ARTERIAL STIFFNESS ASSESSMENT IN ABDOMINALLY OBESE INDIVIDUALS: INSIGHTS FROM CLINICAL OBESITY PHENOTYPES

Ovidiu Mitu[1], R. S. Miftode[1], F. Mitu[1*], Manuela Ciocoiu[2], Ivona Mitu[2]
"Grigore T. Popa" University of Medicine and Pharmacy Iasi, Romania
Faculty of Medicine
1. Department of Medical Specialties (I)
2. Department of Morpho-Functional Sciences (II)
[*]Corresponding author. E-mail: mitu.florin@yahoo.com

ARTERIAL STIFFNESS ASSESSMENT IN ABDOMINALLY OBESE INDIVIDUALS: INSIGHTS FROM CLINICAL OBESITY PHENOTYPES (Abstract): Precise cardiovascular risk assessment remains challenging, especially amidst the dynamic interplay of factors like abdominal obesity, inadequate physical activity and imbalanced diet. This study aims to assess subclinical atherosclerosis in apparently healthy individuals with excess weight, using arterial stiffness as a parameter for cardiovascular risk assessment. **Materials and methods**: A cohort of 67 patients aged 35-75 years, without any prior atherosclerotic pathology, with abdominal obesity and no known chronic illnesses, underwent evaluation. The cohort was stratified based on obesity (BMI≥30kg/m^2), metabolic syndrome (MetS NCEP-ATP III criteria), BMI class, total or trunk adipose tissue percentage, and clinical phenotypes of obesity (metabolically healthy obese - MHO, metabolically unhealthy obese - MUO, metabolically healthy non-obese - MHNO, metabolically unhealthy non-obese - MUNO), where unhealthy is defined by the presence of MetS. Biochemical analysis was performed to assess glucose, TG and HDL-c levels, aiming to detect potential undiagnosed cases of MetS. Adiponectin and leptin measurements were also performed. Hologic QDR Delphi A determined whole body composition with dual-energy-X-ray absorptiometry (DEXA) and Arteriograph® Tensiomed measured parameters of subclinical atherosclerosis. **Results**: Pulse wave velocity (PWV) values did not significantly differ across study groups, including obese versus non-obese individuals, clinical phenotypes of obesity, presence or absence of MetS, groups defined by BMI class, or adipose tissue percentages. Nevertheless, participants with excess weight or with MetS presented lower AIXa values. The groups that did not present MetS (obese and non-obese) showed the highest proportion of patients with PWV values under the age-adjusted theoretical threshold (46.15% and 44.4%, respectively), suggesting a potentially lower vascular age than the biological one. Conversely, the groups with MetS (obese and non-obese) had smaller percentages (26.67% and 16.66%, respectively). Around 30% of patients across clinical obesity phenotypes exhibited PWV values exceeding the theoretical threshold, but under 10 m/s. **Conclusions**: AIXa values are lower in the presence of MetS and in higher BMI subjects, whereas PWV values do not change significantly. Healthy obese individuals demonstrate a vascular age similar to the healthy non-obese group, suggesting enhanced cardiovascular protection. On the other hand, arterial stiffness is reported in a higher percentage of subjects that present MetS (obese or non-obese) compared to subjects without MetS, even though the syndrome is at an early stage. **Keywords**: OBESITY, ADIPOSE TISSUE, ARTERIAL STIFFNESS, SUBCLINICAL ATHEROSCLEROSIS, METABOLIC SYNDROME.

INTRODUCTION

Chronic inflammation, a key feature of the pathophysiology of obesity, is associated with increased arterial stiffness, along with other known cardiovascular risk factors including age or systolic blood pressure (1-3). Nevertheless, studies are conflicting concerning the relationship between adipose tissue and vascular rigidity. Several analyses reported higher pulse wave velocity (PWV) values in patients with obesity measured by BMI or trunk adiposity (4-6), while other studies support the inversed relationship, commonly referred to as the "obesity paradox". Without any doubt, obesity as defined by BMI increases the risk of cardiovascular events. However, this does not consider the percentage of whole-body or trunk adipose tissue, nor the visceral adipose tissue. Therefore, this seemingly paradoxical relationship may be explained by the fact that BMI primarily reflects lean body mass rather than adiposity and the latter is a more robust predictor of cardiovascular mortality and morbidity (7).

After a cardiovascular event a trend toward better prognosis has been observed in the overweight and obese population, linked to the same phenomenon of obesity paradox (8-10). Vascular function has been shown to be unexpectedly better in severely obese individuals compared to moderate or even normal-weight subjects. Even though they exhibit high inflammation, they may still experience partial protection against atherosclerosis, and one possible explanation is enhanced mobilization of endothelial progenitor cells (11).

Accurate estimation of cardiovascular risk remains a challenge, particularly in the context of dynamic changes in metabolic pathways influenced by the presence of modifiable factors like smoking, low dietary intake of fruits and vegetables, insufficient physical exercise, abdominal obesity, diabetes, hypertension, dyslipidemia or non-modifiable factors like age, sex, personal or family history of cardiovascular disease, ethnicity, genetic evidence. This study aims to examine the relationship between arterial stiffness and different measures of obesity in apparently healthy subjects, with no known chronic diseases, in order to reduce at a minimum the bias of factors.

MATERIALS AND METHODS

This prospective study was conducted over a two-year period and included 67 participants recruited based on the following criteria: no history of chronic disease and no prior atherosclerotic events. Pregnant women and individuals who declined to provide informed consent prior to enrolment were not included in the study. All investigations were undertaken by trained personnel within the same clinical and laboratory setting, utilizing standardized equipment and analytical methods throughout the study duration.

Anthropometric parameters were measured using a tape meter at the umbilical (waist circumference) and greater trochanter (hip circumference) level. Whole body composition measurements were assessed with Dual-Energy X-ray Absorptiometry (DEXA) technique, using Hologic QDR Delphy A fan-beam (Hologic Inc., Massachusetts). The biochemical profile for each participant at the study was performed using the spectrophotometric method for

triglycerides, HDL-c and glucose, enzyme-linked immunosorbent assay (ELISA) for adiponectin and leptin, chemiluminescence technique for insulin.

Arterial stiffness was assessed in participants using the Arteriograph® Tensiomed (Budapest, Hungary). The following parameters were measured: pulse wave velocity (PWV), augmentation index (AIXa), aortic pulse pressure (PPao), aortic systolic blood pressure (SBPao), mean arterial pressure (MAP), reflection time (RT), and ejection time. The device's cuff was positioned on the dominant arm, and the length of the aorta up to the iliac bifurcation was estimated based on anthropometric measurements (the distance between the pubic symphysis and the suprasternal notch) (12). To ensure standardized conditions, participants were instructed to rest quietly in a controlled environment prior to the examination, with no alcohol, tobacco or caffeine in the last 10 hours. Talking or movement during measurements was not allowed (13). After recording blood pressure, the device applied an additional pressure of 35 mmHg to facilitate the analysis of pulse wave reflections. The accompanying software calculated the PWV and other hemodynamic parameters.

The study cohort was divided in groups dependent on the obesity status, MetS status and body composition. Four obesity clinical phenotypes were described: metabolically healthy obese (MHO) or non-obese (MHNO) and metabolically unhealthy obese (MUO) or non-obese (MUNO). The obesity status was present if participants presented BMI≥30 kg/m^2. The metabolically unhealthy status was present if the participant presented MetS, which was defined in patients with waist circumference > 88 cm (women) / 104 cm (men) and that presented at least 2 criteria: glucose ≥ 100 mg/dL, HDL-C < 40 mg/dL (men) / < 50 mg/dL (women), TG ≥ 150 mg/dL, TAS/TAD ≥ 130/85 mmHg (14).

The process of data was handled with Microsoft Excel v.16.64 (Microsoft Corporation, USA) and *SPSS version 23.0* (IBM Corporation, USA). Kolmogorov-Smirnov/ Shapiro-Wilk tests were used for assessing data distribution. For normally distributed variables, values of the mean±standard deviation were reported and for non-normally distributed variables, values of the median, along with quartiles. Categorical variables are reported as percentages. For comparative analysis between continuous variables, the independent parametric test one-way ANOVA was used for a normal data distribution and the non-parametric test Mann-Whitney U for a non-normal distribution. For correlation analyses, the Pearson, Kendall's tau-b and Spearman correlation tests were performed. Values of $p<0.05$ were considered statistically significant.

RESULTS

This study included 67 apparently healthy but overweight patients, in whom subclinical atherosclerosis indicators were measured to assess the cardiovascular risk. Among the arterial stiffness parameters, only AIXa, RT, MAP and ejection duration showed a normal distribution according to Shapiro-Wilk test. Table I presents the general data of the parameters evaluating the biochemical profile and subclinical atherosclerosis in the study group. The comparative analysis of the PWV value

between groups did not reveal statistically significant differences, but significant differences were observed regarding the AIXa values (fig. 1).

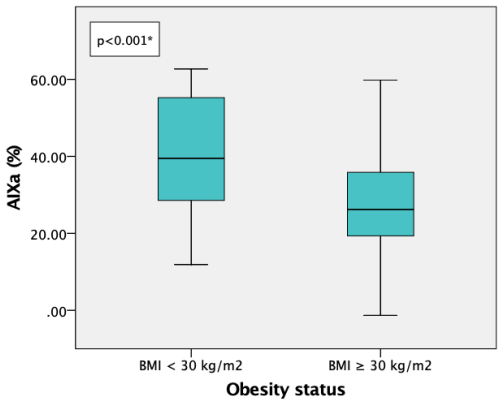
Within the entire sample, of all the anthropometric, biochemical and adipose tissue-related parameters, PWV correlated only with the waist-to-hip ratio. Conversely, AIXa was negatively associated with anthropometric parameters (tab. II).

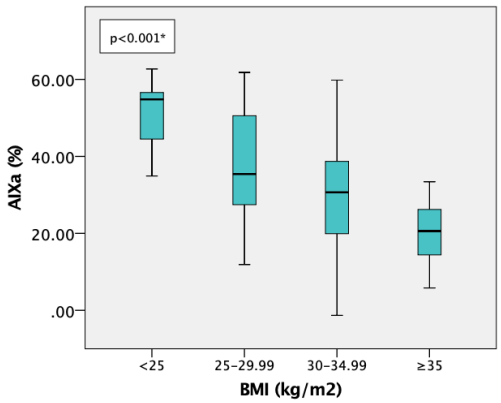
TABLE I.

Descriptive parameters of the study group

Parameter	Mean±S.D.	Min	Max	Median (Q3-Q1)
Parameters of subclinical atherosclerosis				
PWV	9.90±1.76	7.2	14.9	9.7 (2.2)
AIXa	31.87±15.36	-1.3	62.7	30.4 (22.1)
PP	50.09±15.05	29.5	103.1	45.4 (14)
SBPao	138.23±20.94	109.9	233.1	134.8 (21.6)
PPao	52.09±12.65	33	92	50 (12)
MAP	105.49±13.43	83	161	105 (17)
RT	113.84±18.35	71	153	115 (20)
Ejection time	305.22±31.01	215	370	305 (40)
Biochemical parameters				
TG	154.70±92.53	49	488	125 (100)
HDL-c	52.78±14.47	20	85	52 (20)
Glucose	113.43±39.73	76	336	103 (22)
Insulin	18.98±12	2.13	52	16.10 (12.01)
HOMA-IR	5.56±4.74	0.49	27.25	3.85 (3.51)
Adiponectin	13.80±5.41	4.53	28.53	12.96 (7.14)
Leptin	22.93±13.77	2.60	48.98	18.72 (24.05)

*SD= standard deviation, Q3-Q1=difference between superior quartile and inferior quartile.





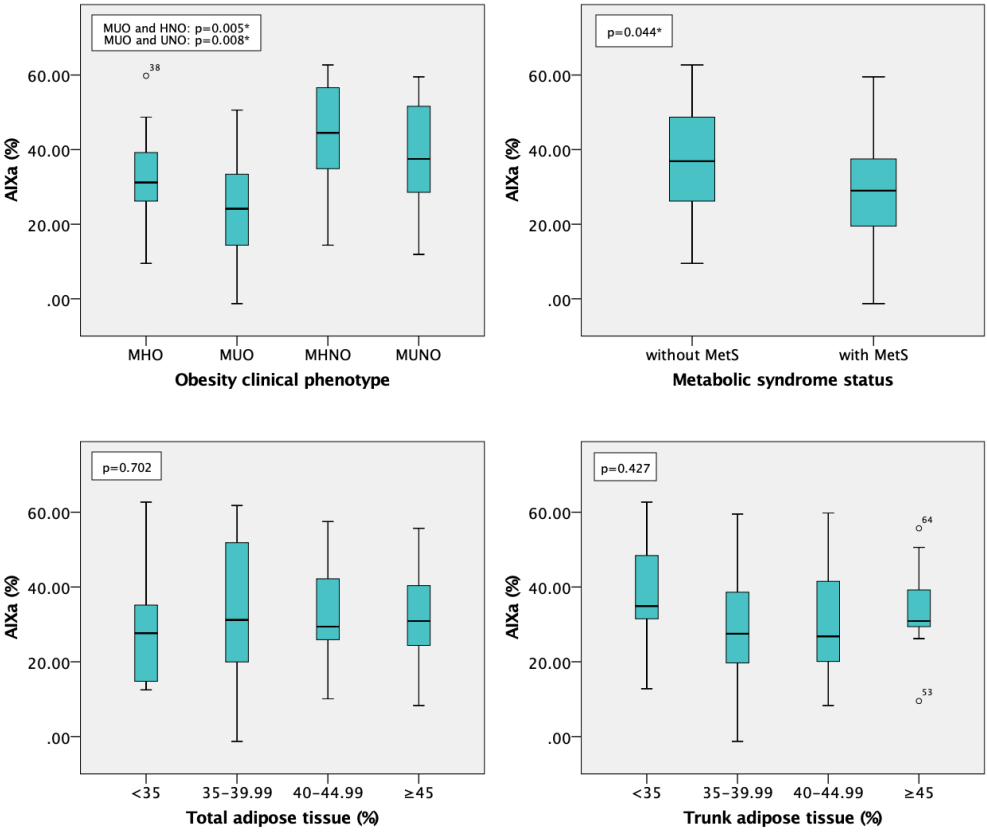


Fig. 1. Comparison of AIXa parameter value across the study groups.

TABLE II.

Correlation between adipose tissue parameters and cardiovascular risk

		PWV	AIXa*	PPao	SBPao
BMI*	r	0.03^{K}	-0.52^{P}	-0.19^{K}	-0.8^{K}
	p	0.75	<0.001	0.03	0.33
Waist circumference	r	0.20^{S}	-0.30^{K}	-0.17^{S}	0.03^{S}
	p	0.10	<0.001	0.16	0.80
Waist-height ratio	r	0.16^{S}	-0.26^{K}	-0.18^{S}	-0.02^{S}
	p	0.19	0.002	0.14	0.85
Waist-hip ratio	r	0.16^{K}	-0.25^{P}	-0.05^{K}	0.13^{K}
	p	0.02	0.04	0.51	0.12
Total adipose tissue (%)	r	-0.08^{S}	0.05^{K}	0.01^{S}	-0.13^{S}
	p	0.49	0.51	0.93	0.29
Trunk adipose tissue (%)*	r	-0.01^{K}	-0.12^{P}	-0.04^{K}	-0.07^{K}
	p	0.87	0.33	0.63	0.42

*normal distribution, PWV=pulse wave velocity, AIXa=aortic augmentation index, PPao=aortic pulse pressure, SBPao=aortic arterial systolic pressure, P=Pearson, S=Spearman, K=Kendall's tau.

From the entire cohort of patients, 61.20% exhibited normal PWV values. Within this subgroup, nearly half presented values below the theoretical PWV, derived from a database of approximately 10,000 measurements from a Central European population. Table III details the distribution of patients and corresponding percentages, stratified by clinical obesity phenotypes.

No statistically significant differences in biomarkers, anthropometric measurements, or adipose tissue parameters were observed between patients with normal PWV values and those with PWV values exceeding 10 m/s within the MHO, MHNO, MUNO subgroups. Statistically significant data for the MUO subgroup are presented in table IV.

TABLE III.

Comparative analysis of real PWV with theoretical PWV across study groups

	MHO	MUO	MHNO	MUNO	Total
Patients with PWV < theoretical value	6	5	4	4	19
Patients with PWV > theoretical value. but under 10 m/s	3	11	3	5	22
% patients with PWV > theoretical value. but under 10 m/s	33.33%	68.75%	42.86%	55.56%	53.66%
Patients with PWV < 10 m/s	9	16	7	9	41
Patients with PWV ≥ 10 m/s	4	14	2	6	26
% patients with PWV ≥ 10 m/s	30.77%	46.67%	22.22%	40%	38.80%

TABLE IV.

Parameters exhibiting statistically significant differences between the MUO group with vascular stiffness and the MUO group without vascular stiffness.

	PWV < 10 m/s			PWV ≥ 10 m/s			
Results of the one-way ANOVA parametric test							
Parameter	Mean ± S.D.	C.I. 95%		Media ± S.D.	C.I. 95%		p
		I.L.	S.L.		I.L.	S.L.	
Adiponectin	13.43±4.30	11.14	15.72	9.92±3.77	7.74	12.10	0.02
Waist circumference	109.19±10.34	103.68	114.69	117.86±8.81	112.77	122.95	0.02
Total adipose tissue (%)	40.39±5.50	37.46	43.32	36.33±5.12	33.37	39.28	0.05
Results of the one-way Mann-Whitney U non-parametric test							
Parameter	Median	Q1-Q3		Median	Q1-Q3		
Insulin	14.45	18.7-21.45		17	30.65-45.22		0.05
HOMA-IR	3.46	4.56-5.26		4.45	10.24-12.77		0.04

*S.D.= standard deviation, C.I.=confidence interval, I.L.= inferior limit, S.L.= superior limit, Q1= inferior quartile, Q3= superior quartile.

DISCUSSION

The present study reports new data on the association between the four obesity clinical phenotypes and cardiovascular risk, also exploring the correlations between markers of subclinical atherosclerosis and

adiposity parameters. Arterial stiffness, as assessed by PWV, AIXa, and PP, is an independent risk factor for cardiovascular mortality (15). Our results suggest that while PWV and PP do not significantly discriminate between groups regardless of obesity status, clinical phenotype of obesity, presence of metabolic syndrome, or body composition, AIXa reports statistically different values. These findings emphasize the need for further studies to clarify the role of AIXa in the assessment of cardiovascular risk. This marker is not as well studied as PWV, but it is associated with known risk factors for cardiovascular disease (16, 17).

In obesity, AIXa has been reported to have both elevated (18) and decreased values (19, 20). In our study, obese patients overall have lower AIXa values than non-obese patients, as well as those with MetS compared to those without MetS. In particular, at the clinical phenotype level, only MUO report significantly lower values than MHNO and MUNO. Consequently, we can assume that obesity together with MetS represents an association that reports low AIXa values in the studied population. Our findings are contrary to those of several previous investigations included in the systematic review and meta-analysis performed by Li P., *et al.* that showed increased PWV and AIX values in obese or overweight subjects (21). Nevertheless, our results are consistent with other investigations that emphasize a better outcome after percutaneous coronary interventions in subjects with high BMI (22) or even improved vascular function in healthy but obese individuals (11).

The decrease in AIXa values could be explained by the effect of insulin. It has a vasodilatory role by stimulating nitric oxide synthesis (23, 24), leading to increased vascular wall elasticity and altered aortic wave reflection. Several studies have reported lower arterial stiffness in obese and/or MetS patients compared to normal-weight patients, due to insulin (25-28). At the same time, metabolic insulin resistance may have vascular effects through non-enzymatic glycation processes leading to collagen cross-linking or through sympathetic activation and smooth muscle cell proliferation, leading to stiffness (29, 30). We cannot establish a cause-and-effect relationship in our study, but insulin and HOMA-IR values are higher in obese patients, with MetS or MetS clinical phenotypes. We can consider the acceptable quality of endothelial function observed in these patients as a consequence of the diagnosis of an early stage of MetS in the study group, with minimal metabolic changes, given that the patients included in the study were apparently healthy. Moreover, we must also consider the fact that the AIXa parameter is influenced by heart rate and does not represent such a reliable parameter of vascular stiffness as PWV.

In the studied population, PWV value is associated with MetS and not with obesity, since the prevalence of patients with abnormal PWV values is higher in MetS patient groups, regardless of the presence of obesity. Recent studies have demonstrated that there is no association between PWV level and obesity (31, 32), but a significant impact of MetS on PWV was confirmed in a prospective, multicenter study with patients from 18 European countries (33). Furthermore, another study identifies PWV as a more effective parameter than SCORE-2 or other grids that measure the risk of cardiovascular disease, to estimate vascular age in patients with MetS (34).

Adiponectin is lower in patients with

abnormal PWV values, although the percentages of total and non-adipose tissue at the trunk level show similar values to those of patients in the normal PWV group. Hypoadiponectinemia has been identified in coronary atherosclerosis and acute coronary syndrome and has been associated with increased arterial stiffness (35, 36).

Several studies have reported a higher cardiovascular risk in MUO patients than in MHO (37, 38). The MHO phenotype in our study presents the highest percentage of patients with PWV below the theoretical value, more precisely below the mean value corresponding to the patient's age. This result implies a lower vascular age than that associated with the patient's biological age, suggesting additional cardiovascular protection. A study conducted on 2,076 participants supports our results, concluding that the progression of arterial stiffness was not increased in MHO patients, contrary to the result obtained for MetS groups, where regardless of the presence or absence of obesity, the evolution of arterial stiffness was significantly unfavorable (39).

CONCLUSIONS

PWV values do not differ significantly in apparently healthy individuals with abdominal obesity, regardless of BMI, MetS, adipose tissue percentage or clinical obesity phenotypes. AIXa values are lower in the presence of MetS and in subjects with higher BMI, however its values are influenced by different factors and therefore it is not such a reliable parameter of vascular stiffness as PWV. Healthy obese individuals demonstrate a vascular age similar to the healthy non-obese group, meanwhile there is an important increase in the number of subjects with MetS-associated arterial stiffness, even though the MetS is at an early stage. Therefore, as long as healthy obese do not develop MetS, their vascular rigidity is considered more likely to be at the level of that for non-obese.

CONFLICT OF INTEREST AND FUNDING

The authors declare no conflict of interest or funding.

REFERENCES

1. McEniery CM, Yasmin, Hall IR, Qasem A, Wilkinson IB, Cockcroft JR; ACCT Investigators. Normal vascular aging: differential effects on wave reflection and aortic pulse wave velocity: the Anglo-Cardiff Collaborative Trial (ACCT). *J Am Coll Cardiol* 2005; 46(9): 1753-1760 / doi: 10.1016/j.jacc. 2005. 07.037.
2. Jain S, Khera R, Corrales-Medina VF, Townsend RR, Chirinos JA. Inflammation and arterial stiffness in humans. *Atherosclerosis* 2014; 237(2): 381-390 / doi: 10.1016/ j.atherosclerosis.2014.09.011.
3. Eikås JG, Gerdts E, Halland H, Midtbø H, Cramariuc D, Kringeland E. Arterial Stiffness in Overweight and Obesity: Association with Sex, Age, and Blood Pressure. *High Blood Press Cardiovasc Prev* 2023; 30(5): 435-443 / doi: 10.1007/s40292-023-00593-2.
4. Corrigan FE 3rd, Kelli HM, Dhindsa DS, *et al*. Changes in truncal obesity and fat distribution predict arterial health. *J Clin Lipidol* 2017; 11(6): 1354-1360 / doi: 10.1016/ j.jacl.2017.08.013.
5. Strasser B, Arvandi M, Pasha EP, Haley AP, Stanforth P, Tanaka H. Abdominal obesity is associated with arterial stiffness in middle-aged adults. *Nutr Metab Cardiovasc Dis* 2015; 25(5): 495-502 / doi: 10.1016/j.numecd.2015.01.002.

6. Kim S, Kyung C, Park JS, *et al*. Normal-weight obesity is associated with increased risk of subclinical atherosclerosis. *Cardiovasc Diabetol* 2015; 14: 58 / doi: 10.1186/ s12933-015-0220-5.
7. Lalazar G. Central obesity: Redefining normal BMI. *Sci Transl Med* 2015; 7: 316ec209.
8. Tutor AW, Lavie CJ, Kachur S, Milani RV, Ventura HO. Updates on obesity and the obesity paradox in cardiovascular diseases. *Prog Cardiovasc Dis* 2023; 78: 2-10 / doi: 10.1016/j. pcad.2022.11.013.
9. Antonopoulos AS, Tousoulis D. The molecular mechanisms of obesity paradox. *Cardiovasc Res* 2017; 113(9): 1074-1086 / doi: 10.1093/cvr/cvx106.
10. Patel N, Elsaid O, Shenoy A, Sharma A, McFarlane SI. Obesity paradox in patients undergoing coronary intervention: A review. *World J Cardiol* 2017; 9(9): 731-736 / doi: 10. 4330/wjc.v9.i9.731.
11. Biasucci LM, Graziani F, Rizzello V, *et al*. Paradoxical preservation of vascular function in severe obesity. *Am J Med*. 2010 Aug; 123(8): 727-734 / doi: 10.1016/j.amjmed.2010.02.016.
12. Horváth IG, Németh Á, Lenkey Z, *et al*. Invasive validation of a new oscillometric device (Arteriograph) for measuring augmentation index, central blood pressure and aortic pulse wave velocity. *J Hypertens* 2010; 28(10): 2068-2075.
13. Tensiomed. Innovative Method to Ease Arterial Stiffness Measurement. https: //www.tensiomed.com. Accessed 4th February 2025.
14. Grundy SM, Cleeman JI, Daniels SR, *et al*. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* 2005; 112(17): 2735-2752.
15. Willum Hansen T, Staessen JA, Torp-Pedersen C, *et al*. Prognostic Value of Aortic Pulse Wave Velocity as Index of Arterial Stiffness in the General Population. *Circulation* 2006; 113(5): 664-670.
16. van Trijp MJCA, Uiterwaal CSPM, Bos WJW, *et al*. Noninvasive Arterial Measurements of Vascular Damage in Healthy Young Adults: Relation to Coronary Heart Disease Risk. *Ann Epidemiol* 2006; 16(2): 71-77.
17. van Trijp MJCA, Bos WJW, van der Schouw YT, *et al*. Non-invasively measured structural and functional arterial characteristics and coronary heart disease risk in middle aged and elderly men. *Atherosclerosis* 2006; 187(1): 110-115.
18. Ounis-Skali N, Bentley-Lewis R, Mitchell GF, *et al*. Central aortic pulsatile hemodynamics in obese premenopausal women. *Journal of the American Society of Hypertension* 2007; 1(5): 341-346.
19. Maple-Brown LJ, Piers LS, O'Rourke MF, *et al*. Central obesity is associated with reduced peripheral wave reflection in Indigenous Australians irrespective of diabetes status. *J Hypertens* 2005; 23(7): 1403-1407.
20. Otsuka T, Kawada T, Ibuki C, Kusama Y. Obesity as an independent influential factor for reduced radial arterial wave reflection in a middle-aged Japanese male population. *Hypertension Research* 2009; 32(5): 387-391.
21. Li P, Wang L, Liu C. Overweightness, obesity and arterial stiffness in healthy subjects: a systematic review and meta-analysis of literature studies. *Postgrad Med* 2017; 129(2): 224-230 / doi: 10.1080/ 00 325481.2017.1268903.
22. Gurm HS, Brennan DM, Booth J, *et al*. Impact of body mass index on outcome after percutaneous coronary intervention (the obesity paradox). *Am J Cardiol* 2002; 90: 42-45.
23. Farb MG, Gokce N. Visceral adiposopathy: a vascular perspective. *Horm Mol Biol Clin Investig* 2015; 21(2): 125-136.
24. Baron AD, Brechtel-Hook G, Johnson A, *et al*. Effect of perfusion rate on the time course of insulin-mediated skeletal muscle glucose uptake. *American Journal of Physiology- Endocrinology and Metabolism* 1996; 271(6): E1067-1072.

25. Tamminen M, Westerbacka J, Vehkavaara S, Yki-Järvinen H. Insulin-Induced Decreases in Aortic Wave Reflection and Central Systolic Pressure Are Impaired in Type 2 Diabetes. *Diabetes Care* 2002; 25(12): 2314-2319.
26. Jahn LA, Hartline L, Rao N, *et al*. Insulin Enhances Endothelial Function Throughout the Arterial Tree in Healthy but not Metabolic Syndrome Subjects. *J Clin Endocrinol Metab* 2016; 101(3): 1198-1206.
27. Lee JW, Lee DC, Im JA, *et al*. Insulin Resistance Is Associated with Arterial Stiffness Independent of Obesity in Male Adolescents. *Hypertension Research* 2007; 30(1): 5-11.
28. Dotson BL, Heiston EM, Miller SL, Malin SK. Insulin stimulation reduces aortic wave reflection in adults with metabolic syndrome. *American Journal of Physiology-Heart and Circulatory Physiology* 2021; 320(6): H2305-312.
29. Airaksinen KEJ, Salmela PI, Linnaluoto MK, *et al*. Diminished arterial elasticity in diabetes: association with fluorescent advanced glycosylation end products in collagen. *Cardiovasc Res* 1993; 27(6): 942-945.
30. Begum N, Song Y, Rienzie J, Ragolia L. Vascular smooth muscle cell growth and insulin regulation of mitogen-activated protein kinase in hypertension. *American Journal of Physiology-Cell Physiology* 1998; 275(1): C42-49.
31. Desamericq G, Tissot CM, Akakpo S, *et al*. Carotid-Femoral Pulse Wave Velocity Is Not Increased in Obesity. *Am J Hypertens* 2015; 28(4): 546-851.
32. Phillips J, McBride CA, Morris E, *et al*. Adiposity, but not Obesity, Is Associated With Arterial Stiffness in Young Nulliparous Women. *Reproductive Sciences* 2018; 25(6): 909-915.
33. Topouchian J, Labat C, Gautier S, *et al*. Effects of metabolic syndrome on arterial function in different age groups. *J Hypertens*. 2018; 36(4): 824-833.
34. Nedogoda SV, Salasyuk AS, Barykina IN, *et al*. Identifying Early Vascular Ageing in Patients with Metabolic Syndrome: Unresolved Issues and a Proposed Novel VAmets Score. *Heart Lung Circ* 2021; 30(11): 1752-1761.
35. el Khoudary SR, Barinas-Mitchell E, White J, *et al*. Adiponectin, systolic blood pressure, and alcohol consumption are associated with more aortic stiffness progression among apparently healthy men. *Atherosclerosis* 2012; 225(2): 475-480.
36. Bielecka-Dabrowa A, Bartlomiejczyk MA, Sakowicz A, *et al*. The Role of Adipokines in the Development of Arterial Stiffness and Hypertension. *Angiology* 2020; 71(8): 754-761.
37. Eckel N, Li Y, Kuxhaus O, *et al*. Transition from metabolic healthy to unhealthy phenotypes and association with cardiovascular disease risk across BMI categories in 90 257 women (the Nurses' Health Study): 30-year follow-up from a prospective cohort study. *Lancet Diabetes Endocrinol* 2018; 6(9): 714-724.
38. Blüher M. The myth of innocent obesity. *Nat Rev Endocrinol* 2017; 13(12): 691-692.
39. Yuan Y, Mu JJ, Chu C, *et al*. Effect of metabolically healthy obesity on the development of arterial stiffness: a prospective cohort study. *Nutr Metab (Lond)* 2020; 17(1): 50.