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Metabolic Syndrome-Associated Risk Factors and High-Sensitivity C-Reactive Protein Independently Predict Arterial stiffness in 9903 Subjects With and Without Chronic Kidney Disease

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Abstract: Metabolic syndrome (MS), high-sensitivity C-reactive protein (hs-CRP), and chronic kidney disease (CKD) are related to cardiovascular diseases. Although MS is common in CKD subjects, the contribution of MS-associated risk factors and hs-CRP to arterial stiffness in CKD has not been well studied.

In this cross-sectional cohort study, we enrolled 9903 subjects who underwent brachial-ankle pulse wave velocity (baPWV) measurements from our database of Health Care Center. CKD was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2. Comparing those grouped with and without CKD, multivariate linear regression analyses were used.

Overall, baPWV was found to have an inverse relationship with eGFR (P for trend <0.001), which increased progressively with the presence of CKD, increasing number of MS-associated risk factors and hs-CRP (P for trend <0.001). In the non-CKD group, age, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting glucose, triglyceride, high-density lipoprotein cholesterol, and hs-CRP independently predicted baPWV, whereas in CKD, eGFR, age, gender, body mass index, SBP, DBP, and fasting glucose remained predictors.

The number of MS-associated risk factors and hs-CRP remains a determinant of arterial stiffness in both CKD and non-CKD groups. The decline of renal function contributes to arterial stiffness only in CKD but not in non-CKD. Our findings suggest that for CKD subjects, renal function, BP, and glycemic control are potential targets for further interventional studies of arterial stiffness.

(*Medicine* 94(36):e1419)

Abbreviations: baPWV = brachial-ankle pulse wave velocity, BMI = body mass index, CKD = chronic kidney disease, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, HDL = high-density lipoprotein, hs-CRPh = igh-sensitivity C-reactive protein, MS = metabolic syndrome, SBP = systolic blood pressure.

INTRODUCTION

Coronary artery disease is the leading cause of death worldwide.[1] Central obesity and insulin resistance are significantly associated with a cluster of cardiometabolic risk factors well-known as metabolic syndrome (MS)[2] that is correlated to cardiovascular disease and type 2 diabetes mellitus.[3] High-sensitivity C-reactive protein (hs-CRP), an inflammatory biomarker, is also associated with insulin resistance[4] and type 2 diabetes mellitus,[5] and is frequently used in clinical practice as the risk factor for coronary artery disease and all-cause mortality.[6,7] However, few studies have combined these major risk factors in cardiovascular disease or mortality prediction.[8]

MS is also widely prevalent in chronic kidney disease (CKD)[9] and has been also implicated as a risk factor for CKD.[10] Meanwhile, CKD is common in community and is associated with an increased risk of cardiovascular disease.[11] An independent, graded association was observed between a reduced estimated glomerular filtration rate (eGFR) and the risk of death, cardiovascular events, and hospitalization in a large, community-based population.[12] Conventional cardiovascular risk factors, including hypertension, dyslipidemia, and diabetes, all of which are common in CKD subjects and are themselves contributory risk factors for CKD, only partially explain the high cardiovascular risk.[13]

Arterial stiffness presented by pulse wave velocity (PWV) has been well studied as a risk predictor for coronary artery disease[14] and all-cause mortality[15] among general populations. Among diabetic patients, it also associated with reduced arterial flow volume in the lower extremities,[16] mortality, and cardiovascular morbidity.[17] However, few studies have simultaneously investigated and compared determinants of arterial stiffness from the pool of MS-associated risk factors and hs-CRP among a large cohort including CKD and non-CKD subjects.

METHODS

Study Design and Population

In this cross-sectional study, we retrospectively analyzed the clinical data of subjects who underwent a self-paid health examination at the Health Care Center of Chang Gung Memorial Hospital, Taoyuan branch, from January 1, 2005 through December 31, 2007. All subjects were required to be afebrile and to have undergone a standardized protocol, including the structured questionnaires covering the personal and family history of chronic diseases and life style, as well as measurements of body weight and height. The inclusion criteria were

18 to 95 years old with a standardized vascular assessment of brachial-ankle PWV (baPWV) measurement. We excluded the subjects with pyuria to minimize the risks for infection or acute renal insufficiency. CKD in the study was defined as an eGFR $<60 \, mL/min/1.73 \, m^2$. These subjects were categorized by CKD or non-CKD, number of MS-associated risk factors and hs-CRP. The correlations with baPWV between groups were analyzed. All subjects provided their written informed consent. The study was approved by the Ethics Committee of the Institutional Review Board of Chang Gung Memorial Hospital (approval number: 102-4175B) and performed according to the ethical principles of the Declaration of Helsinki.

MS-Associated Risk Factors and hs-CRP

The MS-associated risk factors were determined according to the criteria from the third report of the National Cholesterol Education Program expert panel on the detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III)[18] and the American College of Endocrinology Position Statement on Insulin Resistance Syndrome.[2] The 5 MS-associated risk factors defined in the present study included high body mass index (BMI) ($\geq 25 \, kg/m^2$), high blood pressure (BP) ($\geq 130/85 \, mm \, Hg$), high fasting plasma glucose ($\geq 100 \, mg/dL$), low high-density lipoprotein (HDL) cholesterol level ($<40 \, mg/dL$ in men or $<50 \, mg/dL$ in women), and high triglyceride level ($\geq 150 \, mg/dL$). Elevated hs-CRP level was defined as $\geq 3 \, mg/L$. Putting above factors together, we further classified all subjects to Group I by 0 to 2 risk factors, to Group II by 3 or 4 factors, and to Group III by 5 or 6 factors.

Measurements

Eligible subjects completed anthropometric measurements and collection of venous blood samples in the morning after overnight fasting. BMI was calculated as body weight (kg) divided by the square of body height (m). The biochemical tests included assessments of serum creatinine, fasting plasma glucose, triglyceride, HDL cholesterol, and hs-CRP at the central laboratory of Taoyuan Chang Gung Memorial Hospital. The eGFR was calculated by using the Modification of Diet in Renal Disease equation.[19]

Arterial Stiffness as Represented by Pulse Wave Velocity

baPWV was measured by using an automated apparatus (Colin VP-1000, Omron, Kyoto, Japan). The subjects were told to avoid tobacco or any stimulant beverages, such as coffee or alcohol, before the examination. A standardized temperature was kept in the examination room. Four pneumatic pressure cuffs were placed appropriately around both arms and both ankles. Two electrocardiographic electrodes were attached on both wrists, and 1 microphone probe for heart sound detecting was placed at the second intercostal space at the left margin of sternum. After the subjects were kept in a resting supine position for 15 min, the automatically processing procedure started with the simultaneous measurements of BP over 4 extremities by the oscillometric principle, followed by performing the pulse volume recording over right arm and both ankles for 10 sec when the cuff pressures were maintained at the level of 60 mm Hg. The recorded cuff pressure signals are thought to be the pulse volume traces corresponding to the intra-arterial pressure contours. The recorded pulse volume traces provided the pulse transit time between the right arm and right ankle, and between the right arm and left ankle. The assumed length of an arterial segment between the arm and ankle was calculated

automatically from height according to the regression equation: distance $= 0.5934 \times height + 14.401$. Right and left baPWVs were calculated automatically as length/transit time between right arm and both ankles. We calculated the mean of right and left PWVs as the representative baPWV.

Statistical Analysis

Data were analyzed by using SPSS 18.0 software for Windows 7 (SPSS Inc., Chicago, IL) and expressed as the mean ± SD or frequency, as appropriate. All variables were tested for normal distribution using the Kolmogorov–Smirnov test. One-way analysis of variance was applied to compare differences in continuous variables, whereas categorical data were tested by using the Pearson's chi-squared test. When age, gender, individual MS-associated risk factors, and hs-CRP were considered, adjusted risk estimates for PWV were calculated by using multivariate linear regression analyses in the 4 predefined models (Table 1), including prognostic risk factors from published observations, such as eGFR, age, gender, the number of MS-associated risk factors, BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), glucose, triglyceride, and HDL cholesterol.[20] All statistical tests were 2-tailed, and a P value <0.05 indicated statistical significance.

RESULTS

Present study included 9903 subjects with a mean age of 54.7 years, male gender rate of 57%, mean eGFR of $77 \, mL/min/1.73 \, m^2$ with a range from 4 to $189 \, mL/min/1.73 \, m^2$, CKD rate of 11%, and mean baPWV of 1490 cm/sec.

The Relationship Between Arterial Stiffness and the Severity of CKD

Overall, baPWV was negatively correlated with eGFR (P for trend <0.001) (Figure 1). Subjects with an eGFR $>90 \, mL/min/1.73 \, m^2$ had the lowest baPWV, while those with an eGFR $15–29 \, mL/min/1.73 \, m^2$ had the highest baPWV. The baPWV increased progressively with the decline in eGFR.

The Relationship Between Arterial Stiffness and New Risk Group Combined MS-Associated Risk Factors and hs-CRP

Subjects were classified into 3 groups according to the number of MS-associated risk factors and hs-CRP. Within this cohort, 6418 (65%) subjects were classified to Group I, 2909 (29%) to Group II, and 576 (6%) to Group III. Subject demographics, stratified by new risk group, are presented in Table 2. Age, CKD proportion, BMI, SBP, DBP, fasting plasma glucose, triglyceride, and hs-CRP were positively correlated with the number of MS-associated risk factors and hs-CRP (all P for trend <0.001), while eGFR and HDL cholesterol were negatively correlated (both P for trend <0.001). PWV also positively correlated with the number of MS-associated risk factors and hs-CRP (P for trend <0.001). Group III with the most MS-associated risk factors and hs-CRP had the highest age, CKD proportion, BMI, SBP, DBP, fasting plasma glucose, triglyceride level, hs-CRP level, baPWV, and the lowest eGFR, HDL cholesterol level within the 3 groups.

The Relationship Between Arterial Stiffness and the Number of MS-Associated Risk Factors and hs-CRP, Based on Whether CKD Was Present or Not

baPWV increased progressively with the presence of CKD and the risk groups of MS-associated risk factors and hs-CRP

TABLE 1. Baseline Characteristics of 9903 Subjects Enrolled in the Study, Categorized by Different Groups

Variables	Total	Group I	Group II	Group III
N, %	9903 (100)	6418 (65)	2909 (29)	576 (6)
Male, %*	5623 (57)	3487 (54)	1825 (63)	311 (54)
Age, yr*	54.7 ± 12.4	53.5 ± 12.4	56.5 ± 11.9	58.7 ± 11.6
eGFR, mL/min/1.73 m²*	77 ± 16	78 ± 15	74 ± 16	71 ± 18
CKD, N (%)*	1046 (11)	479 (8)	435 (15)	132 (23)
MS risk factors				
BMI, kg/m²*	25 ± 4	23 ± 3	27 ± 3	29 ± 3
SBP, mm Hg*	129 ± 20	124 ± 19	138 ± 19	145 ± 18
DBP, mm Hg*	77 ± 11	75 ± 10	82 ± 11	84 ± 11
Fasting glucose, mg/dL*	102 ± 34	95 ± 23	112 ± 41	135 ± 54
Triglyceride, mg/dL*	143 ± 126	108 ± 60	193 ± 136	280 ± 308
HDL cholesterol, mg/dL*	53 ± 14	57 ± 13	46 ± 11	40 ± 8
hs-CRP, mg/L*	2.8 ± 7.1	1.8 ± 4.9	4.1 ± 9.7	6.5 ± 9.9
Arterial stiffness				
baPWV, cm/sec*	1490 ± 338	1422 ± 301	1598 ± 357	1710 ± 384

Grouping was based on the presence of the number of risk factors, which include 5 MS-associated risk factors and hs-CRP. Group I: 0 to 2 risk factors. Group II by 3 or 4 risk factors. Group III by 5 or 6 risk factors

Definition of risk factors: *MS-associated risk factors*: 1. BMI $\geq$ 25 kg/m²; 2. BP $\geq$ 130/85 mm Hg; 3. Fasting plasma glucose $\geq$ 100 mg/dL; 4. HDL $<$ 40 mg/dL in men or $<$50 mg/dL in women; 5. Triglyceride $\geq$ 150 mg/dL, hs-CRP $\geq$ 3 mg/L.

baPWV = brachial-ankle pulse wave velocity; BMI = body mass index; BP = blood pressure; CKD = chronic kidney disease; hs-CRP = high-sensitivity C-reactive protein; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; MS = metabolic syndrome; SBP = systolic blood pressure.

*P for trend <0.001 for 1-way analysis of variance.

(P for trend < 0.001) (Figure 2). In both non-CKD and CKD, baPWV increased progressively with the increased number of MS-associated risk factors and hs-CRP (all inter-groups $P < 0.001$, except $P = 0.005$ for Group III in non-CKD vs Group I in CKD, and $P = 0.001$ for Group II in CKD vs Group III in CKD). Group I in non-CKD had the lowest baPWV level while Group III in CKD had the highest.

FIGURE 1. The associations between baPWV and renal function. P for trend is for 1-way analysis of variance. $P = 0.008$ for "eGFR = 30–59 mL/min/1.73 m² vs eGFR < 15 mL/min/1.73 m²"; $P = 0.445$ for "eGFR = 15–29 mL/min/1.73 m² vs eGFR < 15 mL/min/1.73 m²"; other inter-groups $P < 0.001$. baPWV = brachial-ankle pulse wave velocity; eGFR = estimated glomerular filtration rate.

Independent Predictors of Arterial Stiffness, Based on the Presence or Absence of CKD

Multivariate liner regression of MS-associated risk factors and hs-CRP as the independent predictors of baPWV in the CKD or non-CKD subjects were conducted by the predefined 4 models.

In non-CKD subjects, all MS-associated risk factors and hs-CRP were independently associated to higher baPWV, with the exception of HDL cholesterol. In addition, older age was another independent risk factor for arterial stiffness. The presence of the higher combined number of MS risk factors and hs-CRP also predicted higher baPWV in the non-CKD patients. All predictors except BMI were positively correlated with higher baPWV.

In CKD subjects, BP (SBP/DBP), fasting glucose, and age persisted to contribute to arterial stiffness, while individual hs-CRP, triglyceride, and HDL failed to show the same association. However, combined number of MS risk factors and hs-CRP remained as an independently positive predictor of increased arterial stiffness in these patients. On the contrary, BMI and eGFR were independently and negatively correlated with baPWV.

Compared to non-CKD subjects, fewer MS-associated risk factors and more non-MS factors including eGFR and gender were demonstrated as determinants of arterial stiffness in CKD subjects.

DISSCUSSION

This is the first large cohort study to simultaneously investigate and compare risk factors for arterial stiffness in CKD and non-CKD subjects. First, we demonstrated that the deterioration of renal function was related to an increased arterial stiffness across the spectrum of eGFR. In previous studies, Kawamoto et al[21] and Wang et al[22] reported a stepwise
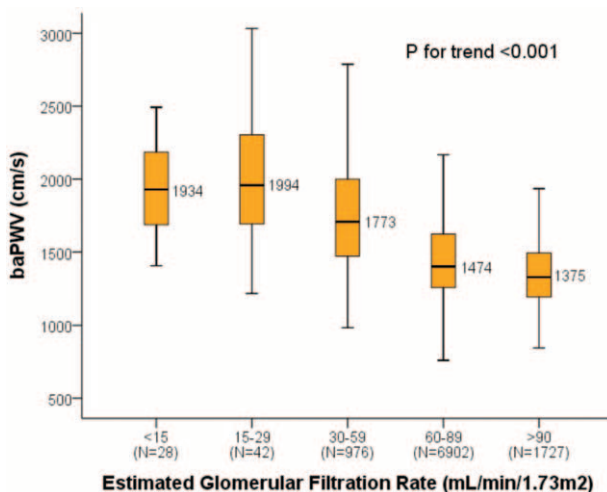
TABLE 2. Multivariate Linear Regression Analyses of MS-Associated Risk Factors and hs-CRP as Independent Predictors of Arterial Stiffness (baPWV) in the Non-CKD or CKD Subjects, by 4 Predefined Models

Variables	Model 1	Model 2	Model 3	Model 4
baPWV in Non-CKD				
eGFR	0.38	0.43[‡]	0.30	0.24
Age	15.53[*]	15.01[*]	13.11[*]	13.22[*]
Gender, male	−26.85[*]	−15.38[†]	3.77	5.30
I, II, III grouping	108.33[*]			
Number of risk factors		53.67[*]	16.16[*]	13.73[*]
MS-associated factor				
BMI			−7.67[*]	−7.81[*]
SBP			5.41[*]	5.49[*]
DBP			1.23[*]	1.27[*]
Fasting glucose			0.88[*]	0.89[*]
Triglyceride			0.07[*]	0.08[*]
HDL cholesterol			−0.62[†]	−0.60[†]
hs-CRP				1.90[*]
r^2	0.414[*]	0.436[*]	0.547[*]	0.544[*]
baPWV in CKD				
eGFR	−4.13[*]	−3.72[*]	−2.98[*]	−2.98[*]
Age	19.00[*]	18.97[*]	18.25[*]	18.62[*]
Gender, male	21.57	23.30	47.07[‡]	43.92[‡]
I, II, III grouping	96.26[*]			
Number of risk factors		59.80[*]	22.97[‡]	23.29[‡]
MS-associated factor				
BMI			−12.97[*]	−13.34[*]
SBP			4.93[*]	4.79[*]
DBP			5.77[*]	5.91[*]
Fasting glucose			1.41[*]	1.49[*]
Triglyceride			−0.01	0.003
HDL cholesterol			−0.83	−0.64
hs-CRP				−0.32
r^2	0.274[*]	0.292[*]	0.458[*]	0.458[*]

Unstandardized regression coefficients (B value), [*]$P \leq 0.001$, [†]$P \leq 0.01$, [‡]$P \leq 0.05$.

baPWV = brachial-ankle pulse wave velocity; BMI = body mass index; CKD = chronic kidney disease; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; hs-CRP = high-sensitivity C-reactive protein; MS = metabolic syndrome; SBP = systolic blood pressure.
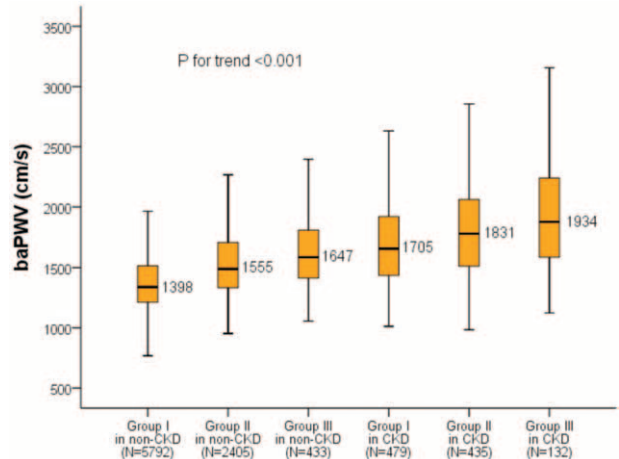

FIGURE 2. The levels of baPWV categorized by the presence of CKD, the number of metabolic syndrome-associated risk factors and hs-CRP. *P* for trend is for 1-way analysis of variance. $P = 0.005$ for "Group III in non-CKD vs Group I in CKD"; $P = 0.001$ for "Group II in CKD vs Group III in CKD"; other inter-groups $P < 0.001$. baPWV = brachial-ankle pulse wave velocity; chronic kidney disease = CKD; high-sensitivity C-reactive protein = hs-CRP.

increase in arterial stiffness corresponding with stages of CKD. Similarly, arterial stiffness was independently associated with the rate of change in renal function in 133 patients with CKD stages 3 and 4.[23] Elias et al[24] also reported that the decline of renal function of 482 community residences was independently related to higher levels of baseline PWV over a mean follow-up of 4.8 years. However, all above studies were small sample sized. Our study is the first large cross-sectional cohort study involving nearly 10,000 subjects to prove the strong negative relationship between eGFR and arterial stiffness.

Second, we showed a stepwise increase in arterial stiffness corresponding with the numbers of MS-associated risk factors and hs-CRP. This finding was comparable to previous data from a small cohort of subjects with minimal comorbidity and eGFR ranging from 8 to 154 mL/min/1.73 m[2].[20] Moreover,

we demonstrated that CKD is a strong risk factor for arterial stiffness across the spectrum of the number of MS-associated risk factors and hs-CRP. Our results suggest that for further studies, the addition of eGFR <60 mL/min/1.73 m[2] to screening based on traditional cardiovascular risk factors may aid in clarifying the associations between arterial stiffness, cardiovascular events, and mortality.

Previous cross-sectional community-based studies reported that PWV was correlated with age, BP, BMI, blood glucose, and abnormal lipid in the multivariate regression analyses,[25,26] and this is similar to our findings in non-CKD. It is interesting that baPWV was negatively correlated with BMI in a large cohort study in Japan,[25] while carotid-femoral PWV was positively correlated with that in the Framingham Heart study.[26] In a cross-sectional population-based study, surveying the associations between different regional PWVs and cardiovascular risk factors, carotid-femoral and heart-femoral PWV positively correlated with BMI, which was negatively correlated with femoral-ankle PWV.[27] Theoretically, arterial stiffness is related to the lumen diameter and distensibility of the artery. A study focusing on the associations between obesity and arterial stiffness reported that BMI was related to increased lumen diameter and reduced distensibility in femoral arteries.[28] As a result, the negative relationship between baPWV and BMI may be attributable to the result of a complex interaction of increasing the lumen diameters of peripheral arteries along of increasing BMI, overwhelming reducing arterial distensibility. Further studies may be needed to clarify the associations between central, peripheral PWV and BMI, and their clinical significances.

A previous study demonstrated that subjects with a lower eGFR have higher risks for death, cardiovascular events, and hospitalization.[12] Meanwhile, PWV, measured as a maker of arterial stiffness, was reported to provide good prognostic significance for coronary artery calcium score in CKD patients,[29] maximum intima-media thickness of the carotid artery,[30] walking time,[31] cardiovascular disease, and all-cause mortality[32,33] in end-stage renal disease patients. In present

study, we found that in CKD, eGFR, age, gender, the number of MS-associated risk factors, hs-CRP, BMI, SBP, DBP, and fasting plasma glucose were independently predicted arterial stiffness. Moreover, eGFR independently predicted arterial stiffness only in CKD but not in non-CKD, whereas dyslipidemia and elevated hs-CRP level predicted arterial stiffness in non-CKD but not in CKD. A study surveying the associations between risk factors for MS and arterial stiffness among CKD patients reported that eGFR was not an independent predictor of arterial stiffness, possibly due to its enrolled subjects having a wide eGFR range of ≤ 90 mL/min/1.73 m^2.[20] It is interesting that 1 report found that in 264 CKD stage 3−5 patients, although eGFR may have independently predicted PWV, the contribution of eGFR did not appear to be clinically meaningful when compared with traditional cardiovascular risk factors.[34] This is similar to our findings, even though eGFR remained an independent predictor of arterial stiffness in the CKD category.

The limitations of our work are the lack of smoking habits and waist circumference, which prevented from defining the diagnosis of MS. In addition, because this was a large cohort of a self-paid health examination, it was difficult to fully ascertain the subjects' current medication and underlying diseases, and it might mean that most of them had minimal comorbidity. In respect of BMI, with concerning the World Health Organization criteria of more than 30 being too high for Taiwanese,[35] the cutoff point of more than or equal to 25 that we used was from the American college of endocrinology position statement on the insulin resistance syndrome,[2] but we are unsure to what extent that this is an appropriate application for Taiwanese. Additionally, since our enrolled subjects were relatively healthy, the number of CKD subjects was far fewer than that of non-CKD. Finally, as this was a cross-sectional but not longitudinal study, we could not completely clarify the long-term causal relationships of arterial stiffness and renal function behind our findings.

In summary, arterial stiffness was negatively correlated with renal function and also increased progressively with the presence of CKD or an increased number of MS-associated risk factors and hs-CRP. The number of MS-associated risk factors and hs-CRP remained a major determinant of arterial stiffness in both CKD and non-CKD. In non-CKD, age, MS-associated risk factors (including BMI, SBP, DBP, fasting glucose, triglyceride, HDL cholesterol), and hs-CRP were independent predictors of arterial stiffness, while in CKD, only eGFR, age, gender, BMI, SBP, DBP, and fasting glucose remained as predictors. The decline of renal function contributes to arterial stiffness only in CKD, but not non-CKD. For non-CKD subjects, the treatments of MS-associated risk factors, including hypertension, hyperglycemia, dyslipidemia, and inflammatory biomarker hs-CRP are potential targets for further interventional studies of arterial stiffness, whereas for CKD subjects, renal function, BP, and glycemic control remain targets.

ACKNOWLEDGMENTS

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