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Evaluation of Arterial Stiffness in Depression Patients

ABSTRACT

Background: It has been known that there is a significant correlation between depression and cardiovascular diseases. However, the reasons behind this correlation that could affect mortality and morbidity were not fully identified. The present study aimed to analyze arterial stiffness diagnosed with ultrasonography, which could be associated with cardiovascular disease risks in depression patients, and to compare the findings with those of healthy controls.

Methods: The study was conducted with 35 depression patients and 35 healthy individuals. Routine complete blood and biochemistry tests were requested for all patients, and their weight and height, waist circumference, and diastolic and systolic arterial blood pressure were measured. Femoral and carotid artery intima-media thickness and other arterial stiffness parameters were determined with Doppler ultrasonography.

Results: It was determined that the systolic pressure ($P = .028$) was higher in the patient group ($P = .028$). Also, the carotid elastic modulus ($P = .048$) was significantly higher in the patient group. A negative and significant correlation was determined between femoral compliance and chlorpromazine equivalent dose ($P = .021$, $r = -0.389$).

Conclusion: It was determined that the systolic blood pressure and carotid elastic modulus arterial stiffness parameters were significantly higher in depression patients. Measurable arterial stiffness parameters should be investigated in depression patients as cardiovascular risk markers. Furthermore, the determination of the effects of psychotropic drugs employed in arterial stiffness treatment could play an important role in the determination of cardiovascular disease risk in these patients.

Keywords: Depression, arterial stiffness, cardiovascular risk, elastic modulus, intima-media thickness

Introduction

Depression is a psychiatric disorder characterized by depressive mood, anhedonia, loss of function, focus problems, lack of energy, appetite loss, sleep disorder, and suicidal ideation.[1] The annual prevalence of depressive disorder, which adversely affects the mental and physical health of adults, is about 8.9 million in the USA.[2,3] Chronic stress elevates the production of proinflammatory cytokines and affects the hypothalamic and adrenal glands, pituitary and sympathetic nervous system in depression. This could lead to endothelial dysfunction, vasoconstriction, platelet activation, hypertension, arrhythmia, and myocardial infarction.[4-10]

In a cohort study on individuals without ischemic heart disease risk based on anamnesis, depression and despair were associated with high ischemic heart disease risk.[11] Chronic inflammation is a known diabetes and cardiovascular disease risk factor in depression.[12] Furthermore, it is known that metabolic syndrome could be common in depression patients, which could lead to cardiovascular diseases.[13] On the other hand, antidepressant treatment could also induce metabolic abnormalities.[14] Previous studies reported that psychotropic drugs could cause glucose intolerance and hyperlipidemia. Also, it was reported that these medicines could induce the development of hypertension via vasoconstriction in vessels due to their anticholinergic effects.[15-16]

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Arterial stiffness is a significant predictor of hypertension, diabetes mellitus, and cardiovascular morbidity and mortality, particularly in elderly individuals.[17] Elevated blood glucose, insulin resistance, obesity, and hypertension induce degenerative pathological changes in the arterial wall due to inflammation and oxidative stress, elevating artery stiffness.[18-21] Intima-media thickening (IMT) caused by endothelial dysfunction is one of the first manifestations of atherosclerosis. The arterial stiffness entails a reduction in vessel resilience and is used to assess stiffness based on distensibility and compliance. Compliance is the adaptation potential of the vessel to pressure changes. Distensibility is the volumetric change during compliance. The measure of the arterial strain under pressure is the elastic modulus. Elevated arterial stiffness leads to the deterioration of the buffering property of carotid and femoral arteries and a decrease in cardiac performance.[22-23] Muela et al[24] reported that arterial stiffness was associated with poor cognitive functions. A prospective study conducted with 37 depression patients with psychotic symptoms reported that depression induced endothelial dysfunction, independent of hypertension in this patient group, and antidepressant and antipsychotic drugs reduced arterial stiffness.[25]

Intima-media thickness, a clinical indicator in early diagnosis of arterial stiffness, could be measured with high-resolution ultrasonography.[26] Ultrasonographic examination of arteries is an easy, non-invasive, and cost-effective method.[27] Depression disorder could lead to metabolic burden. The literature review revealed only a few studies where arterial stiffness was investigated with ultrasonography in depression. The present study aimed to evaluate arterial stiffness in depression disorder.

Material and Methods

Participants

The current study was approved by the Fırat University Research Ethics Board (decision no: 2021/11-38) and conducted in accordance with the Helsinki Declaration (1983). The study was conducted with 43 patients at Mental Health and Diseases Clinic with a diagnosis of depression disorder based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) and met the study criteria, and 35 healthy controls without any mental disorder based on DSM-5 examination. Eight patients subsequently dropped out of the study due to personal reasons. Inclusion criteria included depressive disorder diagnosis, age between 18 and 50, lack of any physical pathology or neurological or metabolic disease, and no drug use other than current psychiatric medication. The control group included 18- to 50-year-old individuals without a history of psychiatric, metabolic, and neurological diseases and drug use.

MAIN POINTS

- *It was determined that systolic blood pressure and carotid elastic modulus arterial stiffness parameters were significantly higher in depression patients.*
- *Although the carotid intima-media thickness was higher in depression patients, the difference was not statistically significant.*
- *The increase in chlorpromazine equivalent dose significantly decreased the femoral compliance in the patient group.*

Participants with a known history of alcohol and substance abuse, metabolic syndrome, hypertension, hyperlipidemia, diabetes, cardiovascular, nephrological, and peripheral artery disease comorbidities, and related drug use were excluded. Since arterial stiffness could increase with age,[28] participants over 50 were also excluded.

Procedure

The present study was conducted at Mental Health and Diseases Clinic between January 2022 and November 2022. After all participants signed the consent form, they completed the sociodemographic questionnaire; routine complete blood and biochemistry tests were performed; and their weight, height, waist circumference, and systolic and diastolic arterial blood pressures were measured. Then, the arterial thickness was measured by a radiologist with Doppler ultrasonography (USG) (XarioTM, Toshiba Medical Systems Corporation, Tochigi, Japan) at Urban Hospital, Radiology Outpatient Clinic.

Hemogram and general biochemistry tests were requested for all participants, and those with pathological findings (fasting blood glucose higher than 100, triglyceride higher than 150 mg/dL, high-density lipoprotein lower than 40 mg/dL in men and 50 mg/dL in women, low-density lipoprotein higher than 130 mg/dL, total cholesterol higher than 220 mg/dL, and creatinine higher than 1.30 mg/dL in women and 1.40 mg/dL in men) were excluded. Diastolic and systolic blood pressures were measured with a manual sphygmomanometer, and diastolic blood pressure higher than 90 mm/Hg and systolic blood pressure higher than 140 mm/Hg were excluded. Furthermore, the waist circumference of the participants was measured manually with a tape measure, and males whose waist circumference was greater than 102 cm and females whose waist circumference was greater than 88 cm, those with a Body Mass Index (BMI) greater than 30 kg/m^2 were also excluded.

Patient antidepressant doses were converted to the fluoxetine equivalent dose with the dose equivalency method to standardize the findings.[29] Also, antipsychotic drug doses were converted to the chlorpromazine equivalent dose with the same method.[30]

Ultrasonography

All procedures were performed with a high-resolution Doppler USG device (Philips Affiniti 50 G, L 12-5 MHz linear probe). Examinations were conducted on the right femoral artery as the patient was in the supine position and on the right carotid artery as the patient's neck was hyperextended. The femoral and carotid artery IMT was measured at 1 cm distal of the carotid communis artery bifurcation (Figure 1). The systolic and diastolic artery diameters were measured in both USG B and M modes (Figure 2).

Arterial thickness was calculated with determined formulas.[22]

- Cross-sectional distensibility = $(SD^2 - DD^2)/(DD^2 \cdot \triangle P)$
- Cross-sectional compliance = $(\pi (SD^2 - DD^2))/(4 \cdot \triangle P)$
- Diastolic wall stress = $(DD/(2 \cdot IMT)) \cdot ((SP + SD)/2)$
- Elastic modulus = (3/(1 + (cross-sectional area of the lumen/cross-sectional area of the wall))/cross-sectional distensibility

where SP is the systolic blood pressure, $\triangle P$ is the pressure difference, DD is the diastolic diameter, and SD is the systolic diameter.

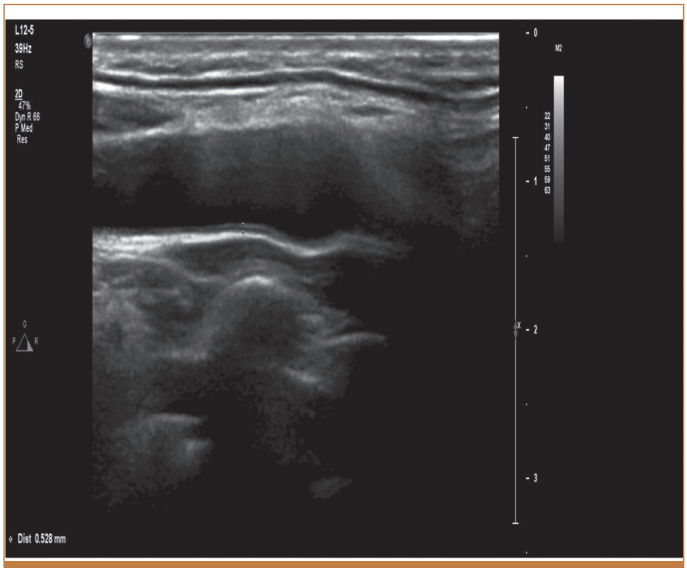

Figure 1. Intima-media thickness measurement of a depression patient.

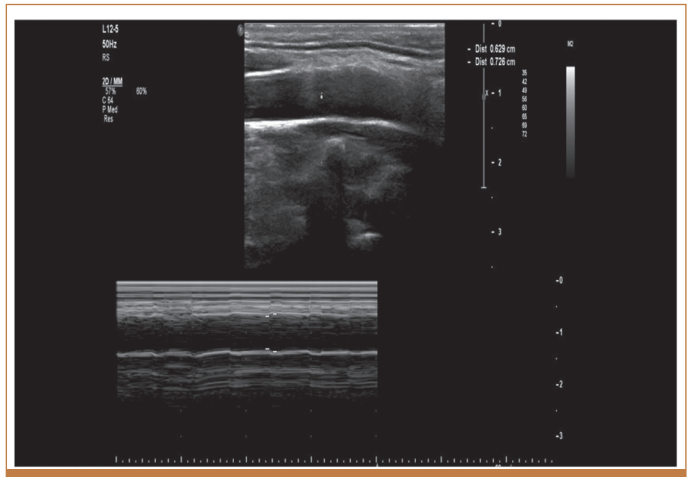

Figure 2. Systolic–diastolic diameter measurements.

Statistical Analysis

Statistical analyses were conducted on Statistical Package for Social Sciences version 22.0 (IBM SPSS Corp.; Armonk, NY, USA) software. The categorical descriptive statistic variables are reported as n (%). The normally distributed data are presented as means and SDs, and the non-normally distributed data are presented as median (minimum–maximum). The chi-square test (Pearson chi-square) was employed in the intra-group comparison of the categorical variables, while the Fisher' exact test was conducted when more than 20% of the data were less than 5. The normal distribution of continuous variables was determined by the Kolmogorov–Smirnov test. The Student's *t*-test was used for those with normal distribution, and the Mann–Whitney *U*-test was used for those who did not show normal distribution in the measurement comparisons of 2 independent groups. The Pearson correlation coefficient was employed for the normally distributed data, while the Spearman correlation coefficient test was used for the non-normally distributed data. The statistical significance was accepted as $P < .05$.

Results

The current study was conducted with 70 participants, 35 patients and 35 controls. The mean patient group age was 35.3 ± 10.7 and the mean control group age was 34.8 ± 8.7, and no significant difference was found between the mean group ages ($P = .835$). Of the patient group, 71.43% were female and 28.57% were male, while 54.29% of the control group were females and 45.71% were males, and there was no significant difference in gender distribution ($P = .138$). There was no significant difference between the patient and control groups according to BMI and other study variables ($P > .05$). Of those in the patient group, 12 (34.3%) used chlorpromazine and 29 (82.9%) used fluoxetine. The mean equivalent dose of chlorpromazine users was 61.2 ± 31.4, and the mean equivalent dose of fluoxetine users was 35.9 ± 13.9 (Table 1).

It was determined that the systolic pressure ($P = .028$) and carotid elastic modulus ($P = .048$) of the patient group were significantly higher when compared to the control group (Table 2, Figure 3).

A negative and significant correlation was determined between chlorpromazine equivalent dose, BMI, and femoral compliance data (Table 3, Figure 4).

Discussion

The systolic blood pressure and carotid elastic modulus arterial stiffness parameters were significantly higher in depression patients in the present study. Although the carotid IMT was higher in the patient group when compared to healthy controls, the difference was not statistically significant.

Gromova et al[31] investigated the impact of depression on cardiovascular disease risk for 10 years in a 25- to 64-year-old male population and reported that depression was a cardiovascular disease risk factor among middle-aged men. Finnish individuals, who exhibited the depression symptom of despair at the beginning of the study, were later diagnosed with hypertension.[32] Several longitudinal studies reported a correlation between depression and hypertension.[33] However, certain studies argued that depression and hypertension were not comorbid.[34] A cohort study conducted with 2981 people demonstrated that depression reduced blood pressure, and antidepressants increased the risk of hypertension.[35] In our study, we determined that depression patients under psychiatric treatment exhibited higher systolic blood pressure. It could be suggested that further studies are required to determine whether there is a correlation between this finding and the use of medicine or the duration of the disease.

It is known that asymptomatic cardiovascular changes do not equally affect all vascular beds. This could be due to the differences between the elastic and muscular structures of the arterial wall and the location of the arteries.[36] Onete et al[37] measured the carotid and femoral pulse wave velocity with applanation tonometry and reported that arterial stiffness was associated with depression, especially in young and middle-age individuals. In another study, it was found that there was a correlation between high arterial stiffness and depression, and the authors argued that metabolic syndrome and inflammatory processes could lead to arterial stiffness.[38] Significantly higher arterial stiffness prevalence was reported in depression patients.[39] In a prospective study conducted with 7013 individuals, carotid stiffness was

Table 1. Patient and Control Group Demographics

		Patient		Control		
		n	%	n	%	*P**
Age, mean ± SD		35.3 ± 10.7		34.8 ± 8.7		.835**
Gender	Female	25	71.43	19	54.29	.138
	Male	10	28.57	16	45.71	
Marital status	Unmarried	18	51.43	16	45.71	.632
	Married	17	48.57	19	54.29	
Education	Primary	19	54.29	10	28.57	.076
	Secondary	10	28.57	18	51.43	
	Tertiary	6	17.14	7	20.00	
Residence	Township	10	28.57	15	42.86	.212
	Urban	25	71.43	20	57.14	
Income	Low	12	34.29	11	31.43	.935
	Medium	18	51.43	18	51.43	
	High	5	14.29	6	17.14	
Employment	Yes	15	42.86	19	54.29	.339
	No	20	57.14	16	45.71	
Smoking	Yes	16	45.71	17	48.57	.811
	No	19	54.29	18	51.43	
Alcohol/substance use	Yes	2	5.71	2	5.71	1.000***
	No	33	94.29	33	94.29	
Psychological disorder in family	Yes	10	28.57	5	14.29	.145
	No	25	71.43	30	85.71	
Self-mutilation	Yes	3	8.57	3	8.57	1.000***
	No	32	91.43	32	91.43	
Suicide	Yes	2	5.71	1	2.86	1.000***
	No	33	94.29	34	97.14	
Medication	Antipsychotic	7	20.00	-		-
	Antidepressant	15	42.86			
	Multiple	13	37.14			
Chlorpromazine equivalent dose, mean ± SD		61.2 ± 31.4		-		-
Fluoxetine equivalent dose, mean ± SD		35.9 ± 13.9		-		-

*Chi-square test.
**Student's *t*-test.
***Fisher's exact test.

Table 2. Comparison of Patient and Control Group BMI, Blood Pressure, and Arterial Pressure Data

	Patient	Control	
	Median (Minimum–Maximum)	Median (Minimum–Maximum)	*P**
BMI, Mean ± SD	24.1 ± 2.3	24.3 ± 2.7	.790**
Systolic pressure	120.0 (100.0-130.0)	118.0 (87.0-130.0)	.028
Diastolic pressure	75.0 (60.0-80.0)	72.0 (59.0-80.0)	.812
Carotid IMT	0.51 (0.29-1.21)	0.49 (0.34-0.68)	.556
Carotid compliance	0.13 (0.03-0.38)	0.14 (0.01-0.47)	.295
Carotid distensibility	0.004 (0.001-0.010)	0.006 (0.001-0.020)	.095
Carotid diastolic wall stress	402.8 (227.0-707.7)	382.7 (224.1-538.0)	.651
Carotid elastic modulus	175.7 (76.1-611.7)	124.9 (37.2-631.0)	.048
Femoral IMT	0.43 (0.19-0.64)	0.43 (0.34-0.73)	.343
Femoral compliance	0.12 (0.01-0.30)	0.15 (0.04-0.43)	.125
Femoral distensibility	0.004 (0.0010-0.010)	0.004 (0.001-0.010)	.877
Femoral diastolic wall stress	500.3 (269.2-1249.9)	463.5 (245.9-784.6)	.272
Femoral elastic modulus	158.5 (45.4-861.8)	163.3 (51.3-522.9)	.986

*Mann–Whitney *U*-test.
**Student's *t*-test.
BMI, body mass index; IMT, intima-media thickness.

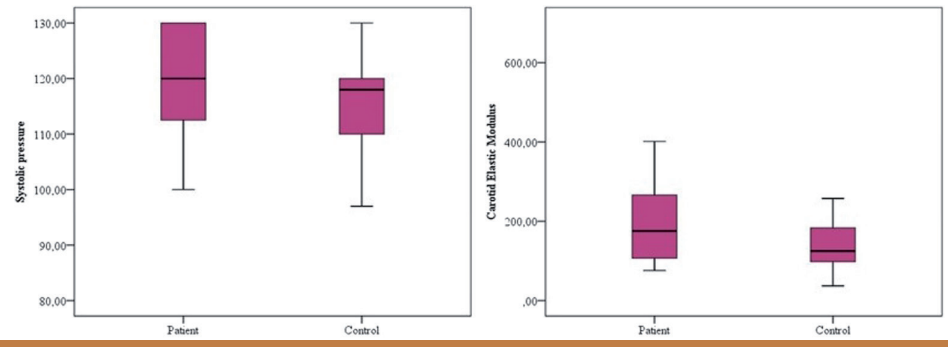

Figure 3. Comparison of the patient and control group systolic pressure and carotid elastic modulus data.

Table 3. Correlations Between Chlorpromazine and Fluoxetine Equivalent Doses, Time of Diagnosis, and Other Variables

	Chlorpromazine Equivalent Dose		Fluoxetine Equivalent Dose	
	*r**	*P*	*r**	*P*
Age	0.163	.614	−0.126	.514
Time of psychiatric diagnosis	0.123	.704	−0.102	.599
Duration of psychotropic drug treatment	0.166	.607	−0.090	.642
BMI**	−0.695	.012	−0.259	.175
Systolic pressure	0.134	.678	−0.271	.155
Diastolic pressure	0.320	.310	0.178	.356
Carotid IMT	0.359	.252	−0.231	.229
Carotid compliance	0.057	.861	−0.037	.847
Carotid distensibility	−0.306	.334	−0.031	.872
Carotid diastolic wall stress	−0.303	.339	0.095	.625
Carotid elastic modulus	0.381	.222	−0.013	.948
Femoral IMT	0.297	.348	−0.215	.263
Femoral compliance	−0.589	.044	0.223	.246
Femoral distensibility	0.043	.893	0.224	.243
Femoral diastolic wall stress	−0.148	.646	−0.015	.940
Femoral elastic modulus	0.507	.092	−0.304	.108

*Spearman correlation coefficient.
**Pearson correlation coefficient.
BMI, body mass index; IMT, intima-media thickness.

examined with high-resolution echo and high arterial stiffness was associated with higher depressive symptom incidence.[40] Consistent with the abovementioned findings, we determined that the carotid elastic modulus, an arterial stiffness parameter, was elevated in depression patients. However, contrary to the present study findings, another study measured the carotid IMT with B-mode USG and determined central arterial stiffness with radial applanation tonometry (2000 version 7, AtCor Medical, Sydney, Australia) and reported that carotid plaques and central artery stiffness were not associated with depression.[41] It was reported that arterial stiffness increased during the acute period in depression patients; however, arterial stiffness was reversible with timely and effective antidepressant treatment.[42] Antidepressant and antipsychotic drugs affect blood pressure.[43] The reason behind the higher arterial stiffness in the patient group in the current study could be the fact that the patient group was not only under antidepressant treatment but also used other psychiatric drugs such as antipsychotics.

High inflammation leads to degenerative pathological changes in the endothelial layer of the vessels and increases arterial stiffness and could elevate cardiovascular risks.[44] In our study, femoral IMT, an arterial stiffness parameter, was lower and carotid IMT was higher in the patients with depression. This suggested that although the inflammation-induced risk of atherosclerosis was expected to be higher in the patient group, the cardiovascular disease risk could be reduced with psychotropic treatment in depression patients. In the present study, a negative and significant correlation was determined between femoral compliance and chlorpromazine equivalent dose and between fluoxetine equivalent dose and arterial stiffness parameters. Baune

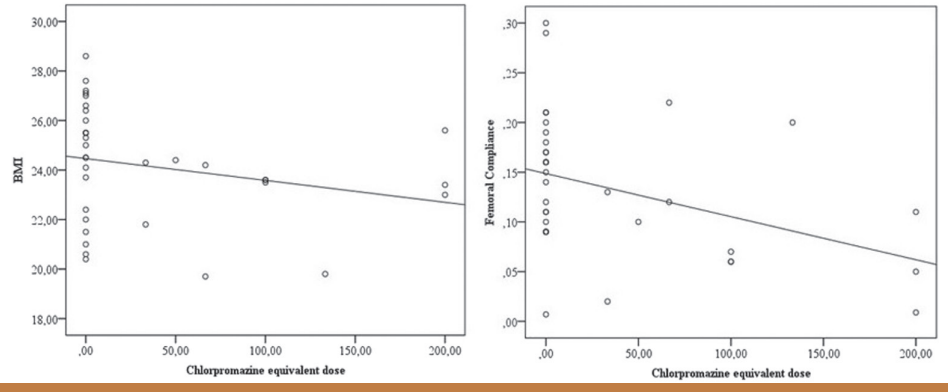

Figure 4. Correlation between chlorpromazine equivalent dose, body mass index, and femoral compliance.

and Eyre[45] reported that antipsychotic drugs reduced inflammation in depression. Although quetiapine and norquetiapine do not affect depression symptoms, it was demonstrated that they increased anti-inflammatory cytokine IL-10 levels and decreased pro-inflammatory cytokine IFN-y levels.[46] Although it was reported that antidepressant treatment facilitated the development of atherosclerotic plaques in the carotid,[47] other studies argued the opposite.[48] To clarify the effect of drugs on arterial stiffness, further studies are needed that would compare the use of isolated antidepressants and isolated antipsychotics and no drug use in depression patients.

The employment of ultrasonography, an inexpensive and noninvasive method, in arterial stiffness diagnosis in depression patients was the strength of the current study. Furthermore, factors that could predispose individuals to atherosclerosis, that is, cardiovascular disease, hypercholesterolemia, hypertension, diabetes mellitus, and metabolic syndrome, were excluded. The limitations of the present study were the small sample size, drug treatment in all depression patients, smoking and alcohol consumption in certain participants, and the cross-sectional study methodology.

In conclusion, it was determined that systolic blood pressure and carotid elastic modulus arterial stiffness parameters were significantly higher in depression patients. Although the carotid IMT was higher in patients with depression, the difference was not statistically significant.

The increase in chlorpromazine equivalent dose significantly decreased the femoral compliance in the patient group. This study provided an insight for future studies that would clarify whether this finding was caused by the antipsychotic treatment or the disease itself. Arterial stiffness should be further examined to determine cardiovascular risk in depression. To understand the etiopathogenesis of arteriosclerosis in this patient group, further studies that would include repeated long-term arterial stiffness measurements with larger samples are required.

Ethics Committee Approval: *The study was approved by Fırat University non-interventional research ethics committee on November 4, 2021 (Approval No: 2021/11-38). Then, the arterial thickness was measured by a radiologist with Doppler ultrasonography (USG) in Elazig Fethi Sekin City Hospital, Radiology Outpatient Clinic.*

Informed Consent: *Informed consent form was signed by all participants in the present study.*

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Concept – B.S.E., S.Y., A.K.K., G.K., S.K.; Design – B.S.E., S.Y., A.K.K.; G.K., M.A., Supervision – S.K., M.A.; Resources – B.S.E., G.K.; Materials – B.S.E., G.K.; Data Collection and/or Processing – B.S.E., O.K.; Analysis and/or Interpretation – B.S.,E., O.K.; Literature Search – B.S.E., G.K., O.K.; Writing – B.S.E., S.Y., A.K.K.; Critical Review – S.K., M.A.*

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