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ORIGINAL PAPER

Arterial Stiffness and COVID-19: Potential Association with Diabetes, Hypertension and Obesity: a Cross Sectional Study

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ABSTRACT

Background: *Cardiovascular diseases account for one-third of deaths worldwide. Arterial stiffness is considered as useful predictor of cardiovascular events as measured by pulse wave velocity. Hypertension promotes collagen production causing increase in vascular thickness and arterial stiffness. Diabetes is a potential risk factor for arterial stiffness causing imbalance between production and degradation of collagen and elastic fibres. Oxidative stress in obesity leads to endothelial dysfunction and increases arterial stiffness. Hyperinflammation in COVID-19 is proposed to stimulate inflammatory cells that produce collagenases and elastases, which disrupt physiology causing increased arterial stiffness. Hence, in this study we attempt to investigate to which extent COVID-19 increases arterial stiffness especially in individuals with conditions including hypertension, diabetes and obesity.*

Objectives: *This study aimed to measure pulse wave velocity (PWV) in post-COVID 19 patients with diabetes, hypertension and obesity and compare it with individuals with comorbidities without COVID.*

Methods: *The study population included 184 individuals in the age group of 30-50 years who were divided into four groups as follows: group I comprised subjects with diabetes (n= 64), group II patients with*

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hypertension (n=40), group III subjects with obesity (n=50) and group IV controls (n=30). Groups I, II and III were further divided into two subgroups each, depending on the presence or absence of COVID-19. Arterial stiffness was assessed in all study participants.

Results: *The results of the present study show a strong correlation between COVID-19 and increased arterial stiffness, particularly in individuals with comorbidities such as diabetes, obesity and hypertension. The mean brachial ankle PWV (baPWV), carotid-femoral PWV (CFPWV) and ankle arterial stiffness index (ASI) was significantly higher among subjects with a history of COVID-19 with hypertension, (p <0.001), followed by high values in obese subjects with COVID-19 and diabetes subjects with COVID-19 when compared to controls.*

Conclusions: *As COVID-19 is associated with increased arterial stiffness, particularly in individuals with comorbidities, undoubtedly it has long-term effects on vascular ageing and physiology. Hypertension was found to be the riskiest factor for increased vascular stiffness in COVID-19 patients.*

Keywords: arterial stiffness, pulse wave velocity, COVID-19, diabetes mellitus, hypertension, obesity.

ABBREVIATIONS

COVID-19: coronavirus disease 2019
AS: arterial stiffness
PVW: pulse wave velocity
SBP: systolic blood pressure
DBP: diastolic blood pressure
FBS: fasting blood sugar
PP: pulse pressure
LbaPWV: left brachial-ankle pulse wave velocity
RbaPWV: right brachial-ankle pulse wave velocity
CF PWV: carotid-femoral pulse wave velocity
R bra ASI: right brachial arterial stiffness Index
L bra ASI: left brachial arterial stiffness Index
R Ank ASI: right ankle arterial stiffness Index
L Ank ASI: left ankle arterial stiffness Index
BMI: body mass index

BACKGROUND

Cardiovascular diseases account for approximately one-third of all deaths worldwide (1). Arteries are an integral part of the cardiovascular system and arterial stiffness (AS) is considered an index of vascular ageing, a useful predictor and an integrated marker of cardiovascular events and mortality (2, 3). While age dependent vascular changes occur typically in the fifth decade of life, there is a strong variability of vascular changes between individuals. Vascular ageing occurs both in micro- and macro-vasculature, which is driven by many risk factors such as diabetes, hypertension, dyslipidemia and chronological ageing.

Arterial stiffness measured by pulse wave velocity (PVW) (gold standard) is one of the earliest noticeable indications of adverse structural and hemodynamic changes within the vessel wall resulting in myocardial infarction, heart failure, stroke and renal damage (4). Brachial-ankle pulse wave velocity (ba PWV) is a measure of systemic arterial stiffness that is measured by analysis of brachial and tibial arterial waves. Carotid-femoral pulse wave velocity (CF PWV) is the reference standard for the measurement of central arterial stiffness.

In December 2019, an outbreak of SARS-CoV-2 infection (COVID-19) was reported in Wuhan, China, which spread worldwide. On the 11th of March 2020, the World Health Organization (WHO) declared it a pandemic, which shook the world, presenting an unprecedented challenge to humanity. Despite the fact that the respiratory symptoms dominate the clinical manifestations of COVID-19, the effects on cardiovascular system are evident. The vascular endothelium is proved to be intimately involved in the pathogenesis of COVID-19. Hyperinflammation and immune mediated vascular response in COVID-19 is proposed to stimulate inflammatory cells that produce collagenases and elastases, which disrupt vascular physiology causing increased AS (5).

Amid the pandemic, the incidence of cardiovascular events like myocardial infraction has been reported to be high in COVID-19 patients,

especially in those with comorbidities such as hypertension, diabetes and obesity. Hypertension has been shown to promote collagen production, causing subsequent increase in vascular thickness and AS (6, 7). Diabetes mellitus is considered one of the potential risk factors for AS by disrupting the balance that exists between the production and degradation of collagen and elastic fibres (8). Obesity results in increased low-density lipoproteins (LDL) leading to endothelial dysfunction and thus, to deposition of minerals such as calcium, which forms patches of plaque, all of which results in increased AS if present for an extended period of time (9).

So far, there have been only a few studies which aimed to assess the impact of COVID-19 on arterial stiffness, although COVID-19 has been reported to increase AS (10). People who have recovered from a chronic period of COVID-19, especially those with co-morbidities such as diabetes, obesity and hypertension, accompanied by AS, are more at risk of developing cardiovascular diseases (11). Measuring AS may therefore identify patients and predict the risk of cardiovascular diseases and prevent morbidity and mortality at an early stage. Hence, in this study we attempt to identify the comorbid conditions that cause greater increase in AS and to investigate to which extent COVID-19 increases AS in individuals especially with conditions like hypertension, diabetes and obesity.

Study objectives

The present study aimed 1) to measure the PWV in post-COVID-19 patients with diabetes, hypertension and obesity; 2) to compare the PWV of post-COVID-19 patients with comorbidities (diabetes, hypertension and obesity) with that of individuals with comorbidities but without COVID-19; and 3) to evaluate the association of COVID-19 with AS and comorbidities (diabetes, hypertension and obesity). ❑

METHODS

We conducted a cross sectional study which included a total population of 184 adults in the age group of 30-50 years. Study participants were divided into four groups: group I (n= 64), group II (n=40), group III (n=50) and group IV (n=30). Groups I, II and III were further divided into two subgroups each: a) individuals with past history of mild and moderate COVID-19 for at least four months after initial infection confirmed by positive real-time reverse transcriptase polymerase chain reaction (rRT-PCR); and b) individuals without a history of COVID-19. Thus, group Ia comprised 32 individuals with H/O diabetes mellitus who had been previously infected with COVID-19 (three or more months); group Ib: 32 individuals with diabetes but without COVID-19; group IIa: 20 individuals with H/O hypertension who had been previously infected with COVID-19; group IIb: 20 individuals with hypertension but without COVID-19; group IIIa: 25 individuals with obesity (BMI >30 Kg/m^2) who had been previously infected with COVID-19; group IIIb: 25 individuals with obesity but without COVID-19; and group IV (control group): 30 individuals who were age and sex matched with the other groups and had no comorbidities and no previous infection with COVID-19.

Exclusion criteria

Pregnant women, people suffering from chronic diarrhea, renal dysfunction, patients with cardiovascular or autoimmune disease, people with a history of smoking and alcohol consumption were all excluded from the study.

Data measurement

After obtaining the approval of the Institutional Ethical Committee (IEC) (reference no. AIIMS/BBN/IEC/July/2022/163), the present study was conducted in a tertiary care centre between July–September 2022. The study was fully explained to participants, whose written informed consent was obtained from all of them. Data regarding patients' past medical history, history of infection with SARS-CoV-2, smoking habits, weight and height was recorded according to standard protocols and body mass index (BMI) was calculated as weight divided by square of height (h^2). Individuals diagnosed with diabetes whose fasting blood sugar (FBS) was higher than 130 mg/dL or 7.0 mmol/L, who were taking insulin or hypoglycemic agents and had a HBA_{1C} >6 were included in group I; subjects with a systolic blood pressure (SBP) higher than 140 mm Hg and diastolic blood pressure (DBP) >90 mm Hg, taking an average of two or more readings at each of two or more visits *as per* Joint National Committee (JNC 8) guidelines or those on anti-

hypertensive drugs were included in group II; and individuals with BMI >30 (considered to have obesity as per WHO classification) were included in group III.

Arterial stiffness was assessed by using a certified oscillometric pulse wave device in all participants (12). The subjects were asked to lie down in supine position on the examination couch and maintain silence throughout the measurement after being seated for at least five minutes. The lower edges of the arm and ankle BP cuffs were placed 2-3 cm above the cubital fossa and 1-2 cm above the superior aspect of medial malleolus, respectively. The central hemodynamic parameters, including central SBP, DBP, pulse pressure (PP) and heart rate were measured. The left and right side brachial-ankle pulse wave velocity (LbaPWV, RbaPWV), carotid-femoral pulse wave velocity (CF PWV), right and left brachial arterial stiffness index (R bra ASI, L bra ASI) and right and left ankle arterial stiffness index (R Ank ASI, L Ank ASI) were recorded. The normal range of baPWV was established as <1400 cm/s and elevated AS was classified as baPWV >1400 cm/s (15, 16), while the reference values for normal CFPWV <760 cm/s and elevated AS were defined as >760 cm/s, with the normal reference value for AS index being 20-70 mm Hg.

The values of PWV collected from participants were compared between subgroups and subsequently among the three study groups, and then with the control group, to determine the extent to which COVID-19 infection contributed to stiffening and to identify the riskiest component out of diabetes, obesity and hypertension.

Statistical methods

Mean ± standard deviation (SD) was calculated for continuous distributed variables. For independent comparison of the continuous and categorical variables of BMI and AS between groups, independent sample t-test were used. Mann-Whitney U test, Kruskal-Wallis test were used to compare the differences in mean parameters across the groups. Data was analyzed with SPPS software 23. The differences between the groups were identified by analyzing the mean value, standard error and 95% confidence interval by determining the p value. All statistical tests were two-sided and statistical significance of P <0.05 was considered significant. ❑

RESULTS

A total of 186 participants aged 30-50 years were recruited for the study, but six of them were excluded from group I b because hypertension co-existed with diabetes. Therefore, the final sample included 180 participants.

In this study, we observed that the mean RbaPWV was higher in group Ia (diabetes subjects with COVID-19) (1261.64 ± 117.13 SD) (p value <0.05) than group Ib (1178.86 ± 101.43 SD) (diabetes subjects without COVID-19) (Table 1).

The mean CFPWV was found to be significantly higher in group IIa (1207.07 ± 237.11 SD) (subjects with hypertension and COVID-19) compared to group IIb (subjects with hypertension but without COVID-19) (980.995 ± 209.525 SD) (p <0.001) (Table 2). The mean right, left baPWV and CFPWV was significantly higher in group IIIa (subjects with obesity and COVID-19)

Group Ia (n= 32) (diabetic subjects with COVID-19)				Group I b (n= 28) (diabetic subjects without COVID-19)			
Parameter	**Mean (M)**	**Standard deviation (SD)**	**Standard error (SE)**	**Mean (M)**	**Standard deviation (SD)**	**Standard error (SE)**	**P value**
R baPWV (cm/s)	1261.64	117.13	28.49	1178.86	101.43	28.12	0.003
L baPWV (cm/s)	1271.00	195.30	34.52	1199.91	132.02	24.95	0.055
CF PWV (cm/s)	829.35	152.38	26.93	785.05	111.08	20.99	0.104
R Bra ASI (mm Hg)	27.866	8.60	1.52	27.36	8.74	1.65	0.411
L Bra ASI (mm Hg)	26.27	9.95	1.76	26.914	9.58	1.81	0.401
R Ank ASI (mm Hg)	40.90	10.29	1.82	38.93	10.23	1.93	0.231
L Ank ASI (mm Hg)	43.09	13.27	2.34	39.96	12.01	2.27	0.172

TABLE 1. Comparison of arterial stiffness parameters among diabetic subjects with diabetes and COVID-19 (group Ia) and without COVID-19 (group Ib) (P value <0.05 was significant)

Group IIa (n= 20) (hypertensive subjects with COVID-19)				Group IIb (n=20) (hypertensive subjects without COVID-19)			
Parameter	**Mean (M)**	**Standard deviation (SD)**	**Standard error (SE)**	**Mean (M)**	**Standard deviation (SD)**	**Standard error (SE)**	**P value**
R baPWV (cm/s)	1683.99	344.99	77.14	1451.80	197.02	44.05	0.006
L baPWV (cm/s)	1695.36	354.07	79.17	1550.63	361.57	80.84	0.104
CF PWV (cm/s)	1207.07	237.11	53.02	980.09	209.52	46.85	0.001
R Bra ASI (mm Hg)	33.88	9.03	2.02	30.46	10.00	2.23	0.132
L Bra ASI (mm Hg)	52.39	10.06	2.96	47.31	18.16	2.17	0.227
R Ank ASI (mm Hg)	50.27	17.6	2.25	46.975	13.73	4.06	0.141
L Ank ASI (mm Hg)	51.15	8.65	3.94	46.10	8.37	3.07	0.257

TABLE 2. Comparison of parameters of arterial stiffness among hypertensive subjects with COVID-19 (group IIa) and without COVID-19 (group IIb) (P value <0.05 was significant)

Group IIIa (n= 25) (obese subjectswith COVID-19)				Group III b (n=25) (obese subjects without COVID-19)			
Parameter	**Mean (M)**	**Standard deviation (SD)**	**Standard error (SE)**	**Mean (M)**	**Standard deviation (SD)**	**Standard error (SE)**	**P value**
R baPWV (cm/s)	1497.12	361.77	73.84	1275.66	160.63	32.12	0.004
L baPWV (cm/s)	1476.00	309.91	63.26	1274.10	140.92	28.18	0.002
CF PWV (cm/s)	1024.92	253.98	51.84	820.16	122.42	24.48	<0.001
RBra ASI (mm Hg)	31.12	8.93	1.82	28.5	7.87	1.57	0.140
LBra ASI (mm Hg)	29.48	11.62	2.37	27.03	9.39	1.87	0.210
R Ank ASI (mm Hg)	46.67	10.90	2.22	37.72	8.32	1.66	<0.001
L Ank ASI (mm Hg)	43.94	14.83	3.02	34.06	9.66	1.93	0.004

TABLE 3. Comparison of arterial stiffness parameters among obese subjects with COVID-19 (group IIa) and without COVID-19 (group IIb) (P value <0.05 was significant)

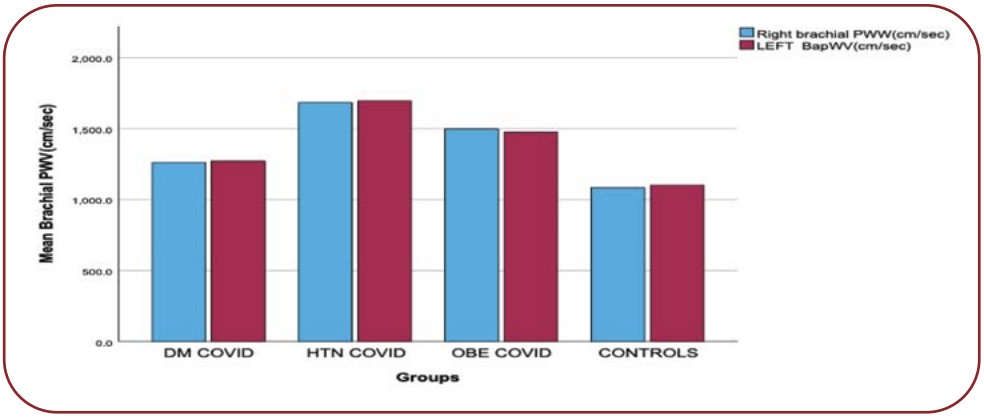

FIGURE 1. Comparison of means of right brachial PWV and left brachial PWV among different groups with COVID-19

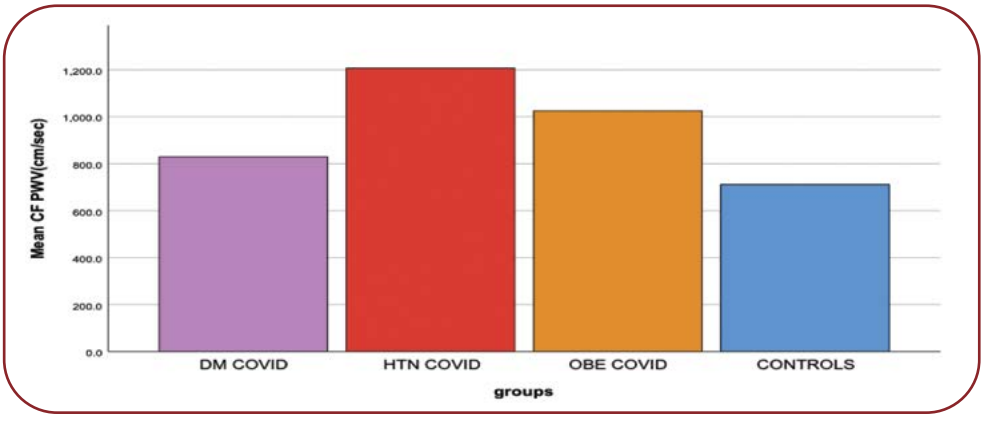

FIGURE 2. Comparison of mean carotid-femoral PWV among different groups with COVID-19

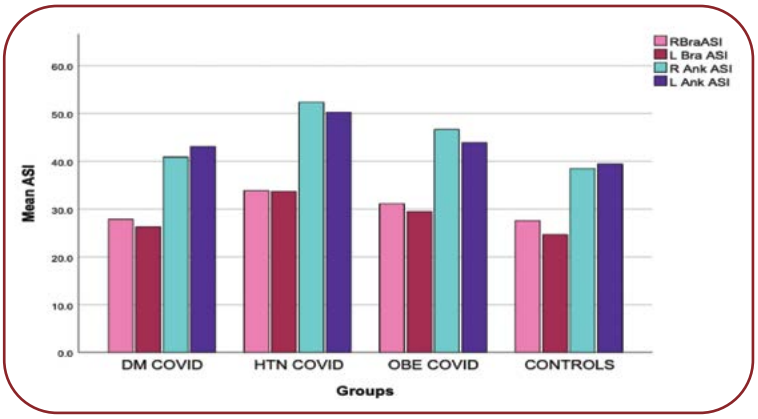

FIGURE 1. Comparison of mean RBraASI, LBraASI, R Ank ASI and L Ank ASI among different groups with COVID-19

(1497.125 ± 361.77 SD, 1476.008 ± 309.91 SD, 1024.92 ± 253.98 SD) ($p < 0.001$) compared to group III b (1275.664 ± 160.63 SD, 1274.140. ± 92 SD, 820.16 ± 122.42 SD) (subjects with obesity but without COVID-19).

The mean right ankle ASI (46.67 ± 10.90 SD) was also found to be significantly high in group IIIa compared to group IIIb (34.06 ± 9.66 SD) (Table 3).

Hence, our findings showed that COVID-19 was positively associated with increased AS, especially in subjects with comorbidities such as hypertension, obesity and diabetes.

In this study we also observed that, among the subjects with a history of COVID-19 wo had hypertension (group IIa subjects), the mean right and left baPWV (Figure 1), CF PWV (Figure 2) and right ankle ASI (Figure 3) was significantly higher ($p < 0.001$), followed by high values in subjects with obesity and COVID-19 (group IIIa) and those with diabetes and COVID-19 (group Ia) when compared to controls.

These values indicate that the impact of COVID-19 on increasing AS was stronger in subjects with hypertension than those with other comorbidities. ❑

DISCUSSION

To our knowledge, the present study was the first research that provided insight on the impact of COVID-19 with comorbidities on AS. The major findings in our study are described below.

Significantly high values of baPWV and CF PWV were important findings in COVID-19 subjects compared to those without COVID-19. Brachial PWV and CF PWV are indices of systemic and central AS. Evidence suggests that COVID-19 causes considerable and significant short-term changes in vascular physiology even in healthy young adults (15). An increase in PWV of 1 m/sec or 100 cm/sec is associated with a 15% higher risk of cardiovascular events and mortality (16). The baPWV is greatly influenced by age; hence, we limited the study population to people aged 30-50 years considering that age was a major confounding factor. As there have been only few studies investigating the effect of COVID-19 with comorbidities on AS, we could not find sufficient literature to corroborate our findings. However, a study by Schnaubelt *et al* (12) on COVID-19 patients, which correlated PWV with the length of hospital stay, revealed that baPWV and CF PWV were higher in non-survivors of COVID-19 patients compared to COVID-19 survivors, which supported our findings. Ratchford *et al* conducted another study which showed that young adults had significantly impaired vascular function and increased AS in adults with COVID-19 compared to young healthy adults without prior COVID-19 (17). The association between COVID-19 and AS could be attributed to the following reasons: 1) systemic hyperinflammation and cytokine release induced by SARS-CoV-2 are likely to impair the integrity of vascular endothelium reducing the bioavailability of nitric increasing AS (16); and 2) SARS-CoV-2 directly infects endothelial cells by binding to endothelial ACE-2 receptors, which subsequently promotes cell injury that results in endothelial dysfunction. Vascular tone modulation is hampered by endothelial cell injury (17).

Hence, the development of early atherosclerosis or increased arterial stiffness may therefore be linked to COVID-19.

Pre-existing hypertension, diabetes and obesity may weaken the resistance of target organs against corona virus and have influence on baPWV. In our results, we observed that the PVW and arterial stiffness index was significantly increased in COVID-19 subjects with hypertension when compared to COVID-19 subjects with obesity and diabetes. Thus, hypertension seems to have amplified the association of COVID-19 and AS. Increased ASI indicates a strong correlation between functioning arteries and atherosclerotic lesions. Hypertensive subjects are prone to increased risk for cardiovascular and renal complications. However, the effect of COVID-19 has long-term impact in these individuals due to increased sympathetic nerve activity, dysregulation of RAS and altered ACE-2 expression, which may cause detrimental structural and functional re-modelling of arteries resulting in increased AS (11, 13). Hypertension is the strongest modifiable risk factor for cardiovascular disease. Speculation continues whether AS is a cause or a sequence of hypertension and whether large arteries or small arteries are affected first. Increased AS can be due to increase in distension pressure, and moreover, sustained increase in blood pressure promotes matrix synthesis causing subsequent increase in vascular thickness and structural stiffening (13, 17).

Many previous studies have demonstrated that obesity was a risk factor for AS. In our study, we have also observed that there was a significant association between individuals with BMI > 30, COVID-19 and AS. Hyperinsulinemia and insulin resistance in obesity is linked to reduction in endothelial NO signaling pathway reducing the vasculo-protective effects of NO leading to endothelial malfunction and acute hyperinflammatory state in COVID-19 may be responsible for development of increased vascular stiffness (18, 19).

We also observed that the baPWV and CF PWV was significantly higher in COVID-19 subjects with diabetes when compared to controls. These results are in consensus with some studies which showed a positive association between AS and diabetes (20-22). A study done by Zheng *et al* showed that AS appeared to precede the increase in fasting blood sugars (FBS) (23).

The availability of cut-off or discriminative values of baPWV and CFPWV is important for better assessment of AS as a marker and early detection and prevention of cardiovascular events. Some studies have reported cut-off values for the general population but did not include individuals with diabetes, hypertension and obesity. To our knowledge, this study is the first of its kind to compare AS among post-COVID-19 diabetic, hypertensive and obese groups.

Limitations of the study

As this study is a cross sectional study, the primary limitation is that the true cause and effect relationship cannot be established. Long-term follow-up studies would help to clarify the factors affecting AS in COVID-19 subjects with comorbidities and their prognostic implications. ❑

CONCLUSIONS

COVID-19 definitely has long-term consequences on vascular ageing and physiology even in young adults, especially in individuals with comorbidities. COVID-19 is significantly associated with elevated arterial stifness due to direct adverse functional and morphological changes in the endothelium of arterial wall. Hypertension appears to be the riskiest factor for increasing arterial stiffness in COVID-19 subjects. Confirmation of our findings in larger population through prospective studies is required in order to optimize risk stratification in individuals with COVID-19 and comorbidities. ❑

Conflicts of interest: none declared.

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