ADMA is a useful marker, but many confounding factors should be considered!

To the Editor,

We read the article entitled "Could plasma asymmetric dimethylarginine level be a novel predictor beyond the classic predictors of stent restenosis?" by Bal et al. (1) published in Anatolian J Cardiol 2014; 14: 491-7. The authors assessed the factors associated with coronary stent restenosis and if there is an association between plasma asymmetric dimethylarginine (ADMA) levels and stent restenosis. They concluded that plasma ADMA levels may be used as a novel marker for stent restenosis beyond the classic stent restenosis markers.

Novel inflammatory markers have been identified in recent years for stent restenosis. One of the major endothelium-derived vasoactive mediators is nitric oxide (NO). A growing body of data indicates that endogenous NO synthase inhibitors, like asymmetric dimethylarginine (ADMA), may be responsible for endothelial vasodilator dysfunction in many individuals with coronary and peripheral arterial diseases and in those with their risk factors, particularly hypertension, diabetes mellitus, hypercholesterolemia, hyperhomocysteinemia, smoking, and aging (2).

First, we have some comments on the present study. Renal failure is one of the most important prognostic variables in patients with cardiovascular disease (3). ADMA is eliminated from the body via renal excretion. The glomerular filtration rate (GFR) provides more accurate knowledge about renal function than the serum creatinine level. A mild reduction in GFR is associated with an increased plasma level of ADMA. The Cockcroft-Gault equation (CGE) and the modification of diet in renal disease (MDRD) are methods for calculating the GFR. However, the CGE and MDRD may estimate different values of GFR according to age (4). Instead of using these methods, the Berlin Initiative Study (BIS) equation (which estimates the GFR more precisely) or Chronic Kidney Disease-Epidemiology Collaboration (CKDEPI) are more useful methods in recent studies (5).

Second, the authors said that plasma ADMA levels were analyzed by using high-performance liquid chromatography (HPLC). This novel assay allows the rapid, reproducible, and available sensitive determination of ADMA compared with ELISA method (2), but many assays are time-consuming and costly and deliver quite unstable results, which are not suitable to differentiate ADMA from SDMA, NMMA, and other methylated arginine analogs. They did not determine other arginine derivatives, such as symmetric dimethylarginine and L-arginine, or assess endothelial function. For this reason, HPLC coupled to mass spectrometric detection (LC-MS/MS) has the clear advantage to be the current gold standard for the differentiation between ADMA and the other methylated arginine derivatives; however, this method is not widely available, and the equipment is comparatively expensive (6).

Furthermore, they used coronary angiography to assess coronary artery stenosis; however, intravascular ultrasonography is the best method to demonstrate neointimal tissue burden completely. They also did not measure other relevant biomarkers, such as homocysteine, lipoprotein (a), and lipoprotein-associated phospholipase A2.

As a conclusion, ADMA is clearly tightly related to oxidative-inflammatory mechanisms of atherosclerosis, and it would have been very helpful to have measured other relevant biomarkers, such as C-reactive protein, homocysteine, lipoprotein (a), and lipoprotein-associated phospholipase A2, to help define that the 2 groups were adequately matched, whether ADMA tracks simply as a covariate with these other biomarkers, and whether differences in ADMA survive and remain statistically significant after adjusting for them (7).

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References

1. Bal UA, Yıldırır A, Aydınalp A, Kaynar G, Kanyılmaz S, Murat K, et al. Could plasma asymmetric dimethylarginine level be a novel predictor beyond the classic predictors of stent restenosis? Anadolu Kardiyol Derg 2014; 14: 491-7. [CrossRef]
2. Böger RH. The emerging role of asymmetric dimethylarginine as a novel cardiovascular risk factor. Cardiovasc Res 2003; 59: 824–33. [CrossRef]
3. Balta S, Demirkol S, Arslan Z, Şahin MA, Yeşil FG, Küçük U. The relation between decreased glomerular filtration rate and nonvalvular atrial fibrillation. Cardiology 2013; 124: 219. [CrossRef]
4. Herzog CA. Kidney disease in cardiology. Nephrol Dial Transplant 2009; 24: 34-7. [CrossRef]
5. Schaeffner ES, Ebert N, Delanaye P, Frei U, Gaedeke J, Jakob O, et al. Two novel equations to estimate kidney function in persons aged 70 years or older. Ann Intern Med 2012; 157: 471-81. [CrossRef]
6. Böger RH, Maas R, Schulze F, Schwedhelm E. Asymmetric dimethylarginine (ADMA) as a prospective marker of cardiovascular disease and mortality--an update on patient populations with a wide range of cardiovascular risk. Pharmacol Res 2009; 60: 481-7. [CrossRef]
7. Kurtoğlu E, Balta S, Karakuş Y, Yaşar E. Other factors ought to be kept in mind when analyzing plasma asymmetric dimethylarginine levels. Am J Hypertens 2014; 27: 500. [CrossRef]

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