclerosis and atherosclerotic disease in patients with CKD.

Numbers of studies have shown that cardiovascular disease became the most common chronic disease with the progress of society and changes of people's life, which was an important burden of global public health in most countries [20-22]. Accumulating evidences suggested that endothelial dysfunction was one of the critical determinants in pathogenesis of atherosclerotic cardiovascular disease, and angiocardopathy such as myocardial infarction, stroke, and vascular remodeling was independently associated with endothelial dysfunction [23-26]. Oxidative stress, inflammatory response and active material imbalance are involved in the progress of vascular endothelial injury [27]. Nitric oxide played a broad role in the physiological and pathological activities of the human body, and it involves in cardiovascular disease, inflammatory response, nerve conduction and respiratory regulation [28]. ADMA, known as an endogenous inhibitor of nitric oxide synthase, may contributed to endothelial dysfunction and organ failure in sepsis by endogenously inhibiting the synthesis of nitric oxide [29].

In 1992, Vallance et al. firstly suggested that elevated ADMA may increase cardiovascular risk in patients with CKD [30]. Miyazaki et al. showed that plasma ADMA levels were positively correlated with risk factors for atherosclerosis, and plasma ADMA levels were associated with carotid intima-media thickness [31]. In the following 17 years, more than 600 studies have thoroughly investigated the relationship between ADMA and adverse cardiovascular disease. These studies almost suggested that ADMA was not only associated with both traditional and nonvolatile risk factors, but also was strongly related with left ventricular hypertrophy and CIMT elevation [32-34]. Koch et al. found that serum ADMA concentrations were significantly elevated in critically ill patients, associated with organ failure and related to short- and long-term mortality risk [35]. However, there were some studies resulted in various extent of relation between ADMA and CIMT negatively. A clinical study of the safety and efficacy of the use of nitric oxide synthase inhibitors in patients with septic shock found that non-selective nitric oxide synthase inhibitors increased mortality in patients, suggesting that plasma ADMA could reduce the risk of death in septic shock patients by increasing response to vasoconstrictors, thus reducing the incidence of hypotension [36]. Due to the inconsistency of the conclusions, we conducted a systematic screen of the relevant literature, following a critically appraise methods, to find the relationship between plasma ADMA concentration and CIMT with CKD.

We comprehensive searched the PubMed, Cochrane Library, and Embase electronic database, with the deadline of March 29, 2017. According to the inclusion and exclusion criteria, 334 articles were retrieved. Then 295 articles were excluded by reviewing the title and abstract because the irrelevant content. After screening full-texts of 39 articles, 33 articles were eliminated for did not meet the inclusion criterias. Therefore, we finally included 6 studies in our research. Across all studies that were enrolled in this meta-analysis, we firstly estimated the correlation coefficient within the 6 articles to estimate the relationship between circulating ADMA levels and CIMT, which represents the linear relationship between two variables, that is the net effect of the variable on the dependent variable. Results showed that the severity of CIMT increased, as the levels of ADMA in these patients fortified. This result indicated that higher circulating ADMA levels were positively correlated with CIMT in patients with CKD. The first concern about our analysis was that the

effects could be caused by confounding factors, taking into account the results may be affected by age, gender, blood lipid levels and blood pressure etc, we used the partial correlation coefficient, which presented the correlation coefficient between ADMA levels and CIMT adjusted for possible confounders. Same result also showed that the higher plasma ADMA level, the thicker the internal carotid artery intima ($P=0.03$). Another concern arised from the heterogeneity among these trials, to hinder the heterogeneity in these included articles, we further used the random effect model to solve the heterogeneity. The I^2 calculation in our meta-analysis was 73% and 62.8%, both R and PR showed significant differences ($P<0.05$) in this model, it served as the evidence for statistical significant heterogeneity across studies, indicating that our results did not exist false negative. Then taking into account the publication bias, it in favor of positive findings influences the distribution of published results. For only published studies were included in our meta-analysis, thus could cause publication bias which tend to overestimate the ADMA effect. At the same time, the negative results of researches were often published in local magazines, and international journals in English were generally incorporated positive results, this may contribute to lingual bias, it can be reduced by increasing sample size. Funnel plot with the standard error of the PR difference plotted against the mean difference of PR of each study, was used to estimate the potential publication bias for the association between plasma ADMA and CIMT. By visually at inspection of funnel plots, no evidence of small-study bias was found for R nor PR. To our knowledge, there was limited large-scale meta-analysis quantifying the association between plasma ADMA levels and CIMT in CKD patients. Our study may contribute to the clinical diagnosis of subclinical atherosclerosis and provide new ideas for treatment.

Conclusion

In the meta-analysis of prospective and cross-sectional studies, we observed the association of circulating levels of ADMA with CIMT in the patients with CKD. These findings suggested that elevated circulating ADMA concentration was not only a marker of subclinical atherosclerosis but also was a predictor of atherosclerotic disease in these patients. Although the results of the research were promising, there were still inadequacies and limitations need to be point out. The number of the included studies and participants of each study were relatively small, the results of meta-analysis still need to be confirmed in longitudinal studies. We hope more longer follow-up, higher quality researches to be made in this related fields.

Disclosure Statement

The authors declare that they have no conflict of interest.

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The following states the contributions of each author to this article. Fang Wang: study design, data collection, data interpretation, literature search and manuscript draft; Ruifang Xiong: data collection, statistical analysis and literature search; Sujuan Feng: study design, statistical analysis, literature search and manuscript draft; Xiangxue Lu: data collection, statistical analysis and data interpretation; Han Li: study design, statistical analysis, literature search and funds collection; Shixiang Wang: data interpretation, literature search and factual content.

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