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Editorial Comment

EDITORIAL COMMENT

Ascorbic acid: a promising agent in chronic kidney disease?

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ABSTRACT

Asymmetric dimethylarginine (ADMA), an endogenous nitric oxide synthase inhibitor, is related with impaired endothelial function and poor outcomes in chronic kidney disease (CKD) patients. In addition, oxidative stress and inflammation are also a common problem in CKD patients, and both have an important role in the development and progression of atherosclerosis and increased cardiovascular events in CKD. Ascorbic acid might be a promising agent in CKD for improving outcome by decreasing oxidative stress and ADMA levels.

Keywords: ascorbic acid, cardiovascular disease, inflammation

In this issue of *Clinical Kidney Journal*, Gillis *et al.* [1] investigated the effect of ascorbic acid on oxidative stress and endothelial function in chronic kidney disease (CKD) and hypertension (HTN). They conducted a crossover study on 20 CKD patients with intravenous saline and ascorbic acid and a cohort of 30 HTN patients. The authors found that baseline ascorbic acid levels were lower in CKD patients compared with HTN patients. In addition, they showed that administration of ascorbic acid significantly reduced the levels of asymmetric dimethylarginine (ADMA) in CKD patients, as well as central blood pressure and augmentation index in both CKD and HTN patients, whereas it increased total antioxidant potential (TAP) and superoxide levels in both groups. This study yielded no significant changes in flow-mediated dilatation (FMD) [2].

ADMA, an endogenous nitric oxide synthase inhibitor, plays an important role in endothelial dysfunction and is associated with poor outcomes in CKD patients [3]. Kanbay *et al.* [3] showed that increased levels of ADMA are associated with a higher risk of all-cause mortality and/or cardiovascular events. Therefore, lowering ADMA levels might improve outcomes in CKD patients. Oxidative stress and inflammation are also a common problem in CKD patients, and both play an important role in the development of atherosclerosis and are independently associated with cardiovascular disease in CKD patients [4–6].

This article presents a broad view of the effects of ascorbic acid on several non-conventional risk factors of cardiovascular disease, with a special focus on the vascular component of cardiovascular disease. The authors used more than one parameter for the assessment of each category (endothelial function, oxidative stress and arterial function), thus enhancing the validity and significance of the results. Examining the effects on endothelial function, oxidative stress and arterial function in the same study allows a compact approach to this topic.

Gillis *et al.* [1] provided extensive data on the antioxidant potential of ascorbic acid and its effect on oxidative stress using a wide variety of biomarkers, including ADMA, TAP, F2-isoprostanes, glutathione (GSH)/glutathione disulfide (GSSG) and oxygen production. Additionally, the evaluation of clinical predictors of the

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change in ADMA levels is noteworthy and builds a bridge between clinical data and molecular biomarkers, implicating its possible future use in clinics. In short, the in-depth investigation of oxidative stress in this article distinguishes it from other studies.

However, the generalizability of the results of this study should be considered. In this study, haemodialysis patients and patients suffering from diabetes were excluded. Although the study included eight peritoneal dialysis patients, the exclusion of haemodialysis patients might have led to bias and hence the results do not represent CKD patients requiring haemodialysis. Moreover, haemodialysis patients, which constitutes the biggest group, decreases the reflectivity of the study. Another previous study done in haemodialysis patients was also excluded patients with diabetes mellitus of which limits the generalizability of their findings since almost half of the CKD patients have diabetes mellitus [7]. Therefore, this aspects needs to be questioned.

Another drawback of this study is the sample size and study design. This is a crossover study combined with a cohort, which makes it constitutionally less reliable than a randomized controlled trial (RCT), and the results would have been ideal as outcomes derived from an RCT. On the other hand, as the authors acknowledge, the sample size was calculated according to the FMD and any statistically significant changes in the other parameters, such as differences in ADMA levels, might have been due to chance. To circumvent this, the authors could have calculated for, and used, the biggest sample size for all parameters investigated.

One small note is that HTN patients were used as controls and these patients might also have vascular dysfunction due to the nature of the disease. This could mask the real difference between CKD patients and healthy subjects, because of possible hidden vascular damage in HTN patients.

Another major drawback of the study is the lack of data on antihypertensive medications. This is a very important issue, given the fact that the study population was composed of CKD and HTN patients who probably were on one or more antihypertensive drugs, although no comparative data were available regarding this issue. We believe that this is a significant concern, since antihypertensive medications may affect endothelial dysfunction and ADMA levels differently. For example, angiotensin-converting enzyme (ACE) inhibitors have beneficial effects on endothelial dysfunction [8]. However, beta-blockers have less favourable effects on endothelial dysfunction compared with ACE inhibitors [9]. Previous studies have shown that treatment with ACE inhibitors and angiotensin receptor blockers (ARBs) reduces ADMA levels in the general population [10–11].

In a recent meta-analysis, a significant reduction in the augmentation index was seen with ACE inhibitors, ARBs, calcium channel blockers and diuretics. However, beta-blockers, alpha-blockers, nicorandil and moxonidine non-significantly reduced the augmentation index. It was concluded that beta-blockers are not as beneficial as the other antihypertensives in reducing central blood pressure and the augmentation index [12]. However, in maintenance haemodialysis patients, it was found that short-term ACE inhibitors increased ADMA levels, whereas ARBs did not [13]. In another study, nebivolol decreased ADMA levels in hypertensive patients [14]. Given this background, the relationship between endothelial dysfunction, ADMA levels and antihypertensive medications is of great importance, and this article lacks this valuable information.

Finally, this article provides new results on ascorbic acid infusion decreasing ADMA levels, as well as blood pressure, which could add to the existing literature. However, it does not resolve the conflict in the current literature about the effect of ascorbic acid on endothelial function, as there is no significant change in FMD. This study is important in terms of new data on the effect of ascorbic acid on oxidative stress, endothelial function and blood pressure. While it adds to the literature, the findings should be evaluated with caution. There is still the need for a randomized, double-blind, placebo-controlled study comprising a bigger sample population, which would include diabetic patients and long-term follow-up, with a view to enhancing the generalizability of the results.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Gillis K, Bell E, Patel RK *et al*. Ascorbic acid lowers central blood pressure and ADMA in chronic kidney disease. *Clin Kidney J* 2018; in press
2. Taddei S, Virdis A, Ghiadoni L *et al*. Vitamin C improves endothelium-dependent vasodilation by restoring nitric oxide activity in essential hypertension. *Circulation* 1998; 97: 2222–2229
3. Kanbay M, Afsar B, Siriopol D *et al*. Relevance of uric acid and asymmetric dimethylarginine for modeling cardiovascular risk prediction in chronic kidney disease patients. *Int Urol Nephrol* 2016; 48: 1129–1136
4. Solak Y, Afsar B, Vaziri ND *et al*. Hypertension as an autoimmune and inflammatory disease. *Hypertens Res* 2016; 39: 567–573
5. Kanbay M, Afsar B, Siriopol D *et al*. Endostatin in chronic kidney disease: associations with inflammation, vascular abnormalities, cardiovascular events and survival. *Eur J Intern Med* 2016; 33: 81–87
6. Kanbay M, Ikizek M, Solak Y *et al*. Uric acid and pentraxin-3 levels are independently associated with coronary artery disease risk in patients with stage 2 and 3 kidney disease. *Am J Nephrol* 2011; 33: 325–331
7. Cross JM, Donald AE, Nuttall SL *et al*. Vitamin C improves resistance but not conduit artery endothelial function in patients with chronic renal failure. *Kidney Int* 2003; 63: 1433–1442
8. Shahin Y, Khan JA, Samuel N *et al*. Angiotensin converting enzyme inhibitors effect on endothelial dysfunction: a meta-analysis of randomised controlled trials. *Atherosclerosis* 2011; 216: 7–16
9. Peller M, Ozierański K, Balsam P *et al*. Influence of beta-blockers on endothelial function: a meta-analysis of randomized controlled trials. *Cardiol J* 2015; 22: 708–716
10. Ito A, Egashira K, Narishige T *et al*. Renin-angiotensin system is involved in the mechanism of increased serum asymmetric dimethylarginine in essential hypertension. *Jpn Circ J* 2001; 65: 775–778
11. Willoughby SR, Rajendran S, Chan WP *et al*. Ramipril sensitizes platelets to nitric oxide: implications for therapy in high-risk patients. *Am Coll Cardiol* 2012; 60: 887–894
12. McGaughey TJ, Fletcher EA, Shah SA. Impact of antihypertensive agents on central systolic blood pressure and augmentation index: a meta-analysis. *Am J Hypertens* 2016; 29: 448–457
13. Gamboa JL, Pretorius M, Sprinkel KC *et al*. Angiotensin converting enzyme inhibition increases ADMA concentration in patients on maintenance hemodialysis – a randomized cross-over study. *BMC Nephrol* 2015; 16: 167
14. Khan BV, Rahman ST, Haque T *et al*. Vascular effects of nebivolol added to hydrochlorothiazide in African Americans with hypertension and echocardiographic evidence of diastolic dysfunction: the NASAA study. *J Cardiovasc Pharmacol Ther* 2012; 17: 291–297

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