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ORIGINAL ARTICLE

Relationship between upper limb peripheral artery stiffness using the radial artery and atherosclerotic parameters

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Abstract
Purpose A new method has been developed for evaluating arterial stiffness using transcutaneous and high-frequency ultrasound. There may be a difference in the clinical significance of peripheral arteries, such as the radial artery (a muscular property), and other medium/large-sized arteries (an elastic property). The aim of this study was to determine the relationship between upper limb peripheral arterial stiffness (ULPAS) using the new method for the radial artery and atherosclerotic parameters in comparison with carotid intima-media thickness (IMT) and cardio-ankle vascular index (CAVI) in a healthy population and a diseased population with hypertension (HT) and diabetes mellitus (DM).
Methods Forty-four apparently healthy individuals (mean age = 26.3 years, men/women = 14/30), 45 patients with drug-treated HT (mean age = 55.3 years, men/women = 17/28), and 37 patients with drug-treated DM (mean age = 55.2 years, men/women = 21/16) were investigated. Body mass index, systolic blood pressure (SBP), diastolic blood pressure (DBP), CAVI, IMT, ultrasonographically measured ULPAS, blood lipid/glucose-related parameters, and C-reactive protein (CRP) were all determined.
Results Among the healthy subjects, ULPAS showed a significantly positive correlation with SBP and CRP. ULPAS showed a different correlation pattern with atherosclerotic parameters from that of IMT and CAVI. The HT subjects had significantly higher ULPAS levels than those with DM. In this diseased population, ULPAS showed a significant positive correlation with SBP and DBP, as well as a significant negative correlation with glucose.
Conclusion These results suggest that ULPAS may provide new information in association with some atherosclerotic conditions as a unique index different from IMT and CAVI.

Keywords Radial artery · Arterial stiffness · CAVI · IMT · Hypertension · Diabetes mellitus

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Introduction

Atherosclerosis is an underlying process in cardiovascular disease (CVD), a major cause of mortality worldwide, and it is important to detect atherosclerotic alteration in order to manage CVD [1]. The International Atherosclerosis Society has pointed out that hypertension (HT) and diabetes mellitus (DM) are major risk factors for CVD [2]. An increase in arterial stiffness is one manifestation of the atherosclerotic changes associated with these risk factors. In HT, shear stress and peripheral vascular resistance are related to arterial stiffness [3]. In DM, hyperglycemia induces both macro- and microvascular stiffness [4].

Among the various methodologies for evaluating the atherosclerotic state in clinical practice, cardio-ankle vascular index (CAVI), measured from brachial and ankle pulse waveforms, is reflective of arterial stiffness independent of blood pressure (BP) [5], and the clinical significance of CAVI in CVD has been recently established [6]. Carotid intima-media thickness (IMT), measured by ultrasound, is a well-established atherosclerotic index connected with arterial stiffness [7].

In addition to impairment of endothelial function [8], the compositional characterization (e.g., lipid, blood clot, fibrous and calcified tissue) of atherosclerotic sites is thought to be a significant aspect of evaluation of regional elasticity/stiffness and plaque rupture [9, 10]. Recently, a noninvasive transcutaneous ultrasonic technology that utilizes the "phased tracking method" was developed in order to evaluate atherosclerotic formation based on the compositional features of the artery wall [9–12]. This method allows the detection of minute changes in the thickness of the layers of the arterial wall by subtracting the displacements of two points set along an ultrasonic beam during a single heartbeat. Arterial wall elasticity is derived from the thickness changes and pulse pressure of each layer divided by the ultrasonic beam. When we use a system based on this technology, the elasticity distribution is seen as the mean elastic modulus [9]. This method has already been used for detecting regional changes in the arterial wall [9] and to assess endothelial function in combination with the flow-mediated dilation test [12]. Higher carotid artery elasticity in smokers as compared with nonsmokers has also been suggested [13]. Recently, a study on the application of this method to the carotid artery in DM patients has shown elasticity levels to be related to such atherosclerotic parameters as BP, pulse wave velocity, and IMT [14].

The radial artery is an upper limb peripheral artery and is categorized as a small artery, so the clinical impact of atherosclerotic manifestation in the radial artery (having a muscular property) may differ from that of the carotid artery (having an elastic property). There are, however, no radial-artery-related clinical data available for this method. Furthermore, although endothelial dysfunction has been implicated in the pathology of large- and medium-sized arteries in HT and DM [15, 16], a smaller artery may show a greater correlation with endothelium-dependent vasodilation than a larger-sized artery [17, 18]. Examination using the radial artery is thus expected to more clearly reflect endothelial function.

Measurements performed by Kanai et al. [9] with this methodology were originally referred to as "elasticity." In the present report, while there may be only a slight difference from the original meaning, we decided to use the term upper limb peripheral artery stiffness (ULPAS) instead of the term elasticity, because arterial stiffness rather than elasticity is clinically used more frequently. That is, a low elasticity (a high mean elastic module) means an increase in stiffness. Therefore, the present study has two aims: (1) to determine the relationships between ULPAS and atherosclerotic parameters in comparison with IMT and CAVI in an apparently healthy population, and (2) to evaluate ULPAS levels in subjects with HT and DM.

Subjects and methods

Two populations were used in this study. A total of 44 individuals who were apparently healthy, drug free, and nonsmokers were enrolled in this study as a healthy population [mean age = 26.3 ± 12.7 (standard deviation, SD) years, men/women = 14/30]. Next, 45 patients treated for HT alone (mean age = 55.3 ± 9.4 years, men/women = 17/28) and 37 patients treated for DM alone (mean age = 55.2 ± 9.6 years, men/women = 21/16) were enrolled as a diseased population. This study was approved by the Ethical Committee of Jichi Medical University and each subject gave his or her informed consent.

The healthy population was composed of drug-free nonsmokers from the general population who volunteered to take part in the present study based on our random invitation to participate in the study. The volunteers were enrolled if they met the following laboratory criteria: body mass index (BMI) of 18.5–24.9 kg/m^2 [19], systolic BP (SBP) <140 mmHg, diastolic BP (DBP) <90 mmHg [20], fasting blood total cholesterol (TC) <220 mg/dL, triglyceride (TG) <150 mg/dL [21], and glucose <126 mg/dL [22]. After 48 subjects were consecutively screened, 4 subjects were excluded because they did not meet the inclusion criteria. Next, patients who had all been referred to Jichi Medical University Hospital were consecutively recruited for the diseased population. HT subjects were limited to those treated with drugs such as angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB), which may affect arterial stiffness [23, 24]. DM subjects were limited to those treated with drugs such as sulfonylurea and insulin, which have not been suggested to affect the stiffness. Information on the prescribed drugs was confirmed by professional interviews and medical records. HT and DM subjects were already diagnosed, respectively, and no patients with both HT and DM were included in this study. In both the healthy and diseased population, no subjects had any known history of CVD, kidney disease or liver disease.

Smoking habits were confirmed through professional interviews, and smokers were defined as current smokers. BMI was calculated as weight divided by the square of body height while wearing light clothes. Blood samples

were collected from the antecubital vein after a 12-h overnight fast without drugs. Serum TC, high-density lipoprotein cholesterol (HDL-C), TG, and plasma glucose were measured by enzymatic methods using an automatic analyzer (Hitachi Co., Ltd., Tokyo, Japan). Low-density lipoprotein cholesterol (LDL-C) was determined by the following equation: TC − (HDL-C) − (TG/5) [25]. Serum CRP was measured using a latex agglutination immune assay (EIKEN Chemical, Co., Ltd., Tokyo, Japan). Plasma insulin was measured by a sandwich enzyme immunoassay (TOSOH Co., Ltd., Tokyo, Japan). Homeostasis model assessment-insulin resistance (HOMA-IR) was calculated by the following formula: (fasting plasma insulin concentration × fasting glucose concentration)/405 [26].

CAVI was determined by oscillometric technology using the VaSera VS-1000 vascular screening system (Fukuda Denshi Co., Ltd., Tokyo, Japan) [5]. CAVI is based on the stiffness parameter calculated using the following formula: $\mathrm{CAVI} = \ln(P_s/P_d) \times 2\rho/\Delta P \times \mathrm{PWV}^2$ (P_s: SBP, P_d: DBP, ρ: blood density, ΔP: pulse pressure, PWV: pulse wave velocity between the aortic and the ankle value). Subjects lay on a bed in a supine position for 10 min before the measurements. SBP and DBP were measured simultaneously. After 5 min of relaxing in the supine position, IMT of the bilateral common carotid arteries was measured by ultrasonography with a 10-MHz probe using the EH54-9DR system (DIASUS, Scotland, UK). IMT levels were determined by the average of the values at points 1, 2, and 3 cm below carotid bifurcation on each side of the artery.

Subsequently, in the same supine position, ULPAS was examined in the right arm based on the previously documented method [9]. In brief, ULPAS was scanned 5 cm above the right wrist, with the palm turned upward. The transducer (8–16 MHz probe) was oriented in a direction perpendicular to the longitudinal axis of the radial artery. The arterial wall was divided into multiple layers by the ultrasound beams. The mean elastic modulus was comprehensively computed in the scanned regions of the arterial wall. The values of the modulus were then automatically calculated after displaying them as color-coded images with histograms. With respect to the elasticity distribution, if lipid (cholesterol)-rich components in the artery were captured, then the ULPAS values could generally be low, while in other cases, the values could be higher.

Statistical analysis

Data are presented as mean ± standard deviation. In the case of parameters with nonparametric distributions (BMI, DBP, IMT, CAVI, TC, LDL-C, TG, insulin, HOMA-IR, CRP, and ULPAS), data are shown as median (interquartile range). In all analyses, the parameters with nonparametric distributions were used after log transformation. Categorical data were compared between the groups by χ^2 test, and continuous data were compared by unpaired t test (in a comparison between HT and DM subjects, age, gender, and smoking habit were adjusted). To investigate the correlations of IMT, CAVI, and ULPAS with other atherosclerotic parameters, Pearson's correlation and a partial correlation test with adjustments for age and gender were used. All statistical analyses were performed by the Statistical Package for Social Science (SPSS) version 16.0 (SPSS Inc., Chicago, IL) for Windows. A p value of <0.05 was considered to be statistically significant.

Results

The characteristics of subjects in the healthy population are shown in Table 1. BMI and IMT levels were significantly higher and HDL-C, insulin, and HOMA-IR levels were significantly lower in men as compared with women. Other atherosclerotic parameters, including CAVI and ULPAS, did not show any significant differences between the genders.

The relationships between IMT, CAVI, ULPAS, and other atherosclerotic parameters in the healthy population are shown in Table 2 (a simple correlation test between bivariables) and Table 3 (a correlation test with adjustments for age and gender). According to the simple correlation test, carotid IMT levels demonstrated a significantly positive correlation with male gender (Table 2), but age- and gender-adjusted correlation tests did not show any relative significance (Table 3). Similarly, in the simple correlation test, CAVI was significantly positively correlated with age, DBP, TC, LDL-C, and CRP, but in the age- and gender-adjusted correlation tests, the significance of these correlations disappeared. ULPAS was significantly positively correlated with SBP and CRP in the simple correlation test, and ULPAS remained significantly positively correlated with SBP and CRP in the adjustment correlation tests.

Furthermore, regarding the relationships between IMT, CAVI, and ULPAS, in a simple correlation test, ULPAS tended to be correlated with IMT ($r = 0.28$, $p = 0.07$) or CAVI ($r = 0.26$, $p = 0.09$) but did not reach a statsistical significance, and there was no correlation between CAVI and IMT ($r = 0.21$, $p = 0.17$). Similarly, in the age- and gender-adjusted correlation tests, ULPAS was not significantly correlated with IMT ($r = 0.19$, $p = 0.36$) or CAVI ($r = 0.19$, $p = 0.26$), respectively. CAVI was not significantly correlated with IMT ($r = 0.0001$, $p = 0.99$).

The comparative characteristics between HT and DM subjects are shown in Table 4. The number of subjects with

Table 1 Clinical characteristics in an apparently healthy population

	All ($n = 44$)	Men ($n = 14$)	Women ($n = 30$)
Age (years)	26.3 ± 12.7	23.9 ± 7.9	25.5 ± 10.5
BMI (kg/m^2)	21.2 ± 1.6	21.9 ± 1.3	20.9 ± 1.6*
HR (bpm)	60.0 ± 10.2	56.7 ± 7.3	61.5 ± 11.2
SBP (mmHg)	111.6 ± 9.2	115.1 ± 9.0	109.9 ± 9.1
DBP (mmHg)	66.0 [63.3–71.5]	66.0 [63.5–69.0]	66.0 [64.0–74.0]
TC (mg/dL)	178.2 ± 24.0	175.5 ± 25.8	179.5 ± 23.4
LDL-C (mg/dL)	97.5 [86.0–116.8]	100.5 [89.0–116.5]	93.5 [84.8–117.3]
HDL-C (mg/dL)	63.8 ± 10.7	58.6 ± 8.7	66.2 ± 10.8*
TG (mg/dL)	68.1 [44.8–86.8]	78.5 [49.0–87.6]	60.1 [44.8–84.6]
Glucose (mg/dL)	88.0 [83.0–97.5]	88.0 [84.5–98.0]	87.5 [82.0–94.5]
Insulin (μm/L)	5.6 ± 3.1	4.2 ± 2.0	6.3 ± 3.4*
HOMA-IR	1.24 ± 0.69	0.94 ± 0.47	1.38 ± 0.74*
CRP (mg/dL)	0.05 [0.02–0.07]	0.05 [0.01–0.07]	0.05 [0.03–0.07]
IMT (mm)	0.41 [0.37–0.46]	0.45 [0.43–0.50]	0.40 [0.37–0.44]*
CAVI	5.71 [5.29–6.04]	5.84 [5.33–6.38]	5.69 [5.27–6.04]
ULPAS (kPa)	231.4 [179.4–295.6]	262.2 [178.5–326.7]	223.3 [178.0–268.7]

Age, HR, HDL-C, and glucose are presented as mean ± standard deviation. Other parameters are presented as median [interquartile range]

BMI body mass index, *HR* heart rate, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *IMT* intima-media thickness, *CAVI* cardio-ankle vascular index, *ULPAS* upper limb peripheral arterial stiffness, *TC* total cholesterol, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *TG* triglyceride, *HOMA-IR* homeostasis model assessment-insulin resistance, *CRP* C-reactive protein

Significance level (men versus women; unpaired *t* test): *$p < 0.05$

ACEI was 6 (13.3%) and that of ARB was 39 (86.7%), respectively. The number of subjects with sulfonylurea was 19 (51.3%), with insulin was 7 (18.9%), and with sulfonylurea plus insulin was 11 (29.8%), respectively. Although HT subjects had significantly lower levels of glucose and HOMA-IR than did DM subjects, HT subjects showed significantly higher ULPAS levels in addition to SBP and DBP levels as compared with DM subjects.

In the case of a combination of HT and DM subjects, in a simple correlation test, ULPAS was significantly positively correlated with SBP ($r = 0.54$, $p = 0.001$) and DBP ($r = 0.34$, $p = 0.002$), and significantly negatively correlated with glucose ($r = -0.23$, $p = 0.04$). In the age- and gender-adjusted correlation test for ULPAS, the following correlations only remained significant: with SBP ($r = 0.53$, $p = 0.001$) and DBP ($r = 0.34$, $p = 0.002$). In similar analyses, IMT and CAVI did not show significant correlations with SBP, DBP, and glucose, respectively.

Discussion

The present study is the first to investigate the stiffness of the "radial artery" using high-frequency transcutaneous ultrasound with an innovative "phased tracking method". Measurement of ULPAS was feasible in a clinical setting. ULPAS levels were significantly positively correlated with SBP and CRP levels in an apparently healthy population. ULPAS did not show a similar correlation pattern with that of IMT and CAVI, and it did not show any correlation with IMT or CAVI, respectively. Moreover, HT subjects had a higher ULPAS level than DM subjects in this study, and ULPAS levels were significantly positively correlated with BP levels. These results suggest that ULPAS may offer information in association with some atherosclerotic conditions with the possibility of a unique index different from IMT and CAVI.

Accumulating evidence has indicated that a slight increase in serum CRP level is a risk parameter of atherosclerosis, even in healthy subjects [27–29]. CRP is considered to interact with the vascular state, especially the endothelium, as a proinflammatory marker. Specifically, CRP promotes potential atherogenesis by inducing monocyte-macrophage activation, tissue factor expression, the release of other procoagulant cytokines, the downregulation of atheroprotective molecules (such as endothelial nitric oxide (NO) and transforming growth factor β-1), etc. [28–30]. The radial artery is an artery with a muscle property, and even a normal range of CRP in vascular smooth muscle cells can induce the increases in several inflammatory molecules within the cell [31]. In addition, the alteration of endothelial NO is reportedly sensitive in a small artery in a healthy population [32]. On the other hand, although there was a prior report showing a weak

Table 2 Relationships between the respective arterial stiffness markers and atherosclerotic parameters in an apparently healthy population

	IMT	CAVI	ULPAS
Age (years)	0.28 (0.07)	0.69 (<0.0001)**	0.21 (0.17)
Gender (men)	0.32 (0.04)*	0.01 (0.96)	0.18 (0.24)
BMI (kg/m^2)	0.10 (0.50)	0.08 (0.63)	0.25 (0.10)
HR (bpm)	0.07 (0.64)	0.10 (0.53)	0.08 (0.60)
SBP (mmHg)	0.23 (0.14)	0.29 (0.06)	0.43 (0.004)**
DBP (mmHg)	0.11 (0.49)	0.38 (0.01)*	0.17 (0.28)
TC (mg/dL)	0.22 (0.15)	0.35 (0.01)*	−0.01 (0.99)
LDL-C (mg/dL)	0.18 (0.24)	0.32 (0.04)*	−0.02 (0.90)
HDL-C (mg/dL)	0.14 (0.35)	−0.03 (0.87)	0.02 (0.90)
TG (mg/dL)	−0.08 (0.59)	0.22 (0.15)	−0.14 (0.35)
Glucose (mg/dL)	0.26 (0.09)	0.21(0.18)	0.07 (0.66)
Insulin (μm/mL)	−0.11 (0.46)	0.05 (0.76)	0.17 (0.28)
HOMA-IR	−0.07 (0.66)	0.07 (0.65)	0.17 (0.27)
CRP (mg/dL)	0.06 (0.68)	0.33 (0.03)*	0.36 (0.02)*

Data are all presented as *r* (*p* value). HR, DBP, IMT, CAVI, ULPAS, TC, TG, glucose, insulin, HOMA-IR, and CRP were log-transformed

BMI body mass index, *HR* heart rate, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *IMT* intima-media thickness, *CAVI* cardio-ankle vascular index, *ULPAS* upper limb peripheral arterial stiffness, *TC* total cholesterol, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *TG* triglyceride, *HOMA-IR* homeostasis model assessment-insulin resistance, *CRP* C-reactive protein

Significance level (Pearson's correlation test): $*p < 0.05$, $**p < 0.001$

Table 3 Age- and gender-adjusted relationships between the respective arterial stiffness markers and atherosclerotic parameters in an apparently healthy population

	IMT	CAVI	ULPAS
BMI (kg/m^2)	−0.10 (0.52)	−0.15 (0.23)	0.16 (0.33)
HR (bpm)	0.10 (0.50)	−0.02 (0.88)	0.09 (0.57)
SBP (mmHg)	0.06 (0.71)	0.09 (0.49)	0.37 (0.02)*
DBP (mmHg)	0.03 (0.84)	0.08 (0.52)	0.13 (0.46)
TC (mg/dL)	0.12 (0.45)	0.04 (0.76)	−0.13 (0.46)
LDL-C (mg/dL)	0.04 (0.80)	0.05 (0.68)	−0.14 (0.39)
HDL-C (mg/dL)	0.27 (0.07)	−0.05 (0.68)	0.08 (0.61)
TG (mg/dL)	−0.22 (0.14)	0.02 (0.86)	−0.25 (0.12)
Glucose (mg/dL)	0.11 (0.50)	−0.13 (0.32)	−0.07 (0.69)
Insulin (μm/mL)	−0.03 (0.85)	0.02 (0.84)	0.24 (0.13)
HOMA-IR	−0.01 (0.94)	0.001 (1.00)	0.22 (0.17)
CRP (mg/dL)	−0.03 (0.86)	0.12 (0.31)	0.32 (0.04)*

The correlation was analyzed with adjustment for age and gender. BMI, SBP, DBP, IMT, CAVI, ULPAS, TC, LDL-C, TG, insulin, HOMA-IR, and CRP were log-transformed

BMI body mass index, *HR* heart rate, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *IMT* intima-media thickness, *CAVI* cardio-ankle vascular index, *ULPAS* upper limb peripheral arterial stiffness, *TC* total cholesterol, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *TG* triglyceride, *HOMA-IR* homeostasis model assessment-insulin resistance, *CRP* C-reactive protein

Significance level (Pearson's correlation test): $*p < 0.05$, $**p < 0.001$

correlation between CRP and radial artery stiffness using the oscillometric method in an older population [33], the method used and the population could affect the results between studies. Also, our result of the significant correlation between SBP and ULPAS might be partly explained by the following knowledge. The small artery is regarded as an important key in the increased resistance of peripheral artery, leading to elevated BP [34]. The impaired NO on peripheral blood vessels in the hypertensive state is well-documented [35]. Accordingly, as claimed previously, the radial artery (as used in the ULPAS measurements), rather than larger arteries, is suitable for examining the vascular state including endothelial function and that evaluation of peripheral arterial stiffness can thus result in an early diagnosis of atherosclerotic processes [17, 18, 36]. Taken together, these findings may support the results that indicate that ULPAS is more obviously correlated to SBP and CRP than to IMT and CAVI. Given that the measure of ULPAS is still quite new, further studies are necessary to establish the associations between ULPAS and atherosclerotic parameters.

In our healthy population, comparisons between IMT, CAVI, and ULPAS indicated a different correlation pattern from atherosclerotic parameters and no interaction with each other. These results are likely compatible with an earlier work [13]. This may not be surprising, because IMT and CAVI do not necessarily yield qualitative information regarding regional elasticity. On the other hand, although our results are relatively different from other earlier results using a similar method on the carotid artery in DM patients [14], differences in the kinds of arteries and study populations could explain the differences. The current results suggest that ULPAS may represent a unique feature in an upper peripheral artery that cannot be evaluated by CAVI and IMT measurements. Further clinical application of ULPAS measurement would establish the specific usefulness of ULPAS.

In the present study, HT subjects were all treated with ACEI or ARB, which can improve arterial stiffness [23, 24]. Even under these conditions, higher ULPAS levels were observed in our HT subjects. To date, there have been no comparative data on arterial stiffness, regardless of arterial size, between HT and DM. HT patients generally have elevated peripheral vascular tone and resistance [3, 34, 37, 38]. DM patients experience worsening enhancement of various metabolic inflammatory and hemostatic changes, accompanied by dysglycemia, thus resulting in vascular damage [4, 39]. Our study also found ULPAS to correlate with BP positively and glucose negatively. In addition, while the study setting was different from ours, BP has been

Table 4 Comparison of atherosclerotic parameters between HT and DM subjects

	All ($n = 82$)	HT ($n = 45$)	DM ($n = 37$)
Age (years)	55.3 ± 9.4	55.3 ± 9.4	55.2 ± 9.6
Gender, men (%)	46.3	37.8	56.8
Smoking (%)	17.1	13.3	21.6
BMI (kg/m^2)	23.9 [21.8–26.4]	24.1 [22.4–26.7]	23.5 [20.7–26.3]
HR (bpm)	65.2 ± 10.1	63.2 ± 9.3	67.7 ± 10.7
SBP (mmHg)	130.9 ± 14.1	134.9 ± 15.0	126.0 ± 11.5*
DBP (mmHg)	82.3 ± 10.2	85.9 ± 10.2	78.0 ± 8.6**
TC (mg/dL)	195.7 ± 36.8	197.8 ± 34.6	193.2 ± 39.7
LDL-C (mg/dL)	114.4 ± 28.7	115.4 ± 28.6	113.0 ± 29.6
HDL-C (mg/dL)	57.7 [45.0–65.0]	61.0 [52.5–66.3]	50.0 [42.0–61.0]
TG (mg/dL)	100.7 [71.8–136.8]	102.0 [64.0–118.0]	99.0 [78.5–153.5]
Glucose (mg/dL)	111.5 [93.0–152.8]	95.0 [89.0–106.5]	155.0 [130.0–202.5]**
Insulin (μm/L)	6.0 [4.0–9.8]	5.7 [4.1–8.1]	7.2 [3.3–11.8]
HOMA-IR	1.8 [1.0–2.9]	1.3 [0.9–2.1]	2.5 [1.2–5.2]**
CRP (mg/dL)	0.05 [0.03–0.11]	0.05 [0.03–0.10]	0.05 [0.03–0.16]
IMT (mm)	0.63 [0.55–0.77]	0.60 [0.54–0.70]	0.70 [0.58–0.83]
CAVI	8.00 ± 1.04	7.84 ± 0.97	8.20 ± 1.11
ULPAS (kPa)	441.5 ± 199.9	485.9 ± 200.6	387.7 ± 188.0*

Age, HR, DBP, ULPAS, TC, and LDL-C are presented as mean ± standard deviation. Other parameters are presented as median [interquartile range]. A comparative test (except for age, gender, and smoking) was performed with adjustments for age, gender, and smoking. BMI, SBP, CAVI, IMT, HDL-C, TG, glucose, insulin, HOMA-IR, and CRP were log-transformed

HT hypertension, *DM* diabetes mellitus, *BMI* body mass index, *HR* heart rate, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *IMT* intima-media thickness, *CAVI* cardio-ankle vascular index, *ULPAS* upper limb peripheral arterial stiffness, *TC* total cholesterol, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *TG* triglyceride, *HOMA-IR* homeostasis model assessment-insulin resistance, *CRP* C-reactive protein

Significance level (unpaired t test or χ^2 test: HT versus DM): $*p < 0.05$, $**p < 0.001$

reported to be a more important determinant of carotid artery stiffness (measured by the same method as ours) than DM (glucose)-related parameters [14]. Given these data, whereas it is possible that HT subjects may show a higher peripheral arterial stiffness than DM subjects, it may be plausible that the BP levels are associated with ULPAS in the diseased state. Further comparisons between ULPAS and the pathologies of HT and DM are thus called for.

There were some limitations to this study. The study sample size was small, which may limit the strength of the conclusions. The cross-sectional approach did not yield any data on causality. In this diseased population with HT and DM, the duration and severity of the disease was not fully examined. Finally, the technique for determining ULPAS is dependent on the ultrasound probe position on the skin. Although we obtained ULPAS data for the left arm, it was sometimes difficult to set the probe on the side, probably because the operator was right-handed. Therefore, ULPAS data for the right arm were used in this study. Moreover, technical differences regarding the size of measured arteries are considered to be an interesting topic to be addressed in future studies.

Conclusions

The present study results suggest that, as a unique index different from IMT and CAVI, ULPAS may provide new information for evaluating upper peripheral arteries in association with some atherosclerotic conditions, as presented in CRP and SBP in a healthy population, and BP in a diseased population with HT and DM. Further studies are needed to establish the clinical significance of ULPAS in atherosclerotic diseases.

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