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REVIEW

Asymmetric dimethylarginine, a biomarker of cardiovascular complications in diabetes mellitus

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Abstract

Cardiovascular (CV) complications are an essential causal element of prospect in diabetes mellitus (DM), with carotid atherosclerosis being a common risk factor for prospective crisis of coronary artery diseases and/or cerebral infarction in DM subjects. From another point of view, asymmetric dimethylarginine (ADMA) has been established as an inhibitor of endogenous nitric oxide synthesis and the relationship between ADMA and arteriosclerosis has been reported. In our study with 87 type 2 DM (T2DM) patients, we have examined whether ADMA and other CV risk factors are the useful predictors of DMCV complications. After the measurement of the respective CV risk factors, we have followed the enrolled T2DM patients for 5 years. We have finally analyzed 77 patients. DMCV complications developed in 15 cases newly within 5 years, and 4 cases recurred. The concentrations of ADMA in plasma were markedly more elevated in 19 DM patients with CV complications than in 58 DM patients without CV complications. Urinary albumin (U-Alb), mean intimal-medial thickness (IMT) and ankle brachial index (ABI) were also higher in patients with CV complications. Multiple regression analyses showed that U-Alb had an influence on the high level of ADMA (standardized $\beta = 6.59$, $P = 0.00014$) independently of age, systolic BP, fibrinogen, mean IMT, plaque score, and ABI. The review indicates what is presently known regarding plasma ADMA that might be a new and meaningful biomarker of CV complications in DM subjects.

Key words: Asymmetric dimethylarginine; Biomarker; Diabetes mellitus; Cardiovascular complications; Incretin

Core tip: Asymmetric dimethylarginine (ADMA) is an emerging independent biomarker for prospective cardiovascular (CV) complications. In our study, the results show that the cases with a high level of ADMA could have diabetes mellitus CV (DMCV) complications in the future within five years. Furthermore, not only ADMA but also urinary albumin was associated with DMCV complications in the multiple regression analyses. The clinical acceptation of this parameter will rely on the availability of therapies to immediately reduce ADMA such as incretin-based drugs, which could support the part of ADMA as an etiologic risk factor.

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INTRODUCTION

Diabetes mellitus (DM) is a complex metabolic disorder and one of the common chronic diseases worldwide. The number of people with DM globally was estimated at 382 million in 2013, and is supposed to reach over 592 million by 2035[1]. Close to 5.1 million deceased in adults aged 20-79 years were attributable to DM in 2013, accounting for 8.4% of the global all-cause mortality in this age group[2]. In addition to the effect on the subjects' life quality, the microvascular [diabetic retinopathy (DR), diabetic nephropathy (DN), and neuropathy] and macrovascular complicating diseases (coronary heart diseases, peripheral artery diseases, and stroke) of DM also increase the global healthcare burden. Approximated planetary healthcare expenditure to care and preclude DM and its complicating diseases are anticipated to total leastwise 548 billion United States dollars (USD) in 2013. By 2035, this number is proposed to surpass some 627 billion USD[3]. Worldwide, DM is probable to be the fifth leading killer[4].

Cardiovascular (CV) complications are an essential causal element of prognosis in type 2 DM (T2DM), with carotid atherosclerosis (CA) being a common risk factor for prospective crisis of coronary artery disease (CAD) and/or cerebral infarction[5,6]. Some molecules, such as high-sensitivity C-reactive protein (CRP), interleukin-18, and hepatocyte growth factor (HGF) would have been presented to be atherosclerotic biomarkers[7-9]. Preclusion of DM and its involvements, early invention of disease stages, and interventions that would act in the presence of hyperglycemia to avoid, retard or inverse the involvements are the principal concerns. Biomarkers have been investigated for understanding the structures of the evolution and progress of DM involvements[10]. This review presents what is currently known regarding plasma asymmetric dimethylarginine (ADMA) level that might be a new and meaningful biomarker of DMCV complications.

ENDOTHELIAL DYSFUNCTION, NITRIC OXIDE AND ADMA

Endothelial dysfunction is distinguished as afflicted nitric oxide (NO)-mediated vascular reaction and is related to maturation of arteriosclerosis and DMCV involvements[11]. NO produced by the vascular endothelium is related to the regulatory mechanisms of the CV system[12]. Since NO is a molecule distributed to important anti-atherosclerotic properties, reduced NO availability may be deemed a crucial risk factor for atherothrombosis and acute CV events. NO is compounded by stereospecific oxidization of the terminal guanidino nitrogen of the amino acid L-arginine by the activity of a group of enzymes known as NO synthases (NOSs)[13]. The major isoform of NOS existing in endothelial cells, eNOS, is constitutively aggressive and transforms the amino acid L-arginine into NO and citrulline. Synthesis of NO can be selectively inhibited by guanidino-substituted analogues of L-arginine which blockade the action site of NOS in competition. In animals, NG-monomethyl L-arginine (L-NMMA) and NG-nitro L-arginine methyl ester have been used as pharmacological tools to reduce NO availability and induce experimental hypertension[14-16]. L-arginine analogues were identified in human plasma and urine[17]. The two L-arginine analogues identified as endogenous inhibitors of NOS were L-NMMA and NG, NG-dimethyl L-arginine (asymmetric dimethylarginine, ADMA). L-NMMA and ADMA were equipotent as NOS inhibitors[17]. Another endogenous arginine analogue (symmetric dimethylarginine, SDMA) was unable to inhibit NOS[17]. As human plasma ADMA concentrations are 10-fold higher than those of L-NMMA[17], ADMA might be regarded as the major endogenous NOS inhibitor. Increased plasma concentrations of ADMA caused impaired NO synthesis, leading to endothelial dysfunction, atherogenesis, and CV disease processes. ADMA and SDMA have been demonstrated to collect in renal failure patients[17].

Though ADMA is somewhat eliminated by the nephros, the predominant metabolism process is decomposition by the dimethylarginine dimethylaminohydrolases (DDAHs) 1 and 2 into dimethylamine and L-citrulline[18,19] (Figure 1). High blood sugar disorders DDAH efficacy in the endothelia and blood vessel involuntary muscle cells in vitro, whereby empowering raised concentrations of ADMA among DM subjects[20]. Chronic ADMA increase in animals induces arteriosclerotic involvements and nephropathy as an outcome of decreased NO production[21]. This indicates a crucial ADMA function in excusing the correlation between vascular endothelial functional impairment,

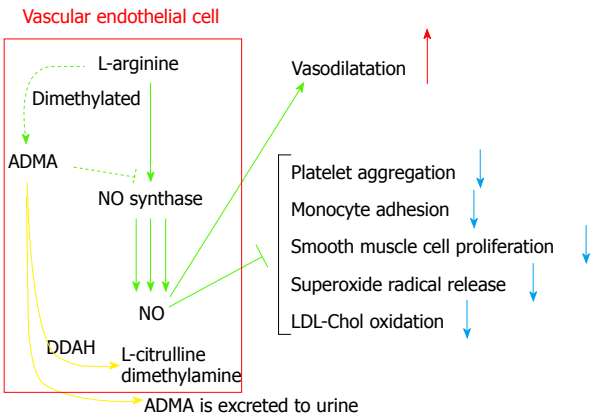

Figure 1 In non-diabetic patients, L-arginine by far outweighs asymmetric dimethylarginine, and active nitrogen oxide modulates vascular tone and structure. DDAH: Dimethylarginine dimethylaminohydrolase; ADMA: Asymmetric dimethylarginine; LDL: Low-density lipoprotein; NO: Nitrogen oxides.

atherogenesis, and DN. It has been demonstrated that ADMA is augmented in conditions such as renal impairment[17,22], DM[23], hypertension[24], and DN[25]. Moreover, it has been indicated that the concentrations of ADMA are prognosticative of CVD and all-cause death rate in preponderantly non-diabetic chronic kidney disease (CKD)[26], end-stage renal disease[27], and CAD[27-29].

PLEIOTROPIC EFFECTS OF ADMA

Vallance *et al*[17] showed that during continuous 3 mg/kg per hour ADMA infusate in *Cavia porcellus*, systolic blood pressure (BP) rose by nearly 15%, as plasma ADMA concentrations rose approximately nine-fold. In the same animal model, bolus injections of 1-30 mg/kg ADMA resulted in a dose-dependent mean arterial BP increment[17]. Gardiner *et al*[30] confirmed in rats the dose-dependent pressor effects of ADMA. De Gennaro Colonna *et al*[31] administered ADMA 10 mg/kg per day subcutaneously *via* an osmotic minipump for 14 d to male adult rats. ADMA-treated rats indicated increased systolic BP, reduced plasma nitrite/nitrate levels, NO-stable end-products and a lower vasorelaxant reaction of the aortic tissues to accumulative acetylcholine concentrations. Isolated perfused cardiac specimens from ADMA-cared rats demonstrated a deterioration of post-ischemic ventricular functional impairment[31]. In humans (healthy male volunteers), an infusion of ADMA at rates of 0.0125 and 0.025 mg/kg per minute increased plasma ADMA concentrations between 2 and 10 μmol/L and remarkably reduced plasma cyclic guanosine monophosphate (cGMP) (the main second messenger of NO) concentrations[32]. The infusion of a higher ADMA dose (0.10 mg/kg per min) importantly reduced stroke volume and heartbeat and raised systemic blood vessel resistance[32]. In another study by Achan *et al*[19], an intravenous injection of 3.0 mg/kg ADMA in healthy volunteers reduced heart rate and cardiac output and elevated BP and systemic vascular resistance. The effects of a suppressor dose of ADMA (0.25 mg/kg per min) were studied by Kielstein *et al*[33] in healthy normotensive male patients. ADMA infusion reduced plasma cGMP concentrations (indicating reduced NO production), decreased effective renal plasma flow, and elevated renovascular resistance. On the other hand, ADMA did not alter plasma renin and noradrenalin levels[33], suggesting the facility of this arginine substance to regulate renal function without impacting the renin-angiotensin and sympathetic systems. Moreover, the effects of ADMA on cerebral vascular tone in humans were researched[34]. An infusion of 0.10 mg/kg ADMA per minute in healthy males elevated vascular stiffness and reduced total cerebral perfusion[34], demonstrating that ADMA might also be related to the pathogenesis of cerebrovascular disease. In a word, respective studies demonstrate that ADMA systemic application in humans suppresses NO production and spoils endothelial action in several regions, *i.e.*, the heart, kidney, and brain.

ADMA AND CV DISEASES

Respective studies have indicated a prognosticative count of ADMA for CV outcomes. The incidence rate of CV endpoints in high risk subjects has been established to be straight and severally connected with elevated concentrations of ADMA in subjects with CAD[28], peripheral arterial occlusive disease[35], T2DM[36], type 1 DM (T1DM)[37] and chronic heart failure[38]. A specific potent relationship between ADMA and hemodynamic factors alike clinical result has been detected in pulmonary arterial hypertension subjects[39]. These forecasting information from experimental studies only reports statistic correlation and does not approve to form the consequence that ADMA is inevitable for prospective CV outcomes. It seems potential that increased ADMA levels are exclusively an epiphenomenon in parallel with other transformations. Nevertheless, animal study outcomes intimate that ADMA indicates not merely a risk biomarker but a risk factor for CV outcomes. It was demonstrated that continuous ADMA infusate for 4 wk resulted in the microangiopathy generation in murine coronary arteries[21]. Overexpression of the ADMA breakdown enzyme DDAH decreased murine ADMA and graft CAD[40]. Moreover, overexpression of DDAH avoided progress of nephropathy by blocking decrease of periductal capillary vessels and tubulointerstitium fibrosis in CKD rats[41]. Konishi *et al*[42] indicated that transgenic mice overexpressing DDAH displayed augmented endothelium rebirth and neointimas after vessel trauma. These discoveries mean that ADMA might straightly endow angiopathy. Nevertheless, it remains to be decided if a proximate ADMA level alteration can decrease CV risk in humans.

PHARMACOLOGICAL TREATMENT FOR CV DISEASES AND ADMA

A particular pharmacologic intervention to impact ADMA is not usable yet. It was demonstrated that

Table 1 Characteristic of subjects

Number of patients	87
Male/female	47/40
Age (yr)	62.6 ± 10.4
BMI (kg/m^2)	23.4 ± 4.2
HbA1C (%)	9.4 ± 2.2
Duration of diabetes (yr)	13.5 ± 10.6
With hypertension	44
With dyslipidemia	32

We enrolled 87 type 2 diabetic patients.

other steps to decrease CV hazard inclusive of survival training in T1DM subjects[43] and in increased CV hazard subjects[44] or weight reduction in pathologically corpulent subjects[45] are able to reduce the levels of circulating ADMA. It was presented that a few agents (*e.g.*, pravastatin, telmisartan or pioglitazone) are able to elevate the action or the generation of the enzyme DDAH and whereby decrease ADMA *via in vitro* experiments[46-48]. In addition, clinical studies indicated that intervention with metformin, ACE inhibitors, angiotensin receptor blockers or alpha-lipoic acid would be able to reduce the levels of circulating ADMA[49-55]. The bibliography on the efficacy of statins on ADMA is contentious[20,56-61]. Meanwhile, one clinical study demonstrated an ADMA decrease during intervention with rosiglitazone, and this was not recognized in a discrete age group[62,63]. However, it remains wondering whether regulation of ADMA by these interventions will straightly affect CV hazard additionally.

ADMA AND DM COMPLICATIONS

DM subjects have an untoward CV hazard character. Increased ADMA levels have been reported in subjects with T2DM and T1DM[23,25]. High blood sugar intrinsically may elevate ADMA levels due to decreased metabolic process. It was indicated that increased blood sugar concentrations can suppress DDAH action in cultivated vascular endothelial cells *via* an *in vitro* study[20]. In addition, clinical studies in subjects demonstrate that ADMA is straightly relevant to blood sugar concentrations[23,64]. Yasuda *et al*[65] reported that rigorous diabetic control might affect anti-atherogenicity outcomes *via* decreasing ADMA concentrations in T2DM subjects. Furthermore, there is proof that insulin resistance is related with elevated ADMA levels[50,62]. This is established by the fact that transgenic mice that overexpress DDAH have decreased ADMA levels and ameliorated insulin sensitivity measured against wild type animals[66]. Several lines of proof suggested that increased levels of ADMA were related with blood glucose control in distinct cohort which applies to the supposition that ADMA might act as a hazard predictive factor for CV outcomes[67,68]. In addition to relations between ADMA and metabolic control, the levels of ADMA might play an important part for the generation of DM involvements as well. ADMA is increased in subjects with T1DM, T2DM or DN with micro- or macroalbuminuria[25,69]. ADMA is correlated with the generation of kidney disorder and might consequently have possible harmful actions in DN subjects[26,70]. In addition, increased ADMA concentrations have been described in T2DM subjects with retinopathy[71]. Thus, it is alluring to hypothesize that ADMA might serve as a pathophysiologic suitable agent for DM involvements. Notwithstanding, high blood sugar remains a principal reason for both elevated ADMA and the generation of DM complicating disease which makes the reading of data more complicated.

ADMA AND CAROTID INTIMA-MEDIA THICKNESS

Augmented intima-media thickness (IMT) has been demonstrated to be a substitute biomarker for prognosticating CV hazard[72]. In a study by Miyazaki *et al*[73], stepwise regression analysis indicated plasma concentrations of ADMA to be remarkably related to carotid IMT. In an epidemiologic survey of 712 people, plasma concentrations of ADMA were assayed along with carotid IMT. On multiple stepwise regression analysis, carotid IMT was conspicuously related with the concentrations of ADMA[74] and the generation of carotid IMT, over a 6-year period, was associated with serum concentrations of ADMA[75]. In the PREVENCION study of 922 grown-up subjects, ADMA remarkably prognosticated carotid IMT even after adaptation for CV hazard parameters, CRP, and kidney function, but did not prefigure carotid-femoral pulse wave velocity, BP, or hemodynamic abnormality[76]. Kocak *et al*[77] determined higher ADMA concentrations in people without already-known arteriosclerotic disease who were on continuous ambulatory peritoneal dialysis and revealed a remarkable positive correlational statistics between the concentrations of ADMA and carotid IMT in these subjects.

OUR EXPERIENCE WITH ADMA

We carried out a clinical study to examine the correlation between the plasma ADMA concentrations and the stage of CA in T2DM subjects[78,79].

In our study with 87 T2DM patients (Table 1), we have examined whether ADMA and other CV risk factors are the useful predictors of DMCV complications. After the measurement of the respective CV risk factors, we have followed the enrolled T2DM patients for 5 years (Figure 2). We investigated the risk factors as follows: ADMA, angiotensin Ⅱ (AT Ⅱ), HGF, advanced glycation end products (AGEs), plasma plasminogen activator inhibitor type 1 (PAI-1), mean IMT, plaque score of the common artery and ankle brachial index (ABI). Furthermore, we measured serum creatinine (Cr), creatinine clearance (CCr), urinary albumin (U-Alb),

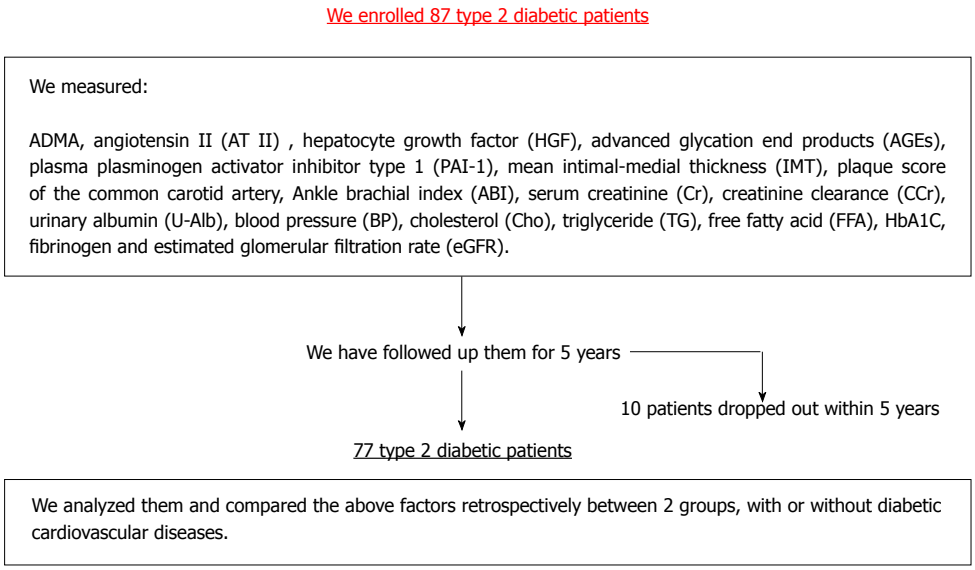

Figure 2 Protocols of our clinical research.

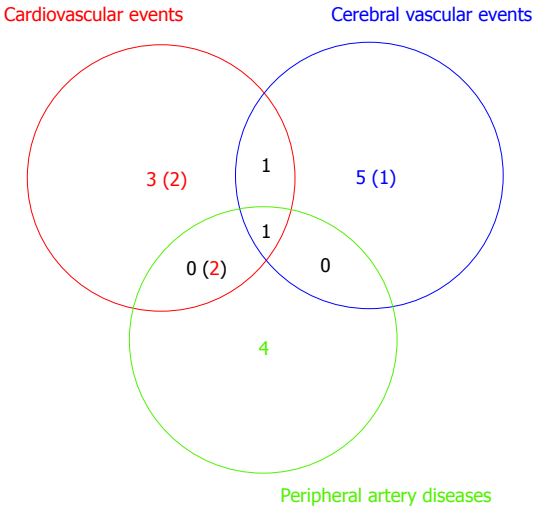

Figure 3 The result of diabetic cardiovascular disease that developed within five years. The numbers without parentheses mean new developments, and the numbers with parentheses mean recurrences.

BP, cholesterol (Cho), triglyceride (TG), free fatty acid (FFA), HbA_{1C}, fibrinogen and eGFR. We compared retrospectively the above factors between two groups with or without CV complications. In addition, we showed results in form of the average ± SD. We have finally analyzed 77 patients. DMCV complications developed in 15 cases (CV events: 5 cases; cerebral vascular events: 7 cases; peripheral artery diseases: 7 cases) newly, and 4 cases (CV events: 4 cases; cerebral vascular events: 1 case; peripheral artery diseases: none case) recurred within 5 years (Figure 3). The concentrations of ADMA in plasma were conspicuously higher in 19 DM subjects with CV complications than in 58 DM subjects without (0.56 ± 0.09 μmol/L *vs* 0.45 ± 0.07 μmol/L, $P < 0.00001$) (Figure 4). U-Alb (319.9 ± 522.6 μg/min *vs* 83.5 ± 199.4 μg/min, $P = 0.008$) and the value of mean IMT (1.39 ± 0.33 mm *vs* 1.16 ± 0.30 mm, $P = 0.006$) were also higher in patients with CV complications. The value of ABI (1.0 ± 0.2 *vs* 1.1 ± 0.2, $P = 0.046$) was lower in patients with CV complications. In the study, the other risk factors (AT Ⅱ, HGF, AGEs, PAI-1, plaque score, Cr, CCr, BP, Cho, TG, FFA, HbA_{1C}, fibrinogen and eGFR) were not associated with the development of the DMCV complications within 5 years. A relative risk of the DMCV complication development reached the highest level (6.81) when the level of ADMA was over 0.54 μmol/L. Multiple regression analyses showed that U-Alb had an influence on the high level of ADMA (standardized β = 6.59, $P = 0.00014$) independently of age, systolic BP, fibrinogen, mean IMT, plaque score, and ABI. Increased levels of ADMA were found in the generation of CA in patients with T2DM[80,81] or gestational DM[82]. Kanazawa *et al*[80] demonstrated that serum ADMA would be a predictive factor of arteriosclerosis and linked to the existence of CV complications in Japanese T2DM subjects, but serum SDMA, a structural isomer of ADMA, was correlated neither with factors for arteriosclerosis nor with the existence of CV complications.

As well as our results, Celik *et al*[83] showed that the concentration of ADMA was higher in diabetic subjects with CV complications compared to diabetic patients without complications. They also reported that the levels of fundamental determinants of ADMA were evaluated in diabetic patients with macrovascular complications, using ADMA as a dependent variable in multiple regression analysis. It was found that the most fundamental determinant of ADMA is total homocysteine (tHcy). Moreover, Krzyzanowska *et al*[84] showed that ADMA is related to clinical CV atherosclerotic disease diagnosis in T2DM, and also concluded that ADMA is associated with total tHcy, U-Alb, Cr, and GFR and that tHcy correlates with

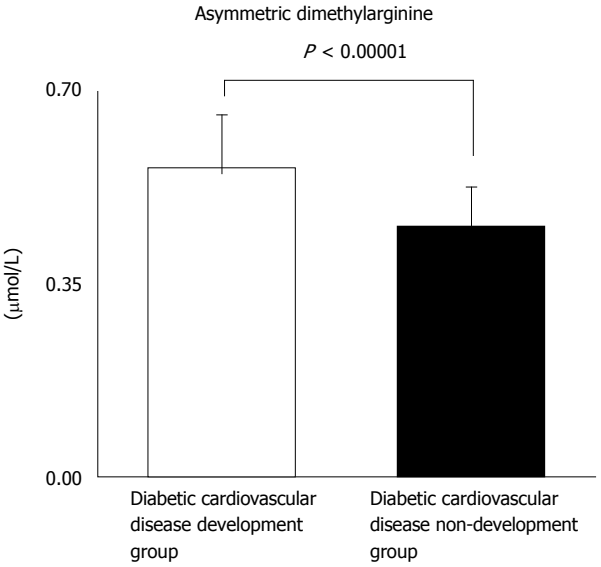

Figure 4 Asymmetric dimethylarginine was significantly higher in diabetic cardiovascular disease development group than in diabetic cardiovascular disease non-development group.

age, ADMA, Cr, GFR, and LDL[84]. Research has also shown that increased tHcy concentration in T2DM is associated with increased CV complications[85,86]. Thus, ADMA may be used to predict the likelihood of developing CV complications in DM patients.

According to these studies, the cases with a high level of ADMA, particularly those complicated with nephropathy, should be followed more carefully to prevent new developments and/or recurrences of the DMCV complications.

ADMA AND INCRETIN-BASED DRUGS

Lately, a novel treatment strategy for the intervention of T2DM that directs the incretin hormones has been generated. These peptide hormones, *i.e.,* glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide, would be secreted from the bowel after a repast and induce insulin secretion in a glucose-dependent manner[87]. Nevertheless, their activity is restricted by prompt deactivation *via* the enzyme dipeptidyl peptidase (DPP)-4. Furthermore, T2DM subjects normally do not react well to glucose-dependent insulinotropic peptide and GLP-1[88,89]. Suppression of DPP-4 will elevate levels of active incretins, so DPP-4 has turned out to be a marker in diabetic control[90-92]. Incretin-based therapy was first made available for the treatment of T2DM in the United States in 2006 and in Japan in 2009[93]. Up to now, seven DPP-4 inhibitors are usable in Japan, including sitagliptin, vildagliptin, alogliptin, linagliptin, anagliptin, teneligliptin, and saxagliptin[93-95]. The elevated intrinsic plasma level of GLP-1 is considered to show protective outcomes on the CV system[96]. Ojima *et al*[97] showed that GLP-1 receptor agonist would inhibit ADMA development in the kidney of streptozotocin-induced DM rats. In addition, serum concentration of ADMA was sought with the DPP-4 inhibitor saxagliptin in an animal experiment[98]. The discoveries of that study indicate that the DPP-4 inhibitors could impact serum concentrations of ADMA. In fact, several DPP-4 inhibitors might reduce ADMA levels in T2DM subjects[99,100].

Incretin-based drugs were found to decrease serum concentrations of ADMA in T2DM subjects. This discovery ought to be backed up with larger-scale prospective randomized trials such as Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction 53 study[101,102] and EXamination of cArdiovascular outcoMes: AlogliptIN *vs* standard of carE in patients with type 2 diabetes mellitus and acute coronary syndrome trial[103] to conclude that incretin-based drugs provide CV protection along with DM regulation.

CONCLUSION

ADMA is a rising distinct biomarker for prospective CV accidents. The clinical adoption of this factor will rely on the accessibility of therapies to straightly lower ADMA such as incretin-based drugs, which could support the function of ADMA as a prolific risk factor. Additional studies would be guaranteed in DM patients especially concerning the possible effects of ADMA on DMCV complicating diseases.

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