

The Difference Value of Global Pulse Wave Velocity between Type 2 Diabetic and Non-diabetic Patients with Chronic Coronary Syndrome

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Abstract

Background: Coronary Heart Disease (CHD) remains a major health issue in Indonesia. CHD could lead to myocardial infarction and sudden death, highlighting the necessity for cardiovascular examination and appropriate management to prevent increased morbidity and mortality rates. One non-invasive method for assessing CHD was measuring arterial stiffness using Global Pulse Wave Velocity (PWVg). This study aimed to assess the difference in PWVg among patients with Chronic Coronary Syndrome (CCS) with or without Type 2 Diabetes (T2DM).

Methods: This was an analytical cross-sectional study to evaluate the difference in PWVg values among CCS patients with or without T2DM. The study used data from medical records and elective coronary angiography at the Dr. M. Djamil Teaching Hospital's cardiac catheterization laboratory, where PWVg was measured by Doppler echocardiography examination of CCS patients from April 2023 to 2024. Normality testing using the Shapiro-Wilk test was performed before analyzing all numerical data, followed by independent t-tests or Mann-Whitney tests to determine intergroup differences.

Results: The study comprised 36 CCS patients, with 18 samples per group (with and without T2DM). In this study, males were more prevalent in the CCS group without T2DM, smoking risk factors were more commonly found in the CCS group without T2DM, higher Random Blood Glucose (RBG) was found in the CCS group with T2DM, and higher Ankle-Brachial Index (ABI) values were observed in the CCS group without T2DM. Based on statistical analysis, there was a significant difference in PWVg values between the CCS group with T2DM and the group without T2DM (8.3 ± 0.7 m/s vs. 7.7 ± 0.5 m/s, $p=0.009$).

Conclusions: T2DM results in higher PWVg values compared to those without T2DM among patients with CCS.

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Introduction

Chronic Coronary Syndrome (CCS) remained a major health concern for communities worldwide.¹⁻² Symptomatic CCS and asymptomatic myocardial ischemia both pose risk for myocardial infarction and sudden death, necessitating cardiovascular screening and proper management to prevent increased morbidity and mortality rates.³⁻⁴ Invasive coronary angiography might be performed when clinical evaluation and non-invasive diagnostics indicate a high risk of obstructive coronary lesions. Only a third of patients without a history of CCS undergoing elective cardiac catheterization have obstructive coronary artery lesions. Diagnostic examinations for CCS could be performed non-invasively using arterial stiffness measurements, intima-media thickness, exercise testing, Magnetic Resonance Imaging (MRI), and Multi-Slice Computed Tomography (MSCT). Specifically, arterial stiffness has increasingly been recognized as a functional and structural marker of cumulative exposure to cardiovascular risk factors.⁵

Increased central arterial stiffness was a process of arteriosclerosis and a consequence of many disease conditions, such as Type 2 Diabetes Mellitus (T2DM), atherosclerosis, and chronic kidney disease. Hyperglycaemia and insulin resistance induce mitochondrial dysfunction, oxidative stress, Advanced Glycation End-products (AGEs), disturbances in mitochondrial Ca^{2+} handling, inflammation, activation of the Renin-Angiotensin-Aldosterone System (RAAS), autonomic neuropathy, endoplasmic reticulum stress, cardiomyocyte death, and microvascular dysfunction. These pathophysiological abnormalities led to arterial stiffness.⁶⁻⁸

Several studies have shown the association between T2DM, pulse wave velocity, and coronary atherosclerosis. In populations of asymptomatic T2DM patients, increased carotid-femoral Pulse Wave Velocity (cfPWV) or brachial-ankle Pulse Wave Velocity (baPWV) values were associated with the presence and progression of coronary stenosis or visible plaques on Coronary Computed Tomography Angiography (CCTA).⁹⁻¹⁰ In a recent study involving 45 T2DM, increased cfPWV values were associated with high-risk coronary plaque types measured by CCTA after a 5-year follow-up.⁹ Nam et al. evaluated 615 asymptomatic individuals and demonstrated that increased baPWV was an independent predictor of obstructive Coronary Artery Disease (CAD) detected via CCTA. Similarly, other studies involving healthy individuals

consistently showed a positive association between PWV and coronary atherosclerosis assessed through luminal narrowing or Coronary Artery Calcium (CAC) scores on CCTA.¹¹⁻¹⁵

Arterial stiffness can cause the early appearance of the cardiac pulsation wave, leading to an increase in central systolic blood pressure, a decrease in diastolic blood pressure, and, consequently, an increase in pulse pressure. Elevated systolic blood pressure increases myocardial oxygen demand, increases ventricular load, thereby inducing left ventricular hypertrophy. Additionally, a decrease in diastolic pressure could jeopardize coronary perfusion, resulting in subendocardial ischemia. Increased pulse pressure and shear stress due to vessel stiffness can lead to arterial remodelling, thickening of arterial wall thickening, and the development of atherosclerotic plaques. Structural and physiological changes in arteries, including vascular tone, thickening of the medial smooth muscle, and modifications in blood viscosity, could alter the rate of arterial pulse wave velocity. After ventricular systole, the pressure generated by the heart was transmitted to the aorta as a wave. Global Pulse Wave Velocity (PWVg) is the time required for a pulse wave to travel from the heart to the peripheral arteries. The velocity of wave transmission will be longer in stiff blood vessels. PWVg could be measured using arterial tonometry or Doppler echocardiography and calculated between the aortic arch and the right common femoral artery by dividing the straight-line distance between them by the transit time.¹⁶⁻²⁰

Arterial stiffness assessment was an easy, fast, non-invasive, radiation-free, and affordable examination. PWVg measurement was considered the gold standard for the direct, noninvasive assessment of arterial stiffness and had independent predictive value for primary coronary events. Several analyses indicated that aortic PWVg had better predictive ability for adverse outcomes in subjects with higher early cardiovascular risk (patients with CAD, kidney disease, hypertension, or T2DM) compared to subjects with lower cardiovascular risk (the general population). Therefore, researchers were interested in investigating the difference in PWVg values in CCS patients with or without T2DM patients.^{9,21}

Methods

Study Design

This was an analytical cross-sectional study to evaluate the difference in PWVg values among CCS

patients with or without T2DM. The study utilized data from medical records and elective coronary angiography at the Dr. M. Djamil Teaching Hospital's cardiac catheterization laboratory, where PWVg from Doppler echocardiography examination of CCS patients was conducted from April 2023 to 2024.

The Inclusion criteria consisted of patients with CCS, a left ventricular ejection fraction of $\geq 50\%$, sinus rhythm, and blood pressure below 140/90 mmHg at the time of examination. Patients presenting with arrhythmia, severe heart failure, significant valvular disease, history of Coronary Artery Bypass Grafting (CABG), acute coronary syndrome, or suboptimal echocardiographic image quality were excluded from participation. Consecutive sampling is used, yielding a sample of 36 respondents.

Before undergoing angiography, all subjects were evaluated for PWVg using Doppler echocardiography equipped with a 3.5-MHz probe. Examinations were performed in a semi-supine position (head of the table elevated at 30°) after at least 10 minutes of rest in a quiet, temperature-controlled room. PWVg was derived from the pulse wave transit time between the aortic arch and the right common femoral artery. The time interval was measured from the onset of the QRS complex on the ECG to the peak of the first systolic upstroke on the Doppler spectral envelope at each sampling site. The distance between the two points was measured using a flexible tape measure, aligned with the transducer positions on the body surface. PWVg

was calculated as the ratio between the measured distance and the difference in transit time ($PWVg = \Delta \text{distance} / \Delta \text{time}$).¹⁹

All Doppler data were digitally stored and analyzed using the echocardiography system's internal caliper software by a trained operator. To minimize inter-observer variability, all echocardiographic measurements, including PWVg determination, were independently validated by two board-certified cardiology consultants with expertise in echocardiography.

Statistical Analysis

A normality test was performed on numerical variables using the Shapiro-Wilk test to assess whether the data were normally distributed. The characteristics of respondents' data on categorical variables were presented in the form of a frequency distribution (frequencies and percentages). Data for numerical variables with a normal distribution were presented in the form of mean and standard deviation. Data for numerical variables with a non-normal distribution were presented in the form of median and minimum-maximum.

Bivariate data analysis was conducted to compare PWVg values in CCS patients with or without Type 2 DM. Data normality was analyzed using the Shapiro-Wilk test. If the data were normally distributed, independent T-tests were performed. If the data distribution was not normal, a non-parametric test, the Mann-Whitney test, was conducted. All analyses were performed using the Statistical Package for Social Sciences (SPSS) program for Windows.

Table 1. Characteristics of study subjects.

Variable	CCS with DM n=18	CCS without DM n=18
Age (years), mean $\pm$ SD	59 $\pm$ 8.1	59.2 $\pm$ 7.9
Sex, n (%)		
Males	10 (55.6%)	16 (88.9%)
Females	8 (44.4%)	2 (11.1%)
Risk Factor, n (%)		
History of Hypertension	11 (61.1%)	13 (72.2%)
Smoker	7 (38.9%)	16 (88.9%)
Family History	3 (16.7%)	3 (16.7%)
BMI (kg/m ²), mean $\pm$ SD	24.5 $\pm$ 2.2	23.8 $\pm$ 3
Cholesterol (mg/dl)		
LDL, mean $\pm$ SD	137.3 $\pm$ 38.2	116.5 $\pm$ 41.8
HDL, median(min-max)	35.5 (28-62)	41.3 (29-67)
Total cholesterol, mean $\pm$ SD	209.2 $\pm$ 40.4	182.7 $\pm$ 48.6
Trygliceride(s), median(min-max)	166.5 (108-428)	141.5 (56-313)

Drugs, n (%)		
ACE-I/ARB	10 (55.6%)	14 (77.8%)
B-blocker	17 (94.4%)	17 (94.4%)
Calcium channel blocker	5 (27.8%)	9 (50%)
Statin	16 (88.9%)	15 (83.3%)
Antiplatelet	18 (100%)	18 (100%)
Nitrate	17 (94.4%)	16 (88.9%)
RBG (mg/dl), mean±SD	202±59.7	110±16.7
Coronary Angiography Result		
CAD 1 VD, n (%)	1 (20%)	4 (80%)
CAD 2 VD, n (%)	3 (37.5%)	5 (62.5%)
CAD 3 VD, n (%)	14 (60.9%)	9 (39.1%)
Echocardiography		
LV EF (%), mean±SD	58.2±5.1	60.6±5
Diastolic dysfunction, n (%)		
Normal	13 (72.2%)	16 (88.9%)
Grade 1	5 (27.8%)	2 (11.1%)
ABI, mean±SD*	1.12±0.09	1.22±0.01
BP Systolic (mmHg), mean±SD	126±9.8	128±7.3
BP Diastolic (mmHg), mean±SD	77.2±7.9	74.7±7.3
Heart Rate (x/min), median (min-max)	66.5 (60-83)	65 (55-87)

CCS, Chronic Coronary Syndrome; DM, Diabetes Mellitus; FH, Familial History; BMI, Body Mass Index; ACE-I, Angiotensin Converting Enzyme Inhibitor; ARB, Angiotensin Receptor Blocker; CAD, Coronary Artery Disease; LDL, Low Density Lipoprotein; HDL, High Density Lipoprotein; RBG, Random Blood Glucose; VD, Vascular Disease; LVEF, Left Ventricular Ejection Fraction; ABI, Ankle Brachial Index; BP, Blood Pressure.

Results

A total of 36 patients who underwent PWVg measurements met the inclusion criteria through consecutive sampling and were taken as research subjects. The basic characteristics of the research subjects are shown in Table 1.

In the patient characteristic data, males were more prevalent in the CCS group without DM; smoking risk factors were more common in the CCS group without DM; higher RBG was observed in the CCS group with DM; and higher ABI values were observed in the CCS group without DM.

Based on the Shapiro-Wilk normality test, the distribution of PWVg group data was found to be normally distributed, allowing the independent-samples t-test to proceed. Table 2 shows the difference in PWVg values in CCS patients with or without Type 2 DM. The mean PWVg values

were obtained as 8.3 ± 0.7 m/s in CCS with Type 2 DM and 7.7 ± 0.5 m/s in CCS without Type 2 DM. The P-value of 0.009 indicates that there was a significant difference in the PWVg values between the CCS group with Type 2 DM compared to those without Type 2 DM.

Discussion

Based on the research findings, the basic characteristics of the research subjects indicated that males were more prevalent in the CCS group without DM, and smoking risk factors were more commonly found in the CCS group without DM. Higher RBG was found in the CCS group with DM, and higher ABI values were found in the CCS group without DM. The majority of the subjects were males. This finding was consistent with research by Yao Lu and colleagues in 2023, which found

Table 2. Difference in PWVg values in CCS patients with or without Type 2 DM.

Variable	CCS with DM n=18	CCS without DM n=18	P-Value
PWVg (m/s), mean±SD	8.3±0.7	7.7±0.5	0.009

PWVg, Global Pulse Wave Velocity; CCS, Chronic Coronary Syndrome; DM, Diabetes Mellitus.

that males had higher PWV values than females. Another study by Bo Hyun Kim and colleagues in 2018 found that males had higher PWV values and a higher risk of Coronary Heart Disease (CHD) with more severe lesions than females. This is because women tend to have better endothelial function and vascular reactivity than men, due to the vasodilatory effects of estrogen on blood vessels.^{10,22-23}

Smoking was a significant risk factor for arterial stiffness, especially in males who tend to have a higher smoking prevalence than females. There was evidence that compliance of large and medium arteries decreased directly after smoking a cigarette. This result was consistent with previous findings that the annual change ratio in baPWV during the study period was significantly greater in sustained heavy smokers (11.0 ± 1.9 cm/s per year) than in non-smokers (5.5 ± 0.6 cm/s per year). These findings were also consistent with the study by Bo Hyun Kim and colleagues in 2018. Smoking had a negative effect on the hemostatic process that could trigger an imbalance between prothrombotic and antithrombotic factors, which could further initiate and exacerbate arterial and thrombotic diseases.^{10, 24-26}

Hirofumi and colleagues found significant differences in PWV between normal subjects and patients with diabetes. Hyperglycemia, insulin resistance, induced metabolic disorders that increase mitochondrial dysfunction, oxidative stress, advanced glycation end products (AGEs), mitochondrial Ca^{2+} handling disorders, inflammation, renin-angiotensin-aldosterone system (RAAS) activation, autonomic neuropathy, endoplasmic reticulum stress, cardiomyocyte death, and microvascular dysfunction. These pathophysiological abnormalities lead to arterial stiffness.^{6-8,27}

In 2011, Peter Wohlfahrt found that high PWV values were associated with higher ABI values. Consistent with this study, the researchers found significant differences in ABI values between CCS patients with and without DM, although both remained within the normal range. Increased ABI values were associated with medial arterial calcification, including calcification of the arterial media and the internal elastic lamina. This calcification was a dysregulation of the balance between calcification promotion and inhibition that often occurs in diabetes mellitus, atherosclerosis, and aging. A study by Masoumeh Sadeghi and colleagues in 2011 showed that ABI values were lower in diabetic patients and statistically significant and associated with CAD occurrence.²⁸⁻²⁹

This study showed a difference in PWVg between the CCS group with type 2 DM and the CCS group without type 2 DM, with mean values of 8.3 ± 0.7 m/s and 7.7 ± 0.5 m/s, respectively. These values were higher than the normal value of 7.1 ± 1.1 m/s. The results of this study were supported by other studies, such as the study by M. Cywnar and colleagues in 2006, in which PWV was significantly higher in CAD patients with type 2 DM than in CAD patients without type 2 DM ($P < 0.01$). Increased arterial stiffness, along with diabetes and other risk factors result in vascular remodeling, increased lumen pressure, and shear stress that accelerate atheroma formation, and stimulate excessive collagen production and deposition in the arterial wall leading to atherosclerosis.¹¹

Consistent with this, Kim and colleagues in 2018 examined patients with type 2 DM complaining of chest pain and found that higher baPWV was a significant predictor of coronary artery stenosis detected by coronary MSCT angiography. The study suggested that baPWV values above the cutoff value of 1.650 cm/s might be an acceptable predictor of silent CAD in diabetic patients. In a more recent study involving 45 patients with type 2 DM, an increase in cfPWV was associated with high-risk coronary plaque type, as measured by CCTA, after 5 years of follow-up. PWV reflects arterial stiffness, which was caused by central elastic components and peripheral muscle components. High PWV values have been observed in patients with cardiovascular risk factors, including hypertension, diabetes, and dyslipidemia. Many studies have evaluated the use of PWV to predict cardiovascular risk, and it has been widely measured in various clinical situations. Nakamura et al. suggested that baPWV might be useful for assessing macrovascular damage, and Choi et al. reported a close relationship between baPWV and cardiovascular disease risk factors of metabolic syndrome.^{9-10,30-31}

There were differences in basic characteristics across several variables, which could affect PWVg results under these conditions. This study only examines the difference in PWVg between those with DM and those without, without accounting for confounding factors in PWVg values, so further studies are needed.

Conclusion

The patient in this study showed that males were more prevalent in the CCS group without T2DM, smoking risk factors were more commonly found

in the CCS group without T2DM, higher random blood glucose (RBG) was found in the CCS group with T2DM, and higher ABI values were observed in the CCS group without T2DM. Statistical analysis showed a significant difference in PWVg between the CCS group with T2DM and the group without T2DM. Diabetes results in higher PWVg values compared to those without T2DM among patients with CCS.

List of Abbreviations

ABI	Ankle-Brachial Index
ACE-I	Angiotensin-Converting Enzyme Inhibitor
AGEs	Advanced Glycation End Products
ARB	Angiotensin Receptor Blocker
baPWV	Brachial-Ankle Pulse Wave Velocity
BMI	Body Mass Index
CAC	Coronary Artery Calcium
CAD	Coronary Artery Disease
CCS	Chronic Coronary Syndrome
cfPWV	Carotid-Femoral Pulse Wave Velocity
CCTA	Coronary Computed Tomography Angiography
CHD	Coronary Heart Disease
ECG	Electrocardiogram
HDL	High-Density Lipoprotein
LDL	Low-Density Lipoprotein
LVEF	Left Ventricular Ejection Fraction
PWVg	Global Pulse Wave Velocity
RAAS	Renin-Angiotensin-Aldosterone System
RBG	Random Blood Glucose
SPSS	Statistical Package for the Social Sciences
T2DM	Type 2 Diabetes Mellitus

Ethical Clearance

This study has received ethical approval from the Ethics Committee of Dr. M. Djamil Hospital / Faculty of Medicine, Universitas Andalas, Padang, Indonesia, and was conducted in accordance with the Declaration of Helsinki.

Publication Approval

All authors are consent to the publication of this manuscript.

Authors Contributions

FY: Conceptualization, study design, data collection, data analysis, manuscript drafting, and final approval. EFE: Study supervision, methodology validation, echocardiography validation, critical revision of the manuscript, and final approval. YRI:

Data interpretation, statistical analysis support, manuscript review, and final approval. HA: Clinical supervision, critical revision of the manuscript, and final approval.

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Conflict of Interest

No conflict of interests.

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Generative AI and AI-Assisted Technologies in the Writing Process

The authors declare that no generative AI or AI-assisted technologies were used in the writing, analysis, or preparation of this manuscript. All work represents the original contributions of the authors.

References

1. Ford ES, Capewell S. Coronary heart disease mortality among young adults in the U.S. from 1980 through 2002: concealed leveling of mortality rates. *J Am Coll Cardiol.* 2007; 50: 2128–32.
2. Nichols M, Townsend N, Scarborough P, Rayner M. Cardiovascular disease in Europe 2014: epidemiological update. *Eur Heart J.* 2014; 35: 2950–59.
3. Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, et al. 2013 ESC guidelines on the management of stable CAD: the Task Force on the management of stable CAD of the European Society of Cardiology. *Eur Heart J.* 2013; 34: 2949–3003.
4. Sajadieh A, Nielsen OW, Rasmussen V, Hein HO, Hansen JF. Prevalence and prognostic

- significance of daily-life silent myocardial ischaemia in middle-aged and elderly subjects with no apparent heart disease. *Eur Heart J*. 2005; 26: 1402-09.
5. Patel MR, Peterson ED, Dai D, Brennan JM, Redberg RF, Anderson HV, et al. Low diagnostic yield of elective coronary angiography. *N Engl J Med*. 2010; 362: 886–95.
 6. Blacher J, Asmar R, Djane S, London GM, Safar ME. Aortic pulse wave velocity as a marker of cardiovascular risk in hypertensive patients. *Hypertension*. 1999; 33: 1111–17.
 7. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2010; 55: 1318–27.
 8. Ben-Shlomo Y, Spears M, Boustred C, May M, Anderson SG, Benjamin EJ, et al. Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects. *J Am Coll Cardiol*. 2014; 63: 636–46.
 9. Funck KL, Laugesen E, Ovrehus K, Jensen JM, Norgaard BL, Dey D, et al. Increased high-risk coronary plaque burden is associated with arterial stiffness in patients with type 2 diabetes without clinical signs of coronary artery disease: a computed tomography angiography study. *J Hypertens*. 2017; 35:1235–43.
 10. Kim BH, Jang JS, Kwon YS, Kim JH, Kim IJ, Lee CW. High brachial ankle pulse wave velocity as a marker for predicting coronary artery stenosis in patients with type 2 diabetes. *Endocrinol Metab*. 2018; 33:88–96.
 11. Cwynar, Marcin et al. “Pulse wave velocity in patients with coronary artery disease or type 2 diabetes mellitus.” *Acta Cardiologica* 61 (2006): 421 - 426.
 12. Braber TL, Prakken NH, Mosterd A, Mali WP, Doevendans PA, Bots ML, et al. Identifying coronary artery disease in asymptomatic middle-aged sportsmen: the additional value of pulse wave velocity. *PLoS ONE*. 2015; 10: e0131895.
 13. Lee JY, Ryu S, Lee SH, Kim BJ, Kim BS, Kang JH, et al. Association between brachial-ankle pulse wave velocity and progression of coronary artery calcium: a prospective cohort study. *Cardiovasc Diabetol*. 2015; 14:147.
 14. Torii S, Arima H, Ohkubo T, Fujiyoshi A, Kadota A, Takashima N, et al. Association between pulse wave velocity and coronary artery calcification in Japanese men. *J Atheroscl Thromb*. 2015; 22:1266–77.
 15. Vishnu A, Choo J, Wilcox B, Hisamatsu T, Barinas-Mitchell EJ, Fujiyoshi A, et al. Brachial-ankle pulse wave velocity is associated with coronary calcification among 1131 healthy middle-aged men. *Int J Cardiol*. 2015; 189:67–72
 16. Liao J, Farmer J. Arterial stiffness as a risk factor for coronary artery disease. *Curr Atheroscler Rep*. 2014;16(2):387.
 17. Ikonomidis I, Makavos G, Lekakis J. Arterial stiffness and coronary artery disease. *Curr Opin Cardiol*. 2015;30(4):422-31
 18. Williams B, Giuseppe M, Wilko S, Enrico A, Michel A, Michel B. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *European Heart Journal*. 2018; 39:3021–104
 19. Palmiero P, Maiello M, Daly DD Jr, Ciccone MM, Nanda NC. Aortic stiffness assessed by global pulse wave velocity in postmenopausal women: an ultrasonographic study. *Echocardiography*. 2012;29(10):1233-8.
 20. Baguet JP, Kingwell B, Dart A, et al. Analysis of the regional pulse wave velocity by Doppler: methodology and reproducibility. *J Hum Hyperten*. 2003;17, 407-12.
 21. Franklin SS et al. Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study. *Circulation*. 1997;96(1):308–15.
 22. Subbiah MT. Estrogen replacement therapy and cardioprotection: mechanisms and controversies. *Brazilian Journal of Medical and Biological Research*. 2002;35(3):271-6
 23. Lyle AN, Raaz U. Killing Me Unsoftly: Causes and Mechanisms of Arterial Stiffness. *Arterioscler Thromb Vasc Biol*. 2017 Feb;37(2): e1-e11
 24. Yu-Jie W, Hui-Liang L, Bing L, Lu Z, Zhi-Geng J. Impact of smoking and smoking cessation on arterial stiffness in healthy participants. *Angiology*. 2013 May;64(4):273-80.
 25. El Khoudary SR, Aggarwal B, Beckie TM, Hodis HN, Johnson AE, Langer RD, Limacher MC, Manson JE, Stefanick ML, Allison MA; American Heart Association Prevention Science Committee of the Council on Epidemiology and Prevention; and Council on Cardiovascular and Stroke Nursing. Menopause Transition and Cardiovascular Disease Risk: Implications for Timing of Early Prevention: A Scientific Statement From the American Heart Association. *Circulation*. 2020 Dec 22;142(25):e506-e532

26. Salehi N, Janjani P, Tadbiri H, Rozbahani M, Jalilian M. Effect of cigarette smoking on coronary arteries and pattern and severity of coronary artery disease: a review. *J Int Med Res*. 2021. Dec; 49:12.
27. Hirofumi Ohnishi, Shigeyuki Saitoh, Satoru Takagi, Jun-ichi Ohata, Takeshi Isobe, Yuka Kikuchi, Hiroshi Takeuchi, Kazuaki Shimamoto; Pulse Wave Velocity as an Indicator of Atherosclerosis in Impaired Fasting Glucose: The Tanno and Sobetsu Study. *Diabetes Care* 1 February 2003; 26 (2): 437–440.
28. Sadeghi M, Heidari R, Mostanfar B, Tavassoli A, Roghani F, Yazdekhasti S. The Relation Between Ankle-Brachial Index (ABI) and Coronary Artery Disease Severity and Risk Factors: An Angiographic Study. *ARYA Atheroscler*. 2011 Summer;7(2):68-73.
29. Wohlfahrt P, Palouš D, Ingrischová M, et al. A high ankle-brachial index is associated with increased aortic pulse wave velocity: the Czech post-MONICA study. *European Journal of Cardiovascular Prevention & Rehabilitation*. 2011;18(6):790-796.
30. Choi KM, Lee KW, Seo JA, Oh JH, Kim SG, Kim NH, et al. Relationship between brachial-ankle pulse wave velocity and cardiovascular risk factors of the metabolic syndrome. *Diabetes Res Clin Pract* 2004;66:57-61.
31. Yamashina A, Tomiyama H, Arai T, Hirose K, Koji Y, Hirayama Y, et al. Brachial-ankle pulse wave velocity as a marker of atherosclerotic vascular damage and cardiovascular risk. *Hypertens Res* 2003;26:615-22.