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ORIGINAL ARTICLE

Frequency of Arterial Stiffness in Insulin Resistance and Type 2 Diabetes Mellitus Patients in Tertiary Hospital.

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Abstract:

Background: Arterial stiffness can predict unfavorable cardiovascular events in patients with various illnesses. It is linked to the presence and progression of diabetes complications such as CVD, retinopathy, neuropathy, and nephropathy.

Method: This cross sectional study aims to investigate the frequency of arterial stiffness in patients with Type 2 DM. This study was done in Department of Biochemistry and Molecular Biology, BSMMU from March 2022 to February 2023.

Results: 95 type 2 diabetes mellitus patients aged 40 to 70 yrs from Endocrinology and Metabolism OPD of BSMMU were included here. Subjects were divided into two groups on the basis of arterial stiffness which was assessed by measuring brachial ankle pulse wave velocity (bapwv). Group 1 had bapwv ≥1815cm/s was considered as type 2 DM patients with arterial stiffness and Group 2 with bapwv <1815cm/s was considered as type 2 DM patients without arterial stiffness. This study included 49 (51.58%) patients in Group 1 and 46 (48.42%) patients in Group 2 among 95 patients. There was no significant difference in male (29) and female (20) gender in Group 1(p= 0.961). Significant differences between the two groups by age (56.96±7.51 in Group 1 and 51.76±8.31 in group 2, p=0.002), systolic blood pressure (128.16±13.79 in G1 and 117.72±10.73 in G2 , p= 0.0001) and diastolic blood pressure (83.98±9.73 in G1 and 79.13±7.84, p=0.009). Also, median values of duration of diabetes, HDL cholesterol (p=0.023) and Fasting insulin (p=0.047) showed significant statistical difference between the two groups.

Conclusion: Increased arterial stiffness has been associated with advancing age, higher SBP and DBP, long diabetes Mellitus, high HDL cholesterol. The risk factors of CVD are more common in type 2 patients with increased arterial stiffness.

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Introduction:

Arterial stiffness is a strong predictor of cardiovascular events and total death even in asymptomatic persons without overt cardiovascular illnesses.[1] Numerous epidemiological studies have found that increased arterial stiffness predicts mortality and morbidity independently of other cardiovascular risk factors, making it a major determining factor for the risk of cardiovascular disease.[2] According to recent research, arterial stiffness is one of the earliest indications of functional and structural changes in the arterial wall.[3] Arterial stiffness, in addition to traditional risk variables, can predict unfavorable cardiovascular events in patients with various illnesses.[4] Diabetes has become a global epidemic. Current estimates by the International Diabetes Federation suggest that approximately 537 million adults (20-79 years) are living with diabetes by 2021.[5] The total people living with diabetes is projected to rise to 643 million by 2030 and 783 million by 2045. 3 in 4 adults with diabetes live in low- and middle-income countries. Almost 1 in 2 (240 million) adults living with diabetes are undiagnosed. Diabetes caused 6.7 million deaths in 2021.Diabetes increases the risk of a range of cardiovascular

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(CV) disorders by doubling or quadrupling the risk, and individuals with diabetes have a lower life expectancy than those without diabetes.[6] Diabetics have a 2-4 times greater risk of dying from heart disease than non-diabetics, according to the American Heart Association.[7] Arterial stiffness is linked to the presence and progression of diabetes complications such as CVD, retinopathy, neuropathy, and nephropathy.[8] Pathophysiological changes involving endothelial cells (ECs), vascular smooth muscle cells (VSMCs), extracellular matrix (ECM) and other functional elements of the vessel wall are responsible for vascular stiffness.[9] These changes are thought to occur early and contribute to premature cardiovascular dysfunction and structural alterations, increasing the risk of CVD morbidity and mortality.[10] Furthermore, increased vascular stiffness is an important early marker for CVD and a predictor of heart attacks and strokes, particularly in those who have insulin resistance, or have type 2 diabetes mellitus.[11] Diabetes can increase arterial stiffness by causing pathological changes in the vascular bed such as decreased nitric oxide bioavailability, increased oxidative stress, chronic low-grade inflammation, increased sympathetic tone and changes in the type or structure of elastin and collagen in the arterial wall.[12] One of the proposed mechanisms for increased arterial stiffness in people with type 2 diabetes is hyperglycemia-induced depletion of endothelial nitric oxide (NO), which then results in endothelial dysfunction.[13] In patients with type 2 DM, the depletion and dysfunction of endothelial progenitor cells (EPCs) have also been linked to dysregulation of the NO system.[14] Arterial stiffness can be assessed using several non-invasive and invasive methods. Due to its non-invasiveness, simplicity, and reproducibility, pulse wave velocity (PWV) is the most widely and frequently used tool for determining arterial stiffness.[3] The most reliable method for measuring arterial stiffness is carotid-femoral pulse wave velocity (cfPWV), which also serves as a reference standard.[15] Accurate measurement of cfPWV levels necessitates specialized training and a time-consuming procedure that has yet to be used in routine clinical practice.[16] Brachial-ankle pulse wave velocity (baPWV) is a unique measure of systemic arterial stiffness that is measured by brachial and posterior tibial arterial wave analyses. BaPWV measurement is simple and reproducible, and it has been widely used in East Asian countries for more than a decade.[17] This study aims to investigate the frequency of arterial stiffness in patients with Type 2 DM.

Materials and Methods

Type of study: Cross sectional study

Place of study: Department of Biochemistry and Molecular Biology, BSMMU, Dhaka.

Time of study: From March 2022 to February 2023

Study population:

Study population included a total of 95 type 2 diabetes mellitus patients from Endocrinology and Metabolism OPD of BSMMU who came to Biochemistry department for investigations. Age of the study subjects were 40-70 yrs.

Study procedure:

Total 95 type 2 diabetes mellitus patients were sent to vascular duplex scan to measure brachial ankle pulse wave velocity to identify the arterial stiffness.

Inclusion Criteria

- Type 2 DM patients aged between 40 to 70 yrs of age.
- Duration of diabetes mellitus for ≥5 yrs.
- Either sex.

Exclusion Criteria

- Participants with history of cardiovascular diseases
- Participants having systemic diseases like chronic liver disease, chronic kidney disease.
- Participants who are suffering from any immuno-suppressive diseases like cancer, lupus.
- Pregnant women.
- Participants who are taking immunosuppressive drugs.

Operational Definition:

Arterial Stiffness

A crucial indicator of vascular changes is arterial stiffness (AS), which is the result of a complex interaction between structural and functional elements of the elastic artery wall.[18] It is distinguished by an increase in pulse wave velocity along the arterial tree.[19] Diabetes mellitus type 2 (T2DM) has been linked to increased arterial stiffness and an increased risk of cardiovascular (CV) disease.[20] Atherosclerotic risk factors and arterial stiffness are closely related, and arterial stiffness can predict both the short- and long-term prognosis for cardiovascular diseases in diabetics.[21]

It can be assessed by pulse wave velocity (PWV), a simple, noninvasive, and widely used tool in clinical practice.[22]

A proposed surrogate end point for CV disease is the brachial-ankle pulse wave velocity (baPWV), which is calculated as the ratio of the distance between the brachial and tibial arteries to the pulse wave transit time between these two arteries (CVD).[23] According to several studies, an abnormal baPWV is a marker of the severity of arteriosclerosis and is linked to poor CV outcomes in people with diabetes.[24]

PWV is calculated by dividing travelled distance by travel time.[17] In baPWV measurements, the brachial arterial wave is used to substitute for the proximal aortic wave. The path length formula is used to calculate the brachial-ankle distance, which is expressed as 1.3 × c + d " b with b, c, and d indicating heart-brachial, heart-femoral, and femoral-ankle lengths. As all these lengths are expressed as linear equations of height as so, brachial ankle distance is also expressed as a linear equation of height. Recently, this height-based path length has been validated by comparing the path length determined by using the magnetic resonance imaging (MRI) method.[25]

Mechanism of Arterial Stiffness in Type 2 Diabetes

Endothelial cell dysregulation, vascular smooth muscle cell dysregulation, extracellular matrix dysregulation, and adaptive immunological responses all play a role in the development of vascular stiffness in the cardio renal metabolic syndrome.[10] Endothelial cells (ECs) and vascular smooth muscle cells (VSMCs) have intricated interactions that are critical for modulating vascular function and tone. NO produced by EC possesses vasodilatory and anti-atherogenic characteristics, including inhibition of VSMC proliferation and migration, platelet activation and adhesion, and leukocyte adhesion and migration.[26] Vasodilator chemicals including NO, endothelium-derived hyperpolarizing factor (EDHF), prostacyclin (PGI2), and vasoconstrictor substances like angiotensin II (Ang II) and thromboxane A2 are secreted by the EC and tightly regulate vascular tone.[13] Additionally, it has been suggested that EC dysfunction mediates the alterations in the vasculature that result in fibrosis and stiffness in insulin resistance and DM.[27]

Insulin metabolic signaling, which comprises the IRS-1/phosphatidylinositide 3-kinases (PI3K), protein kinase B (Akt), and cGMP signaling pathways, generally causes vasodilation in VSMCs. This signaling results in a decrease in the amount of free intracellular calcium and the sensitivity of the contractile apparatus to calcium..[28] Thus, insulin resistance in VSMCs impairs vascular vasodilation.

Brachial Ankle Pulse Wave Velocity:

PWV is calculated using following formula. PWV=L (cm)/TT (s) Here, Length (L) in centimeter and transit time in second. The path length formula is critically important during measurement of PWV. In baPWV measurements the brachial-ankle distance is calculated. Brachial-ankle distance is expressed as 1.3 × c + d – b with b , c, and d indicating heart-brachial, heart-femoral, and femoral-ankle lengths. All these lengths are expressed as linear equations of height.[29]

The time interval between the wave front of the brachial wave form and that of the ankle waveform was defined as the time interval between the brachium and ankle ("Tba).[30]

Results:

This cross sectional study was conducted at the department of Biochemistry and Molecular Biology, BSMMU. Total 95 participants were selected from outpatient department of Endocrinology and Metabolism, BSMMU. The study subjects were divided into two groups on the basis of arterial stiffness. Arterial stiffness was assessed by measuring brachial ankle pulse wave velocity (bapwv). Group 1 included 49 out of 95 type 2 diabetes mellitus patients and group 2 included 46 out of 95 type 2 diabetes mellitus patients. The study participants with bapwv ≥1815cm/s was considered as group 1 (type 2 DM patients with arterial stiffness).

Table-I

Grouping of the study subjects on the basis of arterial stiffness by measuring brachial ankle pulse wave velocity (n=95).

Group	Number of participants(n)	Percentage (%)
Group 1 (Type 2 DM Patients with arterial stiffness bapwv ≥1815cm/s)	49	51.58
Group 2 (Type 2 DM Patients without arterial stiffness bapwv<1815cm/s)	46	48.42

bapwv: brachial ankle pulse wave velocity

Results were expressed as frequency and percentage.

Table I showed that the study subjects were divided into two groups on the basis of arterial stiffness. Arterial stiffness was assessed by measuring brachial ankle pulse wave velocity (bapwv). Group 1 included 49 out of 95 type 2 diabetes mellitus patients and Group 2 included 46

out of 95 type 2 diabetes mellitus patients .The study subjects with bapwv ≥1815cm/s was considered as type 2 DM patients with arterial stiffness and patients with bapwv<1815cm/s was considered as type 2 DM patients without arterial stiffness.

Table-II

Distribution of the study subjects according to gender (n=95)

	Group 1 (Type 2 DM Patients with arterial stiffness bapwv ≥1815cm/s) n=49	Group 2 (Type 2 DM Patients without arterial stiffness bapwv<1815cm/s) n=46	P value
Sex			
Male	29(59.18)	27(58.7%)	0.961
Female	20(40.82)	19(41.3%)	

Chi square test was done to measure the level of significance.

Data were expressed in frequency and percentage. Table a! showed no significant difference in gender between the two groups.

Table-III

Distribution of the study subjects by anthropometric and clinical parameters.

Variables	Group 1 (Type 2 DM Patients with arterial stiffness bapwv ≥1815cm/s) n=49	Group 2 (Type 2 DM Patients without arterial stiffness bapwv<1815cm/s) n=46	P value
Age(years) (mean ± SD)	56.96±7.51	51.76±8.31	.002c
Duration of diabetes (years) (Median with IQR)	10 (8-14.5)	8 (5.75-12.5)	.025G”
SBP(mmHg) (mean ±SD)	128.16±13.79	117.72±10.73	.000C”
DBP(mmHg) (mean ±SD)	83.98±9.73	79.13±7.84	.009C”
BMI (mean ±SD)	25.86±3.87	24.45 ±3.35	.087
Waist circumference (cm) (mean ±SD)	95.32±10.01	91.85±8.36	.071

Results were expressed as mean ±SD in case of normal distribution and as median with interquartile range (IQR), in case of skewed distribution. C”Unpaired t-test (for normal distribution) and G”Mann –Whitney U test (for skewed distribution) were performed to measure the level of significance. P value ≤.05 was considered as significant.

This table showed significant differences in age, systolic blood pressure and diastolic blood pressure between the two groups. Also, median values of duration of diabetes showed statistical significance.

Table -IV

Comparison of the of the biochemical parameters of the study subjects between two group (n=95).

Biochemical parameters	Group 1 (Type 2 DM Patients with arterial stiffness bapwv ≥1815cm/s) n=49	Group 2 (Type 2 DM Patients without arterial stiffness bapwv <1815cm/s) n=46	P value
Fasting plasma glucose(mmol/L) (Median with IQR)	8.20 (6.50-10.35)	7.20 (5.80-9.50)	.113
Total cholesterol (mg/dl) (Median with IQR)	147 (116.50-194)	152.50 (126.75-180.25)	.938
HDL Cholesterol(mg/dl) (mean ±SD)	32.55±8.5	37.20±10.98	.023C”
LDL cholesterol (mg/dl) (Median with IQR)	76 (50-121)	80 (62-109)	.794
Triglyceride (mg/dl) (Median with IQR)	175 (136.50-262.50)	157 (119.50-225.25)	.136
Fasting insulin(µIU|L) (Median with IQR)	15.69 (8.50-23.98)	11.20 (8.28-14.97)	0.047G”

Results were expressed as mean ±SD in case of normal distribution and as median with interquartile range (IQR), in case of skewed distribution.

Table IV showed differences between two study groups regarding biochemical parameters using C”Unpaired t-test (for normal distribution) and G”Mann –Whitney U test (for skewed distribution). P value ≤05 was considered as significant. HDL cholesterol showed significant difference between two groups and is higher in group 1. Fasting insulin showed significant statistical difference between the two groups. Rest of the parameters showed no statistical significance between two groups.

Discussion:

The rising global prevalence of type 2 diabetes mellitus (DM) and its complications places an increasing strain on healthcare systems.[31] T2DM has been linked to arterial stiffening and an increased risk of cardiovascular disease.[20] Previous studied showed that insulin resistance may be crucial for the development of arterial stiffness and cardiovascular disease.[32] A popular and reliable method

for determining insulin resistance is the homeostasis model assessment of insulin resistance (HOMA-IR).[33] Type 2 DM patients with bapwv ≥1815cm/s was considered as group 1. Type 2 DM patients with bapwv<1815cm/s was considered as group 2.Group 1 included 49 out of 95 type 2 diabetes mellitus patients. Group 2 included 46 out of 95 type 2 diabetes mellitus patients. In each study subject, the following parameters were done: fasting plasma glucose, fasting serum lipid profile, fasting serum insulin level, HOMA-IR index. In this study, mean ±SD of age was 56.96±7.51 years in group 1 participants (Type 2 Diabetic patients with arterial stiffness) and 51.76±8.31 years in group 2 participants (Type 2 Diabetic patients without arterial stiffness). The mean ±SD of age of the study participants was 54.44±8.29 years. In a study in China, Wang et al. revealed that mean ±SD of age of type 2 diabetic participants was 54.6±12 years which is almost similar to the findings of the present study.[8] This study showed that there was significant difference among median values of duration of diabetes between the two groups (10 yrs in group 1 participants and 8 yrs in group 2 participants. This observation had a consistency with the study of Kim et al.[22] In the present study, mean ±SD of systolic blood pressure, diastolic blood pressure, body mass index and waist circumference were higher in group 1 than group 2. Among them mean ±SD of systolic blood pressure (Table IV) raised in group 1 and the difference was statistically significant (P value- .000) between the two groups. Diastolic blood pressure also raised in group 1in comparison to group 2 (83.98±10.56 vs 78.91± 8.23) and the difference was statistically significant (P value- .011). However, according to Wu et al. almost similar findings were observed between group1 (type 2 DM patients with arterial stiffness) and group 2 (type 2 DM patients without arterial stiffness). But mean ±SD of body mass index (Table IV) and waist circumference did not show any significant statistical difference between the two groups. This observation had an consistency with the study of Wu et al.[34] In the present study, median values of fasting plasma glucose and fasting triglyceride were higher in group 1 participants in comparison to group 2 participants but did not show any significant statistical difference between the two groups. But mean ±SD of HDL is lower in group 1 in comparison to group 2 and showed significant statistical difference between the two groups (P-.023). In this study, median values of fasting serum insulin showed significant statistical difference between the two groups.

Conclusion:

Increased arterial stiffness has been associated with increased risk of CVD. Diabetes Mellitus is a well-established risk factor for cardiovascular disease (CV). Arterial stiffness is a pathway linking diabetes to increased cardiovascular risk. Previous studies have demonstrated an independent association between IR and cardiovascular events. Moreover, IR-related indexes are associated with increased arterial stiffness.

References:

1. Bonarjee, V.V.S. (2018) Arterial Stiffness: A Prognostic Marker in Coronary Heart Disease. Available Methods and Clinical Application. *Frontiers in Cardiovascular Medicine*. 5 (June), 1–6.
2. Einarson, T.R., Acs, A., Ludwig, C. & Panton, U.H. (2018) Prevalence of cardiovascular disease in type 2 diabetes: A systematic literature review of scientific evidence from across the world in 2007-2017. *Cardiovascular Diabetology*. 17 (1), 1–19.
3. Ikonomidis, I., Makavos, G. & Lekakis, J. (2015) Arterial stiffness and coronary artery disease. *Current Opinion in Cardiology*. 30 (4), 422–31.
4. Kim, J., Song, T.J., Song, D., Lee, K.J., Kim, E.H., Lee, H.S., Nam, C.M., Nam, H.S., Kim, Y.D. & Heo, J.H. (2014) Brachial-ankle pulse wave velocity is a strong predictor for mortality in patients with acute stroke. *Hypertension*. 64 (2), 240–46.
5. International Diabetic Federation (2021) *IDF Diabetes Atlas.* http://diabetesatlas.org/atlas/tenth-edition/
6. Emerging, T. & Factors, R. (2011) Diabetes Mellitus, Fasting Glucose, and Risk of Cause-Specific Death. *The new england journal o f medicine*. 364(9), 829-41.
7. Mondal, R., Ritu, R.B. & Banik, P.C. (2021) Cardiovascular risk assessment among type-2 diabetic subjects in selected areas of Bangladesh: concordance among without cholesterol-based WHO/ISH, Globorisk, and Framingham risk prediction tools. *Heliyon*. 7 (8), e07728.
8. Wang, S., Shi, J., Peng, Y., Fang, Q., Mu, Q., Gu, W., Hong, J., Zhang, Y. & Wang, W. (2021) Stronger association of triglyceride glucose index than the HOMA-IR with arterial stiffness in patients with type 2 diabetes: a real-world single-centre study. *Cardiovascular Diabetology*. 20 (1), 1–10.
9. Jia, G. & Sowers, J.R. (2014) Endothelial dysfunction potentially interacts with impaired glucose metabolism to increase cardiovascular risk. *Hypertension*. 64 (6), 1192–93.
10. Jia, G., Aroor, A.R., DeMarco, V.G., Martinez-Lemus, L.A., Meininger, G.A. & Sowers, J.R. (2015) Vascular stiffness in insulin resistance and obesity. *Frontiers in Physiology*. 6 (Aug), 1–8.
11. Jia, G., Aroor, A.R. & Sowers, J.R. (2014) Arterial stiffness: A nexus between cardiac and renal disease. *CardioRenal Medicine*. 4 (1), 60–71.
12. Cameron, J.D. & Cruickshank, J.K. (2007) Glucose, insulin, diabetes and mechanisms of arterial dysfunction. *Clinical and Experimental Pharmacology and Physiology*. 34 (7), 677–82.
13. Creager, M.A., Lüscher, T.F., Cosentino, F. & Beckman, J.A. (2003) Diabetes and vascular disease. Pathophysiology, clinical consequences, and medical therapy: Part I. *Circulation*. 108 (12), 1527–32.

14. Hamed, S., Brenner, B. & Roguin, A. (2011) Nitric oxide: A key factor behind the dysfunctionality of endothelial progenitor cells in diabetes mellitus type-2. *Cardiovascular Research*. 91 (1), 9–15.

15. Sugawara, J. & Tanaka, H. (2015) Brachial-Ankle Pulse Wave Velocity: Myths, Misconceptions, and Realities. *Pulse*. 3 (2), 106–13.

16. Katakami, N., Osonoi, T., Takahara, M., Saitou, M., Matsuoka, T. aki, Yamasaki, Y. & Shimomura, I. (2014) Clinical utility of brachial-ankle pulse wave velocity in the prediction of cardiovascular events in diabetic patients. *Cardiovascular Diabetology*. 13 (1), 1–11.

17. Munakata, M. (2014) Brachial-Ankle Pulse Wave Velocity in the Measurement of Arterial Stiffness: Recent Evidence and Clinical Applications. *Current Hypertension Reviews*. 10 (1), 49–57.

18. Zieman, S.J., Melenovsky, V. & Kass, D.A. (2005) Mechanisms, pathophysiology, and therapy of arterial stiffness. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 25 (5), 932–43.

19. Townsend, R.R., Wilkinson, I.B., Schiffrin, E.L., Avolio, A.P., Chirinos, J.A., Cockcroft, J.R., Heffernan, K.S., Lakatta, E.G., McEniery, C.M., Mitchell, G.F., Najjar, S.S., Nichols, W.W., Urbina, E.M. & Weber, T. (2015) *Recommendations for Improving and Standardizing Vascular Research on Arterial Stiffness: A Scientific Statement from the American Heart Association*.

20. Paneni, F., Beckman, J.A., Creager, M.A. & Cosentino, F. (2013) Diabetes and vascular disease: Pathophysiology, clinical consequences, and medical therapy: Part i. *European Heart Journal*. 34 (31), 2436–46.

21. Prenner, S.B. & Chirinos, J.A. (2015) Arterial stiffness in diabetes mellitus. *Atherosclerosis*. 238 (2), 370–79.

22. Kim, J.M., Kim, S.S., Kim, I.J., Kim, J.H., Kim, B.H., Kim, M.K., Lee, S.H., Lee, C.W., Kim, M.C., Ahn, J.H. & Kim, J. (2020) Arterial stiffness is an independent predictor for risk of mortality in patients with type 2 diabetes mellitus: The REBOUND study. *Cardiovascular Diabetology*. 19 (1), 1–9.

23. Laurent, S., Cockcroft, J., Van Bortel, L., Boutouyrie, P., Giannattasio, C., Hayoz, D., Pannier, B., Vlachopoulos, C., Wilkinson, I. & Struijker-Boudier, H. (2006) Expert consensus document on arterial stiffness: Methodological issues and clinical applications. *European Heart Journal*. 27 (21), 2588–2605.

24. Maeda, Y., Inoguchi, T., Etoh, E., Kodama, Y., Sasaki, S., Sonoda, N., Nawata, H., Shimabukuro, M. & Takayanagi, R. (2014) Brachial-ankle pulse wave velocity predicts all-cause mortality and cardiovascular events in patients with diabetes: The Kyushu prevention study of atherosclerosis. *Diabetes Care*. 37 (8), 2383–90.

25. Sugawara, J., Hayashi, K. & Tanaka, H. (2014) Arterial path length estimation on brachial-ankle pulse wave velocity: Validity of height-based formulas. *Journal of Hypertension*. 32 (4), 881–89.

26. Herouvi, D., Karanasios, E., Karayianni, C. & Karavanaki, K. (2013) Cardiovascular disease in childhood: The role of obesity. *European Journal of Pediatrics*. 172 (6), 721–32.

27. Oberleithner, H. (2014) Vascular endothelium: A vulnerable transit zone for merciless sodium. *Nephrology Dialysis Transplantation*. 29 (2), 440–46.

28. Doronzo, G., Russo, I., Mattiello, L., Anfossi, G., Bosia, A. & Trovati, M. (2004) Insulin activates vascular endothelial growth factor in vascular smooth muscle cells: Influence of nitric oxide and of insulin resistance. *European Journal of Clinical Investigation*. 34 (10), 664–73.

29. Munakata, M. (2015) Brachial-Ankle Pulse Wave Velocity: Background, Method, and Clinical Evidence. *Pulse*. 3 (3–4), 195–204.

30. Yamashina, A., Tomiyama, H., Takeda, K., Tsuda, H., Arai, T., Hirose, K., Koji, Y., Hori, S. & Yamamoto, Y. (2002) Validity, reproducibility, and clinical significance of noninvasive brachial-ankle pulse wave velocity measurement. *Hypertension Research*. 25 (3), 359–64.

31. Zheng, Y., Ley, S.H. & Hu, F.B. (2018) Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nature Reviews Endocrinology*. 14 (2), 88–98.

32. Ma, X., Dong, L., Shao, Q., Cheng, Y., Lv, S., Sun, Y., Shen, H., Wang, Z., Zhou, Y. & Liu, X. (2020) Triglyceride glucose index for predicting cardiovascular outcomes after percutaneous coronary intervention in patients with type 2 diabetes mellitus and acute coronary syndrome. *Cardiovascular Diabetology*. 19 (1), 1–14.

33. Marcovina, S., Bowsher, R.R., Miller, W.G., Staten, M., Myers, G., Caudill, S.P., Campbell, S.E. & Steffes, M.W. (2007) Standardization of insulin immunoassays: Report of the American Diabetes Association Workgroup. *Clinical Chemistry*. 53 (4), 711–16.

34. Wu, Z., Wang, J., Li, Z., Han, Z., Miao, X., Liu, X., Li, X., Wang, W., Guo, X. & Tao, L. (2021a) Triglyceride glucose index and carotid atherosclerosis incidence in the Chinese population: A prospective cohort study. *Nutrition, Metabolism and Cardiovascular Diseases*. 31 (7), 2042–50.