Carotid intima-media thickness is a novel predictor of new onset of hypertension in normotensive subjects

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Abstract
Increased carotid intima-media thickness (IMT) in individuals without hypertension might indicate other factors promoting the atherosclerotic process that are often simultaneously clustered in individuals. The present study tested the hypothesis that carotid IMT predicts new onset of hypertension in the normotensive subjects.

A total of 867 participants were enrolled from our yearly physical checkup program and their carotid IMT was measured. After a baseline examination, the subjects were followed up for a median of 1091 days with the endpoint being the development of hypertension.

At baseline, the carotid IMT value was 0.75 ± 0.16 mm. Hypertension developed in 184 subjects during the follow-up (76.9/1000 person-years). The incidence of hypertension was increased across the tertiles of the carotid IMT value (39.6, 70.0, and 134.5/1000 person-years in the first, second, and third tertiles, respectively, P < .001 by log-rank test). Multivariate Cox-hazard analysis after adjustment identified carotid IMT, taken as a continuous variable, as a significant predictor of new-onset hypertension (hazard ratio = 7.08, 95% confidence interval = 3.06–15.39). Furthermore, multivariate linear regression analyses indicated a significant correlation between the carotid IMT at baseline and yearly increases in systolic blood pressure during the follow-up period (β = 0.189, P < .001).

Carotid IMT is an independent predictor of hypertension onset in normotensive subjects. The findings also suggested a close association between increased carotid IMT and blood pressure.

Abbreviations: AUC = area under the curve, CI = confidence interval, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, FPG = fasting plasma glucose, HDL = high-density lipoprotein, HR = Hazard ratio, HT = hypertension, IMT = intima-media thickness, LDL = low-density lipoprotein, ROC = receiver operating characteristics curve, SBP = systolic blood pressure.

Keywords: blood pressure, hypertension, intima-media thickness, normotensive, predictor

1. Introduction
Primary prevention of cardiovascular diseases contributes to an extension of healthy life expectancy. Accordingly, preventing or retarding atherosclerotic processes is one of the most important strategies in public health, with hypertension onset one of the major risk factors to target. Unfortunately, the risk of cardiovascular events in hypertensive patients remains high even with strict management of blood pressure, compared to normotensive individuals not taking antihypertensive medication.[1,2] Thus, primary prevention of hypertension is crucial in further reducing cardiovascular morbidity and mortality.

Assessing the target organ damage in hypertensive patients is important for accurately ascertaining the impact of increased blood pressure and the sensitivity of individuals to such increases. Indeed, carotid intima-media thickness (IMT) is an index of atherosclerotic vascular damage that is closely associated with blood pressure levels.[3] Conversely, an increase in carotid IMT suggests the presence of atherosclerotic risk factors, and in individuals without hypertension it suggests that risk factors other than hypertension play a major role in accelerating the process of atherosclerosis. The diagnosis of metabolic syndrome is based on the fundamental concept that each component of the condition is not coincidentally clustered and that there are close associations among the components. Thus, an increase of blood pressure might also cluster around risk factors that promote the increase in carotid IMT in individuals without hypertension.

While carotid IMT in hypertensive patients is an important marker of hypertensive organ damage,[4] this index is not widely considered with respect to blood pressure in normotensive subjects. Thus, we investigated whether carotid IMT predicts new onset of hypertension in the normotensive subjects.
2. Methods

2.1. Study design

We conducted a cohort study from July 2008 to June 2013 to investigate the impact of carotid IMT assessed by ultrasound examination on the incidence of hypertension, using participants who visited our hospital for a yearly physical checkup from July 2008 to December 2011. The study protocol was in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Eshu Hospital. All participants gave written informed consent to participate before the start of the study and at each study visit.

2.2. Study participants and procedures

Participants who underwent carotid ultrasound examination as a part of a routine checkup program (n=1419) were screened for eligibility for the present study. Participants aged 25 years or older, those without hypertension, and those without a history of coronary heart disease or stroke were enrolled (n=867) and followed up with the endpoint being the onset of hypertension. Blood pressure was measured 3 times at 2-minute intervals during a sitting position after 5 minutes rest. The mean of the second and third measurements was taken as the blood pressure. Hypertension was defined as systolic blood pressure (SBP) ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or if they used antihypertensive medications. Participants were defined as having dyslipidemia if their high-density lipoprotein (HDL) cholesterol level was < 40 mg/dL, if their low-density lipoprotein (LDL) cholesterol level was ≥ 140 mg/dL, if their triglyceride level was ≥ 150 mg/dL, or if they used antidyplidemic medications. Participants were defined as having diabetes mellitus if their fasting plasma glucose (FPG) level was ≥ 126 mg/dL or if they started antihypertensive medication during the follow-up period, changes in blood pressure were calculated using data obtained before the prescription of antihypertensive drugs. P < .05 was considered significant.

3. Results

Table 1 summarizes the baseline characteristics of subjects in the present study. Cross-sectional analysis using a multiple linear regression model revealed that carotid IMT was correlated with age (r=0.406, P < .001), male gender (r=0.119, P= .011), body mass index (r=0.081, P= .018), SBP (r=0.100, P=.002), FPG (r=0.077, P=.017), LDL-cholesterol (r=0.062, P=.049), and HDL-cholesterol (r=–0.071, P= .029). The actual follow-up period of the present study was 2393 person-years and the median follow-up period per participant was 1091 days (range 177–1815 days). During the follow-up, 184 subjects developed cumulative incidence rates of new-onset hypertension. The significance of differences in the cumulative incidence rates was evaluated by the log-rank test and adjusted by multivariate Cox proportional hazard regression models. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated.

![Table 1](image)

Table 1 Baseline characteristics of study subjects.

| Total        | Low IMT  | High IMT |
|--------------|----------|---------|
| (n=867)      | (n=410)  | (n=457) |
| Age, y       | 59.1 ± 8 | 55.8 ± 8 | 62.0 ± 7 \( ^* \) |
| Gender, male, n (%) | 385 (44.4%) | 168 (41.0%) | 217 (47.5%) |
| Body mass index, kg/m² | 22.2 ± 2.8 | 22.0 ± 2.8 | 22.4 ± 2.9 |
| SBP, mm Hg   | 119.8 ± 11.8 | 118.0 ± 11.8 | 121.4 ± 11.5 \( ^* \) |
| DBP, mm Hg   | 73.9 ± 7.8 | 73.2 ± 8.0 | 74.3 ± 7.7 |
| Heart rate, bpm | 62.7 ± 6.6 | 63.4 ± 8.9 | 62.0 ± 8.2 |
| Serum creatinine, mg/dL | 0.72 ± 0.16 | 0.71 ± 0.15 | 0.72 ± 0.17 |
| eGFR, ml/min per 1.73m² | 97.1 ± 10.2 | 99.4 ± 9.4 | 95.1 ± 10.4 |
| Uric acid, mg/dL | 5.09 ± 1.23 | 5.03 ± 1.22 | 5.14 ± 1.23 |
| FPG, mg/dL   | 95.9 ± 13.0 | 94.6 ± 11.0 | 97.0 ± 14.6 \( ^* \) |
| LDL cholesterol, mg/dL | 124.9 ± 27.2 | 124.3 ± 27.4 | 125.5 ± 27.1 |
| HDL cholesterol, mg/dL | 60.6 ± 13.6 | 62.0 ± 14.6 | 59.3 ± 12.6 |
| Triglyceride, mg/dL | 102.5 ± 57.4 | 103.3 ± 62.3 | 101.8 ± 52.8 |
| Hemoglobin, g/dL | 13.6 ± 1.3 | 13.6 ± 1.3 | 13.6 ± 1.2 |
| IMT, mm | 0.75 ± 0.16 | 0.63 ± 0.07 | 0.68 ± 0.14 \( ^* \) |
| Diabetes mellitus, n (%) | 62 (7.2%) | 17 (4.1%) | 45 (9.8%) |
| Dyslipidemia, n (%) | 378 (43.6%) | 158 (38.5%) | 220 (48.1%) |
| Current smoking status, n (%) | 112 (12.9%) | 58 (14.1%) | 54 (11.8%) |
| Family history of HT, n (%) | 209 (24.1%) | 107 (26.1%) | 102 (22.3%) |

Values are mean ± standard deviation, the number (%) of participants. Subjects were divided into low IMT group or high IMT group using the cut-off value (0.75 mm) obtained from the receiver operating characteristics curve analysis for the new onset of hypertension. BP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, FPG = fasting plasma glucose, HDL = high-density lipoprotein, HT = hypertension, IMT = intima-media thickness, LDL = low-density lipoprotein, SBP = systolic blood pressure. \( ^* \) P < .05.

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Chi-square test was used for comparisons between categorical data. The Kaplan-Meier method was applied to calculate the yearly change in blood pressure. In participants who started antihypertensive medication during the follow-up period, changes in blood pressure were calculated using data obtained before the prescription of antihypertensive drugs. P < .05 was considered significant.

2.3. Measurement of IMT

The carotid artery was imaged with an ultrasound system (ProSound SSD-3500SV; Aloka Co., Ltd, Tokyo, Japan). The bilateral common carotid arteries were examined at 1- to 2-cm proximal sites to the carotid bifurcation on a longitudinal, 2-dimensional ultrasound image. The IMT in the posterior wall of the common carotid artery was measured as the distance from the leading edge of the first echogenic line (lumen-intima interface) to the leading edge of the second line (media-adventitia interface). IMT was measured at 3 points, the maximal site and 10 mm distal and proximal of the maximal site, at each side of the common carotid artery, and the average of the 6 measurements was taken as the IMT value. The examiners of the ultrasound images had no access to the subjects’ medical information.

2.4. Statistical analysis

All analyses were performed using IBM SPSS statistics 24 software (Chicago, IL). Data in the text and tables are expressed as mean ± standard deviation or the number and percentage of participants. Differences between two means that had a normal distribution were compared using the unpaired Student’s t test. Chi-square test was used for comparisons between categorical data. The Kaplan-Meier method was applied to calculate the cumulative incidence rates of new-onset hypertension. The significance of differences in the cumulative incidence rates was evaluated by the log-rank test and adjusted by multivariate Cox proportional hazard regression models. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated.
hypothesis (21.2%, 76.9 per 1000 person-years), with a higher incidence in males (24.7%, 90.8 per 1000 person-years) than in females (18.5%, 66.1 per 1000 person-years; P < .05). By retrospective analysis, carotid IMT was greater in subjects with (0.83 ± 0.19 mm) than without future hypertension (0.73 ± 0.15 mm; P < .001), although most variables at baseline were different between subjects with and without future hypertension (Table 2).

Univariate analysis and multivariate Cox-hazard regression analysis adjusted for age, gender, body mass index, SBP, heart rate, serum creatinine, uric acid, FPG, LDL-cholesterol, HDL-cholesterol, current smoking habit, and family history of hypertension at baseline revealed that carotid IMT measured at baseline was an independent predictor of future hypertension (Table 3). The cut-off value, area under the curve (AUC), sensitivity, and specificity for new onset of hypertension was 0.75 mm, 0.667, 59.8, and 66.5, respectively, based on receiver operating characteristics (ROC) curve analysis. Then, subjects were divided into 2 groups using the cut-off value obtained from the ROC curve analysis to compare the risk of future hypertension (see Table 1); by multivariate Cox-hazard regression analysis, those subjects with increased IMT had a 63% increase in risk (Table 4, Model A). The incidence of hypertension in the low and high IMT groups was 47.1 and 103.5 per 1000 person-years, respectively. Subjects were then divided into tertiles according to the carotid IMT value and the incidence of hypertension was analyzed by the Kaplan–Meier method. The IMT value in the first, second, and third tertiles was 0.59 ± 0.06, 0.75 ± 0.04, and 0.93 ± 0.15 mm, respectively, and the incidence of hypertension was increased across the tertiles (39.6, 70.0, and 134.5 per 1000 person-years in the first, second, and third tertiles, respectively, P < .001 by log-rank test; Fig. 1). Multivariate Cox-hazard regression analysis demonstrated that HR (95% CI) was increased with increasing carotid IMT values (Table 4, Model B). In addition, the carotid IMT value at baseline significantly correlated with yearly increases in SBP during the follow-up period by univariate and multivariate liner regression analyses (r = 0.176, P < .001 and r = 0.192, P < .001, respectively) (Table 5).

4. Discussion
The present study demonstrated that carotid IMT assessed by ultrasound sonography is a significant determinant of future

| Table 2 |
| --- |
| Retrospective analysis of study subjects’ characteristics at baseline. |
| Without future HT | With future HT |
| --- | --- |
| Age, y | 58.4 ± 9.0 | 61.7 ± 7.6* |
| Gender, male, n (%) | 290 (42.5%) | 95 (51.6%) |
| Body mass index, kg/m² | 22.1 ± 2.8 | 22.7 ± 2.7* |
| SBP, mm Hg | 118.2 ± 11.8 | 125.7 ± 11.0* |
| DBP, mm Hg | 73.1 ± 7.6 | 76.9 ± 8.1* |
| Heart rate, bpm | 62.4 ± 8.6 | 63.6 ± 8.5 |
| Serum creatinine, mg/dL | 0.71 ± 0.14 | 0.75 ± 0.21* |
| eGFR, mL/min per 1.73m² | 97.8 ± 9.6 | 94.5 ± 11.6* |
| Uric acid, mg/dL | 5.05 ± 1.24 | 5.22 ± 1.19 |
| FPG, mg/dL | 95.2 ± 12.2 | 98.4 ± 15.4* |
| LDL cholesterol, mg/dL | 125.8 ± 26.4 | 121.7 ± 30.1 |
| HDL cholesterol, mg/dL | 61.0 ± 13.5 | 58.9 ± 14.0 |
| Triglyceride, mg/dL | 101.8 ± 56.9 | 105.2 ± 63.0 |
| Hemoglobin, g/dL | 13.5 ± 1.4 | 13.8 ± 1.3 |
| IMT, mm | 0.73 ± 0.14 | 0.83 ± 0.19 |
| Yearly increase in SBP, mm Hg/year | −0.36 ± 0.66 | 6.38 ± 11.1 |
| Yearly increase in DBP, mm Hg/year | −0.52 ± 4.10 | 2.63 ± 8.00 |
| Diabetes mellitus, n (%) | 45 (6.6%) | 78 (41.3%) |
| Dyslipidemia, n (%) | 302 (44.2%) | 76 (41.3%) |
| Current smoking status, n (%) | 86 (12.6%) | 26 (14.1%) |
| Family history of HT, n (%) | 154 (22.5%) | 55 (29.9%)* |

Values are mean ± standard deviation, the number (%) of participants.

Univariate analysis and multivariate Cox-proportional hazard regression analyses for future development of hypertension.

| Variable at baseline | Hazard ratio (95% CI) | P | Hazard ratio (95% CI) | P |
| --- | --- | --- | --- | --- |
| Age, y | 1.039 (1.020–1.057) | <.001 | 1.022 (1.001–1.044) | .036 |
| Gender, male | 1.387 (1.038–1.853) | .027 | 0.957 (0.631–1.452) | .838 |
| Body mass index, kg/m² | 1.079 (1.028–1.133) | .002 | 1.054 (0.994–1.116) | .080 |
| SBP, mm Hg | 1.060 (1.044–1.076) | <.001 | 1.051 (1.034–1.067) | <.001 |
| DBP, mm Hg | 1.067 (1.045–1.090) | <.001 | — | — |
| Heart rate, bpm | 1.019 (1.002–1.036) | .024 | 1.010 (0.993–1.028) | .259 |
| Serum creatinine, mg/dL | 3.737 (1.774–7.874) | .001 | 3.358 (1.324–8.497) | .011 |
| Uric acid, mg/dL | 1.129 (1.004–1.269) | .042 | 1.012 (0.870–1.177) | .879 |
| FPG, mg/dL | 1.016 (1.006–1.026) | .002 | 1.006 (0.995–1.017) | .324 |
| LDL cholesterol, mg/dL | 0.995 (0.989–1.000) | .057 | 0.994 (0.988–1.000) | .039 |
| HDL cholesterol, mg/dL | 0.983 (0.978–0.995) | .057 | 1.002 (0.990–1.015) | .698 |
| Triglyceride, mg/dL | 1.001 (0.999–1.003) | .497 | — | — |
| Current smoking status | 1.123 (0.742–1.700) | .584 | 1.456 (0.933–2.273) | .098 |
| Family history of HT | 1.382 (1.008–1.864) | .045 | 1.687 (1.214–2.345) | .002 |
| IMT, mm | 13.39 (6.770–26.43) | <.001 | 7.080 (5.058–16.33) | <.001 |
| IMT, 0.1 mm | 1.298 (1.211–1.387) | <.001 | 1.216 (1.118–1.329) | <.001 |

All variables included in the multivariate analysis are listed in the table.

CI = confidence interval, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, FPG = fasting plasma glucose, HDL = high-density lipoprotein, HT = hypertension, IMT = intima-media thickness, LDL = low-density lipoprotein, SBP = systolic blood pressure.
development of hypertension in normotensive subjects. Since yearly increases in blood pressure are also independently correlated with carotid IMT, this index is also strongly associated with the process by which the future hypertension might develop.

In the present study, although retrospective analysis indicated a significant increase in carotid IMT in subjects with future hypertension, most variables investigated at baseline were different between subjects with and without future hypertension. Conversely, prospective analysis taking carotid IMT as a continuous variable after adjustment for important variables identified this carotid index as an independent predictor of new-onset hypertension. To confirm and explore these initial results, we performed further analyses after dividing the subjects into 2 or 3 groups according to the carotid IMT value to find that the risk of developing hypertension increased even within the normal range of carotid IMT (below 1.1mm). The cutoff value obtained from ROC curve analyses in general (0.75 mm; that is also the median carotid IMT value in the present study) is not considered to indicate hypertensive organ damage, but our subjects with carotid IMT >0.75 mm had an increased risk of future hypertension. Although the AUC, sensitivity, and specificity was not sufficiently high to propose this value as a cutoff for predicting hypertension per se, the predictive value of carotid IMT for future hypertension was relatively high based on the analysis of subjects divided into tertiles. The concept that carotid IMT is an independent predictor of new-onset hypertension is further supported by the present analysis showing an...

| Variable at baseline | Model A | | | Model B | | |
|----------------------|---------|---------|---------|---------|---------|
| Age, y               | 1.028 (1.007–1.050) | .009 | 1.019 (0.998–1.041) | .083 |
| Gender, male         | 1.036 (0.684–1.570) | .868 | 1.016 (0.670–1.542) | .939 |
| Body mass index, kg/m² | 1.057 (0.997–1.121) | .062 | 1.055 (0.996–1.119) | .069 |
| SBP, mm Hg           | 1.051 (1.034–1.068) | <.001 | 1.050 (1.034–1.067) | <.001 |
| Heart rate, bpm      | 1.009 (0.992–1.027) | .284 | 1.013 (0.996–1.031) | .139 |
| Serum creatinine, mg/dL | 3.253 (1.302–8.127) | .012 | 3.482 (1.384–8.759) | .008 |
| Uric acid, mg/dL     | 0.983 (0.846–1.141) | .817 | 0.993 (0.857–1.151) | .929 |
| LDL cholesterol, mg/dL | 1.008 (0.997–1.019) | .146 | 1.007 (0.996–1.018) | .206 |
| HDL cholesterol, mg/dL | 0.995 (0.898–1.001) | .100 | 0.995 (0.898–1.000) | .071 |
| Current smoking status | 1.471 (0.942–2.297) | .090 | 1.421 (0.911–2.124) | .121 |
| Family history of HT  | 1.655 (1.191–2.300) | .003 | 1.658 (1.194–2.304) | .003 |
| High IMT (vs. Low IMT) | 1.629 (1.149–2.304) | .006 | — | — |
| IMT-first tertile     | —       | —       | 1 (reference) | — |
| IMT-second tertile    | —       | —       | 1.600 (1.029–2.490) | .037 |
| IMT-third tertile     | —       | —       | 2.636 (1.654–4.201) | <.001 |

Model A: Subjects were divided into 2 groups according to the cut-off value obtained from receiver operating characteristics curve analysis.
Model B: Subjects were divided into tertiles.
All variables included in the multivariate analysis are listed in the table.
CI = confidence interval, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, FPG = fasting plasma glucose, HDL = high-density lipoprotein, HT = hypertension, IMT = intima-media thickness, LDL = low-density lipoprotein, SBP = systolic blood pressure.

Table 5
Univariate and multivariate regression analyses demonstrating the relationship between baseline variables and yearly increase in systolic blood pressure.

| Variable at baseline | Univariate | | | Multivariate | | |
|----------------------|------------|---------|---------|------------|---------|
| Age, y               | 0.095 | .006 | 0.058 | .124 |
| Gender, male         | 0.043 | .129 | –0.115 | .022 |
| Body mass index, kg/m² | –0.001 | .974 | 0.035 | .345 |
| SBP, mm Hg           | –0.253 | <.001 | –0.317 | <.001 |
| DBP, mm Hg           | –0.142 | <.001 | — | — |
| Heart rate, bpm      | 0.009 | .803 | 0.075 | .029 |
| Serum creatinine, mg/dL | 0.042 | .227 | 0.071 | .117 |
| Uric acid, mg/dL     | 0.043 | .221 | 0.044 | .301 |
| LDL cholesterol, mg/dL | 0.132 | <.001 | 0.121 | .001 |
| HDL cholesterol, mg/dL | –0.050 | .147 | –0.073 | .032 |
| Triglyceride, mg/dL  | –0.066 | .056 | –0.042 | .237 |
| Current smoking status | 0.001 | .997 | — | — |
| Family history of HT  | 0.100 | .004 | 0.099 | .004 |
| IMT, mm              | 0.176 | <.001 | 0.189 | <.001 |

All variables included in the multivariate analysis are listed in the table.
DBP = diastolic blood pressure, FPG = fasting plasma glucose, HDL = high-density lipoprotein, HT = hypertension, IMT = intima-media thickness, LDL = low-density lipoprotein, SBP = systolic blood pressure.
independent correlation with changes in SBP and baseline IMT. However, it should be noted that several other factors have also been associated with the development of hypertension, including increased blood pressure within the normal range, family history of hypertension, obesity, impaired glucose tolerance, reduced glomerular filtration rate, urinary albumin, and left ventricular hypertrophy assessed by electrocardiography. statins, might reduce an individual’s risk of hypertension and, thereby, cardiovascular disease. Further study will be necessary to determine the effects of such interventions to reduce carotid IMT. The interpretation of the present results is limited by the following points. First, the study subjects were participants in our annual physical checkup program, so blood pressure was measured only once a year. Data on ambulatory blood pressure monitoring or home blood pressure measurement were not available and white coat hypertension cannot be excluded from our study. Moreover, follow-up data on blood pressure were not available in all participants and, thus, the diagnosis of hypertension may have not been definite. Second, IMT was measured manually by a number of different trained technicians and the presence or absence of plaque was not evaluated in this study. Third, effects of medications such as antidiabetic or antidiyslipidemic drugs could have affected the results. In conclusion, the index of carotid IMT is significantly associated with both the development of hypertension and yearly increases in blood pressure in normotensive subjects. Carotid IMT is a novel predictor of future hypertension as well as a marker of hypertensive organ damage.

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