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Association between chronic kidney disease and carotid intima-media thickness in relation to circulating CD34-positive cell count among community-dwelling elderly Japanese men

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HIGHLIGHTS

- Carotid intima-media thickness (CIMT) was associated with chronic kidney disease (CKD) in participants with a high CD34+ cell count.
- No association was observed for participants with a low CD34+ cell count.
- Endothelial repair activity might determine those associations.

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ABSTRACT

Background and aims: Endothelial injury is well-known as a process that can lead to chronic kidney disease (CKD) and atherosclerosis. Hematopoietic activity is known to be associated inversely with CKD and positively with atherosclerosis. Since bone-derived progenitor cells (CD34-positive cells) contribute to endothelial repair (including the progression of atherosclerosis), understanding the association between CKD and carotid intima-media thickness (CIMT), in relation to circulating CD34-positive cell count, may be an efficient means of clarifying the mechanisms underlying endothelial activity.
Methods: We conducted a cross-sectional study of 570 elderly Japanese men aged 60–69 years, who underwent a general health check-up. Participants were stratified as per a median circulating CD34-positive cell count (1.01 cells/μL).
Results: Independent of the known cardiovascular risk factors, CIMT was found to be positively associated with CKD in the participants with high circulating CD34-positive cell counts but not in participants with low counts. Odds ratios were 1.40 (1.04, 1.89) for participants with high and 1.01 (0.72, 1.43) for participants with low circulating CD34-positive cell counts after adjustment for known cardiovascular risk factors at 95% confidence intervals for CKD with one standard deviation increment of CIMT.
Conclusions: A positive association between CIMT and CKD was observed among participants with high circulating CD34-positive cell counts but not among participants with low counts. Endothelial repair activity might determine the association between CKD and CIMT.

1. Introduction

Chronic kidney disease (CKD) is known to be associated with increased arterial stiffness (for example, atherosclerosis) [1], as well as lower hematopoietic activity that causes anemia (i.e., lower hemoglobin values) [2].

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Hemoglobin levels have been shown to be positively associated with hypertension [3,4], hypertension-induced vascular damage as evaluated by the presence of hepatocyte growth factor (HGF) [5], and increased arterial stiffness [6]. In addition, hematopoietic stem cells (immature cells, such as CD34-positive cells) that are derived from bone marrow play a major role in vascular homeostasis [7–9]. Therefore, higher bone marrow activity as evaluated by higher hemoglobin levels, should be positively associated with increased arterial stiffness [5,6].

These studies illustrate a paradoxical phenomenon: although CKD is known to be associated with lower bone marrow activity, it is also associated with atherosclerosis, which is related to higher bone marrow activity.

CD34-positive cells have been shown to differentiate not only into endothelial cells [10,11] but also into foam cells that contribute to atherosclerosis [11]. In addition, the overall count of the circulating CD34-positive cells divided by the median count could act as an important determinant of the association between high-density lipoprotein cholesterol (HDLc) and hypertension [12], triglycerides (TG) and blood pressure [13], HGF and atherosclerosis [14], and height and circulating CD34-positive cell count [15]. These studies indicate that circulating CD34-positive cell count could act as a surrogate marker of active vascular remodeling relating to the progression of atherosclerosis.

Therefore, investigating the association between carotid intima-media thickness (CIMT) and CKD by the median circulating CD34-positive cell count may be an effective means of understanding the mechanisms that underlie the association between CIMT and CKD.

We conducted a cross-sectional study in 570 elderly Japanese men, aged 60–69, who had undergone a general health check-up during 2013–2015.

2. Materials and methods

2.1. Study population

The total number of male residents, aged 60–69 years, in 2015 (estimated by the National Institute of Population and Social Security Research in March 2013) was 3264 in Goto city and 1010 in Saza town [16]. The study population comprised 617 male residents, aged 60–69 years, from Goto city and Saza town that are located in the western part of Japan; these had undergone an annual medical check-up from 2013 to 2015 as recommended by the Japanese government.

Members of this population without serum (n = 38) and CIMT data (n = 1) were excluded from analysis. Additionally, to avoid the influence of the occurrence of inflammatory diseases, participants with high white blood cell counts (≥10,000 cells/μL [n = 8]) were excluded. The remaining participants, comprising 570 men, with a mean age of 65.5 years (standard deviation (SD): 2.6; range: 60–69), were enrolled in the study.

2.2. Data collection and laboratory measurements

Trained interviewers obtained information on smoking status, drinking status, as well as the use of anti-hypertensive, lipid-lowering, and glucose-lowering agents.

Systolic and diastolic blood pressures on the right arm were recorded by a trained observer using a blood pressure measuring device (HEM-907; Omron, Kyoto, Japan) after at least 5 min of rest in a sitting position.

Body weight and height of participants, while wearing light clothing, were measured using an automatic body composition analyzer (BF-220; Tanita, Tokyo, Japan); body mass index (BMI [kg/m^2]) was calculated as well. Fasting blood samples were collected in a heparin sodium tube, an EDTA-2K tube, and a siliconized tube. Fresh samples (within 24 h from the drawing) from the heparin sodium tube were used to determine the CD34-positive cell count. The Beckton Dickinson Biosciences Trucount™ technology, an accurate and reproducible single-platform assay cited in the International Society of Hematotherapy and Graft Engineering (ISHAGE) guidelines [17] and supported by automated software on the BD FACSCant™ II system, was used to measure the count of circulating CD34-positive cells.

Samples from the EDTA-2K tube were used to measure the counts of white blood cells (WBC) and platelets using an automated procedure at SRL, Inc. (Tokyo, Japan). Serum TG, serum HDLc, hemoglobin A1c (HbA_{1C}), γ-glutamyltranspeptidase (γ-GTP), and serum creatinine contents were measured using standard laboratory procedures at SRL, Inc. (Tokyo, Japan). Glomerular filtration rate (GFR) was estimated using an established method that was recently proposed by a working group of the Japanese Chronic Kidney Disease Initiative [18]. The equation adapted for use here was: GFR (mL/min/1.73 m^2) = 194 × (serum creatinine (enzyme method))$^{-1.094}$ × (age)$^{-0.287}$.

CKD was defined as GFR < 60 mL/min/1.73 m^2.

CIMT was determined by ultrasonography of the left and right common carotid arteries by an experienced vascular technician using a LOGIQ Book XP with a 10-MHz transducer (GE Healthcare, Milwaukee, WI, USA). Maximum values for left and right CIMT were calculated using an automated digital edge-detection software (Intimascope; MediaCross, Tokyo, Japan) and a protocol that has been described in detail elsewhere [19]. The values of right and left CIMT without plaque measurement were calculated and the maximum CIMT value was used for analysis.

2.3. Statistical analyses

Since circulating CD34-positive cell count determines the influence of cardiovascular risk factors on atherosclerosis [14,20], study participants were stratified by circulating according to the CD34-positive cell counts (median values) as described previously [12–15,20].

Characteristics of the study population as per the counts of circulating CD34-positive cells have been expressed here as mean ± standard deviation. A trend test was performed with a regression model to determine mean values. Simple correlation and multiple linear regression analyses of circulating CD34-positive cell count and GFR after adjustment for relevant confounding factors, based on median circulating CD34-positive cell count (0.93 cells/μL), were conducted. Since CD34-positive cell count, TG, and γ-GTP had a skewed distribution, logarithmic transformations were performed for these factors.

Logistic regression models were used to calculate odds ratios at 95% confidence intervals to determine the influence of CIMT on CKD.

Our study was conducted to clarify the mechanism that may possibly underlie the endothelial repair activity associated with both atherosclerosis and CKD. Even though habitual and medication statuses could influence the endothelial activity, these factors may not have acted as confounding factors in the present analysis because endothelial repair activity works secondary to the habitual and medication statuses, which have similar effects on CKD and atherosclerosis. Adjustments for confounding factors were made using two models. In the first model, adjustment was made only for age. The second model included other possible confounding factors, namely, BMI (kg/m^2), systolic blood pressure (mmHg), HDLc (mg/dL), TG (mg/dL), HbA1C (%), and γ-GTP (U/L).

To evaluate the association between CIMT and circulating CD34-positive cells using the latter's count, we performed simple correlation and multiple linear regression analyses among the subjects without hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg) since it may mask the beneficial influence of CD34-positive cells on prevention of atherosclerosis [21]. In multiple regression analysis, age, BMI (kg/m^2), systolic blood pressure (mmHg), HDLc (mg/dL), TG (mg/dL), HbA1C (%), platelets (× 10^4/μL) and γ-GTP (U/L) were considered to be confounding factors.

For sensitivity analysis, we repeated the aforementioned analysis of the models with further adjustments for habitual status (drinking status

Table 1
Characteristics of the study population as per circulating CD34-positive cell count.

	Low CD34-positive cell count (< 1.01 cells/μL)	High CD34-positive cell count (≥1.01 cells/μL)	p
No. of participants at risk	286	284	
Age, years	65.7 ± 2.5	65.3 ± 2.6	0.042
Systolic blood pressure, mmHg	134 ± 18	135 ± 17	0.746
Diastolic blood pressure, mmHg	81 ± 13	81 ± 11	0.727
Anti-hypertensive medication use, %	39.2	48.6	0.023
Body mass index (BMI), kg/m^2	22.8 ± 3.0	23.9 ± 2.8	< 0.001
Current smoker, %	11.5	13.4	0.506
Current drinker, %	37.8	50.0	0.243
Serum HDL-cholesterol (HDLc), mg/dL	58 ± 14	56 ± 15	0.108
Serum triglycerides (TG), mg/dL	110 ± 84	126 ± 94	0.032
Use of lipid lowering medication, %	11.9	16.9	0.088
Hemoglobin A1c (HbA1c), %	5.6 ± 0.6	5.8 ± 0.7	0.003
Use of glucose lowering medication, %	7.7	10.2	0.293
Serum γ-glutamyltranspeptidase (γ-GTP), U/L	46 ± 40	53 ± 77	0.189
Glomerular filtration rate (GFR), mL/min/1.73m^2	72.9 ± 15.2	73.0 ± 14.5	0.934
Platelets, × 10^4/μL	20.9 ± 5.1	22.9 ± 5.0	< 0.001
White blood cells (WBC), cell/μL	5032 ± 1274	6143 ± 1316	< 0.001
Carotid intima-media thickness (CIMT), mm	0.92 ± 0.20	0.94 ± 0.20	0.421

Values: mean ± standard deviation. Current drinker: alcohol consumption ≥69 g/week.

[no, current (≥69 g/week)] and smoking status [no, current]) and medication status (taking anti-hypertensive agents [no, yes], lipid-lowering agents [no, yes], or glucose-lowering agents [no, yes]).

All statistical analyses were performed with the SAS system for Windows (Version 9.4; SAS Inc., Cary, NC). As was done in a previous study [22], values of $p < 0.05$ for main effects and $p < 0.2$ for interactions were considered statistically significant.

3. Results

3.1. Characteristics of the study population as per circulating CD34-positive cell count

Participants with high circulating CD34-positive cell counts showed significantly higher anti-hypertensive medication use, BMI, TG, HbA1c, platelets, and WBC but had significantly lower age than those with lower circulating CD34-positive cell counts (Table 1).

3.2. Associations between circulating CD34-positive cell count and other variables as per the CD34-positive cell count

Independent of known cardiovascular risk factors, GFR was significantly inversely associated with circulating CD34-positive cell counts as seen in participants with high circulating CD34-positive cell counts, while BMI and platelets were significantly positively associated with circulating CD34-positive cell counts as seen in participants with low counts (Table 2).

3.3. Association between glomerular filtration rate (GFR) and other variables as per the CD34-positive cell count

Independent of the known cardiovascular risk factors, the circulating CD34-positive cell counts were slightly, but significantly, inversely associated with GFR in participants with high circulating CD34-positive cell counts, while platelets were slightly, but significantly,

Table 2
Simple correlation and multiple linear regression analyses of associations between circulating CD34-positive cell count and other variables adjusted for confounding factors by CD34-positive cell count.

	r	(*p*)	B	β	*p*
High CD34-positive cell count (≥1.01 cells/μL)					
No. of participants at risk	284				
Age	−0.07	0.225	−0.01	−0.08	0.180
Systolic blood pressure	0.05	0.360	0.002	0.08	0.165
Body mass index (BMI)	0.07	0.240	0.004	0.02	0.725
Serum HDL-cholesterol (HDLc)	−0.11	0.075	−0.001	−0.04	0.549
Serum triglycerides (TG)	0.15	0.009	0.11	0.12	0.090
Hemoglobin A1c (HbA1c)	−0.004	0.942	−0.03	−0.04	0.466
Serum γ-glutamyltranspeptidase (γ-GTP)	0.04	0.499	0.02	0.03	0.658
Glomerular filtration rate (GFR)	−0.12	0.035	−0.004	−0.12	0.042
Platelets	0.02	0.676	0.002	0.02	0.760
Low CD34-positive cell count (< 1.01 cells/μL)					
No. of participants at risk	286				
Age	0.03	0.652	0.005	0.03	0.597
Systolic blood pressure	0.03	0.605	0.0001	0.004	0.943
Body mass index (BMI)	0.14	0.017	0.02	0.17	0.009
Serum HDL-cholesterol (HDLc)	−0.09	0.127	−0.0003	−0.01	0.856
Serum triglycerides (TG)	0.03	0.601	0.03	0.04	0.597
Hemoglobin A1c (HbA1c)	0.04	0.505	−0.002	−0.003	0.956
Serum γ-glutamyltranspeptidase (γ-GTP)	−0.10	0.080	−0.08	−0.14	0.050
Glomerular filtration rate (GFR)	−0.03	0.622	−0.0004	−0.01	0.809
Platelets	0.17	0.004	0.01	0.17	0.005

r (*p*): simple correlation coefficient (*p*-values); B: parameter estimate; β: standardized parameter estimate; *p*: *p*-values for multivariable linear regression models. CD34-positive cell count, TG, and γ-GTP were calculated as logarithmic values.

Table 3
Simple correlation and multiple linear regression analyses of associations between glomerular filtration rate (GFR) and other variables adjusted for confounding factors by CD34-positive cell count.

	r	(*p*)	B	β	*p*
High CD34-positive cell count (≥1.01 cells/μL)					
No. of participants at risk	284				
Age	−0.07	0.233	−0.43	−0.08	0.188
Systolic blood pressure	0.09	0.143	0.07	0.08	0.200
Body mass index (BMI)	−0.06	0.303	−0.17	−0.03	0.610
Serum HDL-cholesterol (HDLc)	0.19	0.002	0.11	0.11	0.133
Serum triglycerides (TG)	−0.10	0.090	−1.09	−0.04	0.583
Hemoglobin A1c (HbA1c)	−0.09	0.137	−1.15	−0.06	0.351
Serum γ-glutamyltranspeptidase (γ-GTP)	0.11	0.064	2.45	0.12	0.068
Platelets	0.06	0.334	0.18	0.06	0.300
Circulating CD34-positive cell	−0.12	0.035	−3.78	−0.12	0.042
Low CD34-positive cell count (< 1.01 cells/μL)					
No. of participants at risk	286				
Age	−0.16	0.006	−0.80	−0.13	0.022
Systolic blood pressure	0.02	0.747	0.02	0.02	0.739
Body mass index (BMI)	−0.08	0.158	−0.53	−0.10	0.104
Serum HDL-cholesterol (HDLc)	0.03	0.640	−0.12	−0.11	0.112
Serum triglycerides (TG)	−0.11	0.066	−5.93	−0.20	0.006
Hemoglobin A1c (HbA1c)	−0.05	0.390	−0.21	−0.01	0.892
Serum γ-glutamyltranspeptidase (γ-GTP)	0.09	0.139	4.79	0.21	0.003
Platelets	0.13	0.029	0.38	0.13	0.034
Circulating CD34-positive cell	−0.03	0.622	−0.57	−0.01	0.809

r (*p*): simple correlation coefficient (*p*-values); B: parameter estimate; β: standardized parameter estimate; *p*: *p*-values for multivariable linear regression models. CD34-positive cell count, TG and γ-GTP were calculated as logarithmic values.

positively associated with GFR in participants with low counts (Table 3).

3.4. Chronic kidney disease (CKD) in relation to carotid intima-media thickness (CIMT) as per circulating CD34-positive cell count

CIMT was significantly positively associated with CKD in participants with high circulating CD34-positive cell counts but the two variables showed no association in participants with low counts. These associations remained unchanged after further adjustments for other known cardiovascular risk factors (Table 4).

3.5. Effect of associations between carotid intima-media thickness (CIMT) levels and two circulating CD34-positive cell categories on chronic kidney disease (CKD)

An investigation of the effects of the associations between CIMT and the two CD34-positive cell categories (high and low) on CKD revealed a significant interaction. The adjusted p-value for the effect of this interaction was $p = 0.106$ for the crude model and $p = 0.072$ for the fully adjusted model.

3.6. Circulating CD34-positive cell count and carotid intima-media thickness (CIMT) as per circulating CD34-positive cell level among participants without hypertension

Among the study population, 166 participants with high circulating CD34-positive cell counts and 164 participants with low counts were diagnosed to not have hypertension. By simple correlation analysis, a significantly inverse association between circulating CD34-positive cell count and CIMT was observed (simple correlation coefficient (r) = -0.18, $p = 0.017$) in participants with high counts, while no significant association was observed for participants with a low count ($r = -0.02$, $p = 0.776$). These associations remained unchanged even after further adjustment for possible confounding factors (parameter estimate [B] = -0.07; standardized parameter estimate [β] −0.18, $p = 0.032$ for

Table 4
Odds ratios (ORs) and 95% confidence intervals (CIs) for chronic kidney disease (CKD) in relation to carotid intima-media thickness (CIMT) stratified by circulating CD34-positive cell count.

	Carotid intima- media thickness (CIMT) tertiles			*p* for trend	1 SD increment of CIMT (0.20 mm)
	T1 (low)	T2	T3 (high)		
High CD34-positive cell count (≥1.01 cells/μL)					
No. of participants	86	102	96		
No. of cases (%)	10 (11.6)	14 (13.7)	23 (24.0)		
Age-adjusted ORs	1.00	1.18 (0.49, 2.83)	2.33 (1.02, 5.28)	0.031	1.34 (1.00, 1.78)
Multivariable ORs	1.00	1.16 (0.47, 2.84)	2.35 (1.02, 5.43)	0.031	1.40 (1.04, 1.89)
Low CD34-positive cell count (< 1.01 cells/μL)					
No. of participants	101	90	95		
No. of cases (%)	12 (11.9)	17 (18.9)	11 (11.6)		
Age-adjusted ORs	1.00	1.49 (0.66, 3.37)	0.85 (0.35, 2.07)	0.721	1.01 (0.73, 1.40)
Multivariable ORs	1.00	1.45 (0.63, 3.37)	0.83 (0.33, 2.08)	0.672	1.01 (0.72, 1.43)

Chronic kidney disease (CKD) is defined as glomerular filtration rate (GFR) < 60 (mL/min/1.73 m^2). Multivariable ORs: adjusted further for age and SBP, BMI, HDLc, TG, HbA1C, and γ-GTP.
SBP: systolic blood pressure. BMI: body mass index. HDLc: HDL-cholesterol. TG; triglycerides. HbA1c: hemoglobin A1c. γ-GTP: γ-glutamyltranspeptidase. Carotid intima-media thickness (CIMT) tertiles are: < 0.83 mm for T1, 0.83–0.97 mm for T2, and ≥0.98 for T3.

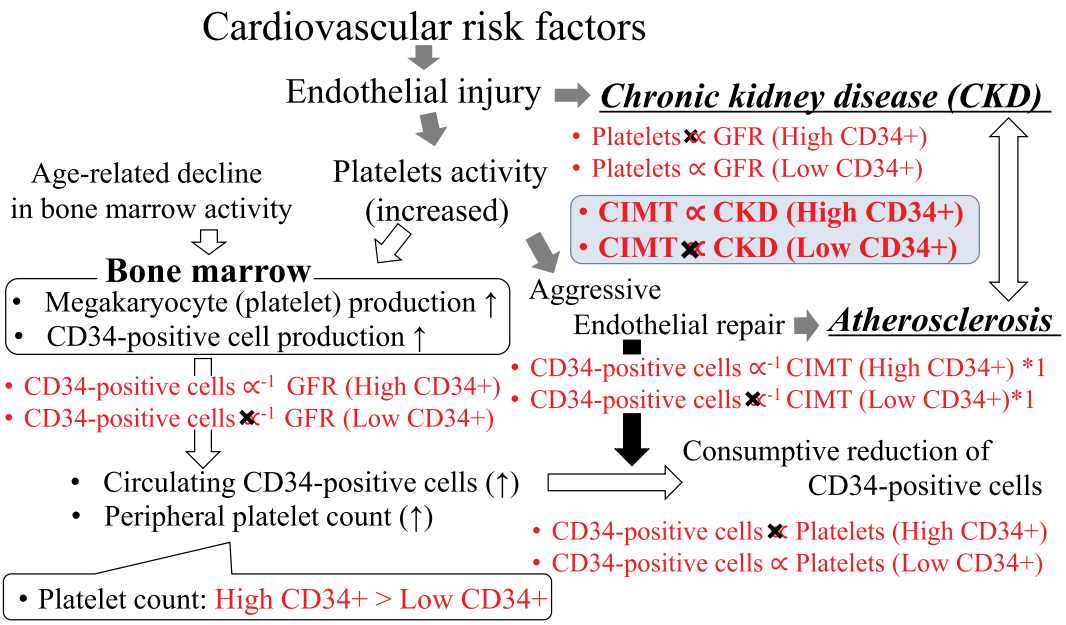

Fig. 1. Possible mechanisms underlying the association between chronic kidney disease and carotid intima-media thickness.
Relations marked in red were observed in this study. *1: analyses were performed in participants without hypertension. CKD: chronic kidney disease. CIMT: carotid intima-media thickness. High CD34^{+}: participants with a high circulating CD34-positive cell count. Low CD34+: participants with a low circulating CD34-positive cell count. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

participants with high counts and B = −0.02, β = −0.04, $p = 0.566$ for participants with low circulating CD34-positive cell counts).

The sensitivity analysis showed associations similar to the main results.

4. Discussion

The major findings of this study was that even though a significantly positive association between CIMT and CKD was observed for participants with high circulating CD34-positive cell counts, no significant association was observed for participants with low counts.

Endothelial dysfunction was recognized as one of the initial mechanisms that led to glomerular injury and atherosclerosis (increased arterial stiffness) [23]. A previous 2-year follow-up study with 2751 participants revealed that baseline CIMT acts as a predictor of CKD development [24].

Since a high circulating CD34-positive cell count might indicate active endothelial repair [12–15], circulating CD34-positive cell count could influence the association between CIMT and CKD. Similarly, in our study, we found out that a significantly positive association between CIMT and CKD was limited to participants with high circulating CD34-positive cell counts only. However, the underlying mechanism remains unclear. Fig. 1 summarizes the possible mechanisms underlying these associations.

Platelets promote the mobilization of bone marrow-derived CD34-positive cells into peripheral blood [25]. Furthermore, platelets not only induce the differentiation of CD34-positive cells into endothelial progenitor cells and endothelial cells but also into foam cells [10,11] that are a well-known contributing factor the development of atherosclerotic lesions. Therefore, being an initial cellular contributor in this process, platelets play an important role in the development of atherosclerotic lesions [26]. Participants with high CD34-positive cell counts should have an elevated endothelial repair activity [12–15, 20,21,27,28], which is a known contributing factor for the development of atherosclerosis because endothelial injury stimulates CD34-positive cell production and platelet production. Therefore, the positive association between CKD and CIMT was observed to be limited to participants with high circulating CD34-positive cell counts. Our finding that participants with high circulating CD34-positive cell counts had significantly higher platelet counts as well than those with low circulating CD34-positive cell counts partly explains this phenomenon since elevated platelet counts could indicate a higher vascular remodeling activity [21,29].

Furthermore, aggressive endothelial repair should cause a consumptive reduction in circulating CD34-positive cells but not in platelet counts [15,20]. Therefore, we found a significantly positive association between platelet and circulating CD34-positive cell counts only in participants with low circulating CD34-positive cell counts.

We also observed that platelet counts were positively associated with GFR only in participants with low circulating CD34-positive cell counts. These associations also support the abovementioned mechanisms, since platelets should serve as an indicator of appropriate endothelial repair in participants without a strong influence of consumptive reduction in CD34-positive cell counts (i.e., low circulating CD34-positive cell counts).

Although consumptive reduction in circulating CD34-positive cell counts appears to be associated with the progression of atherosclerosis, atherosclerosis is only a single aspect of endothelial repair. Therefore, the degree of consumptive reduction in circulating CD34-positive cell counts could act as an indicator of active endothelial repair, which is beneficial for the maintenance of renal function. In our study, circulating CD34-positive cell count was slightly but significantly inversely associated with GFR among participants with high circulating CD34-positive cell counts. When we limited the analysis to subjects without hypertension, since hypertension might mask the beneficial influence on prevention of atherosclerosis [21], circulating CD34-positive cell count was observed to be significantly inversely associated with CIMT in participants with high CD34-positive cell counts but not in participants with low counts.

Furthermore, for participants with low circulating CD34-positive cell counts, not only the degree of endothelial injury but also age-related reduction in bone marrow activity influenced the association between CIMT and CKD, which resulted in no significant association being observed between the two variables.

The strengths of our study are that, unlike other epidemiological studies, we conducted multi-faceted analyses, which aided clarification

of many associations in a simple study population; all of our results could be explained by simple mechanisms as well.

The clinical implications of our study are that although CIMT has been reported to be a predictor of CKD previously [24], our study showed that the absence of the progression of atherosclerosis does not indicate a low risk of developing CKD; we also demonstrated that hematopoietic activity might determine the association between CKD and CIMT. In addition, our results provide an efficient knowledge for development of a more accurate diagnosis procedure for vascular complications that are frequent in subjects with accelerated atherosclerosis.

Potential limitations of this study warrant consideration. Although platelet count itself might act as an indicator of endothelial repair activity [20,21], platelet activity, but not platelet count itself, has been shown to induce differentiation of CD34-positive cells into endothelial and foam cells [10,11]. Further analysis with data on platelet activity, such as platelet-derived stromal cell-derived factor 1, is required. Although we observed no significant association between CKD and CIMT in participants with low circulating CD34-positive cell counts, CKD could be associated with reduced endothelial function due to a deficient endothelial repair process. However, no data on endothelial function was available for review here. Further analyses that include endothelial function-related data, such as flow-mediated dilation (FMD), are necessary. Finally, because this was a cross-sectional study, causal relationships could not be established.

In conclusion, we observed a significantly positive association between CIMT and CKD in participants with high circulating CD34-positive cell counts, but no significant association was observed for participants with low counts. These findings provide an important a piece of knowledge to clarify the mechanisms that underlie endothelial maintenance in relation to CIMT and CKD.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Author contributions

YS designed the study and performed the statistical analyses, interpreted the data, and drafted the manuscript and revised it. SS, YuN, JK, HY, MN, KK, SK, and YaN assisted with the design of the study, were involved in data collection, and checked the manuscript. HY, SK, YaN, and TM participated in the study concept and checked the manuscript. TM was the general coordinator and also designed the study. All authors read, revised, and approved the final version.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2019.02.004.

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