Original Article

Association of depression with common carotid artery intima media thickness and augmentation index in a large Urban South Indian population- The Chennai Urban Rural Epidemiology Study (CURES - 138)

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ABSTRACT

AIM: The aim of the study was to assess the relationship of depression with carotid intima media thickness and augmentation index in Asian Indians. **Research Design and Methods**: For this study, 1505 subjects were randomly selected from a population based study conducted in Chennai, South India. Right common carotid artery intima medial thickness [IMT] was determined using high-resolution B-mode ultrasonography. Augmentation index [AI] was measured using the Sphygmocor apparatus. Depressive symptoms were assessed using a previously validated instrument, the Patient Health Questionnaire -12 (PHQ -12). **Results**: Of the 1505 subjects included in this study, depressive symptoms were present in 16.6% (n = 250) of the subjects. The mean IMT and AI values among subjects with depression were significantly higher than those without depression [0.83 ± 0.43 mm vs 0.73 ± 0.12 mm, $P < 0.001$] and IMT was higher in females with depression while AI was higher in males with depression. However, both IMT and AI were higher among those with depression in both genders. In multiple logistic regression model, depressive symptoms were associated with IMT even after adjusting for age, gender, body mass index, fasting plasma glucose, serum cholesterol and hypertension (Odds ratio [OR] =2.17, 95% Confidence intervals [CI]:1.01- 4.63, $P = 0.047$) but in the case of AI, the significance was lost in the adjusted model (OR = 1.01, 95% CI: 0.991-1.02, $P = 0.445$). **Conclusion:** Among Asian Indians, presence of depressive symptoms was associated with carotid intima media thickness and Augmentation index, even after adjusting for potential confounders.

Key words: Asian Indians, atherosclerosis, augmentation index, depression, diabetes, intima media thickness, South Asians

Introduction

The association between depression and cardiovascular disease has been well demonstrated.[1,2] Earlier studies have shown that negative emotions precede heart attacks and that depression is a risk factor for the development of coronary heart disease.[3,4] A 21 year follow-up study by Barefoot *et al.*[5] reported that depressive symptoms were predictive of myocardial infarction.

The thickness of the common carotid artery intima-media (IMT) measured by ultrasound is a marker of preclinical atherosclerosis. Increased IMT correlates with cardiovascular risk factors[6,7] severity of coronary atherosclerosis[8] and predicts cardiovascular events.[9] IMT has been validated in several studies to be a robust marker

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for atherosclerosis. The study conducted by Baldassarre *et al*. showed that carotid IMT can provide a reliable index of carotid atherosclerosis.[10] Earlier studies conducted in the western population have reported 'hopelessness' to be related to increased carotid IMT among middle-aged men,[11] and negative feelings were shown to be associated with increased carotid IMT among hypertensive men.[12] Jones and coworkers[13] showed that among middle-aged women, a lifetime history of major depression was associated with carotid plaques. A relationship between arterial calcification and depression has also been reported among elderly people.[14]

It has also been shown that the arterial stiffness is a determinant of blood pressure. Conversely, hypertension has been shown to be associated with depression.[15] One measure of arterial stiffness is augmentation index which has been used in several studies.[16-18]

Few studies have looked at the association of depression with atherosclerosis in a general population and most studies have been done in European subjects. South Asians in general and Asian Indians in particular have an increased susceptibility to premature coronary artery disease (CAD).[19,20] There is no data on the association between depression and subclinical atherosclerosis in this ethnic group. The present study examines the association between depressive symptoms and two measures of subclinical atherosclerosis, i.e., IMT and arterial stiffness in an urban south Indian population. For the purpose of this paper, the terms depression and depressive symptoms are used interchangeably, although the PHQ measures depressive symptoms and does not provide a definite diagnosis of depression.

Materials and Methods

The Chennai Urban Rural Epidemiology Study [CURES] was done on a representative sample of 26,001 individuals aged ≥ 20 years in Chennai, South India. The methodology of the study has been published elsewhere.[19] Briefly, in Phase 1 of the urban component of CURES, 26,001 individuals were recruited based on a systematic random-sampling technique; details of the sampling are described on our website (http://www.drmohansdiabetes.com/under the link 'Publications'). In Phase 2 of CURES, all the known diabetic subjects in Phase 1 were invited to the center for detailed studies on vascular complications. In Phase 3, every tenth subject in Phase 1(n = 2600) was invited for special studies including detailed anthropometric measurements and biochemical tests. For this study, we randomly selected (using computer-generated numbers by startrek.com) 1505 subjects from a Phase 3 of CURES. Ethical Committee approval was obtained from the Institutional Ethics Committee of Madras Diabetes Research Foundation. Informed Consent was obtained from all the study subjects.

In all participants, a questionnaire was administered to assess the demographic and socioeconomic characteristics including age, sex, years of education, family and individual income, health behavior, health status including a detailed medical history and personal habits like smoking and alcohol. The PHQ-9 is a well accepted tool to assess depressive symptoms in population based studies.[21] PHQ –9 measures the depressive symptoms during the past 2 weeks. We earlier modified the PHQ -9 by splitting two questions to make it culturally appropriate and validated it against the PHQ-9.[21] The correlation between PHQ-12 and PHQ-9 was 0.913 and a score of >4 and has a predictive value of 76.7%.[21] The PHQ-12 has been used by us in several of our earlier studies.[22-24]

All the investigations were carried out on the same day and the average gap between the PHQ administration and lab tests, IMT and AI measurements was one to two hours.

Anthropometric measurements including weight, height and waist measurements were obtained using standardized techniques according to the Anthropometric Standardization Reference Manual.[19] The body mass index (BMI) was calculated using the formula, weight (kg)/height in m^2.

Blood pressure was recorded in the sitting position in the right arm using the mercury sphygmomanometer (Diamond Deluxe Blood Pressure apparatus, Pune, India). Blood pressure readings were recorded to the nearest 2 mm Hg. Two measurements were taken 5 minutes apart and the mean of the two was recorded as the blood pressure reading.

A fasting blood sample was taken, after ensuring 8 hours of overnight fasting, for estimation of plasma glucose and serum lipids using a Hitachi 912 Autoanalyser (Roche Diagnostics GmbH, Mannheim, Germany) utilizing kits supplied by Boehringer Mannheim (Mannheim, Germany). Fasting and 2 hour plasma glucose estimations were done by the glucose oxidase method. Diagnosis of diabetes and IGT was based on WHO Consulting Group criteria, i.e. 2-h venous plasma glucose ≥11.1 mmol/l, and ≥7.8 and <11.1 mmol/l, respectively.[25]

Glycated hemoglobin (HbA1c) was estimated by the high pressure liquid chromatography using the variant machine (BIORAD, Hercules, California). Serum cholesterol (CHOD-PAP method) and serum triglycerides (GPO-PAP method) were measured.

High-density lipoprotein (HDL) cholesterol was estimated by CHOD-PAP method after precipitating low-density lipoprotein and chylomicron fractions by the addition of phosphotungstic acid in the presence of magnesium ions and very low-density lipoprotein. Low density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula.[26]

Measurement of IMT

The method used for the measurement of carotid IMT has been described in earlier publications[17,27] but will be briefly outlined here. IMT of the right common carotid artery (CCA) was determined using a high-resolution B-mode ultrasonography system (Logic 400; GE, Milwaukee, WI) having an electric linear transducer mid frequency of 7.5 MHz**.** The images obtained were recorded and photographed. The scanning was done for an average of 20 min. The IMT was measured as the distance from the leading edge of the first echogenic line to the second echogenic line during the diastolic phase of the cardiac cycle.[18] Six well-defined arterial wall segments were measured in the right carotid system: The near wall and far wall of the proximal 10 mm of the internal carotid artery, the carotid bifurcation beginning at the tip of the flow divider and extending 10 mm below this point, and the arterial segment extending 10 mm below the bifurcation beginning at the tip of the flow divider and extending 10 mm below this point and the arterial segment extending 10 mm below the bifurcation in the right common carotid artery.[28] The mean of the six measures were taken as the carotid IMT reading. Images were captured using a special grabber card, and the measurements were performed offline, manually. All scanning were conducted by a trained ultrasonologist who was unaware of the clinical status of the study subjects. The reproducibility of the IMT measurement was examined by conducting another scan 1 week later on 20 subjects by the same sonographer. The mean difference in IMT between the first and second measurements was 0.02 mm, the SD was 0.06 mm, and the mean difference ranged between -0.09 mm to +0.09 mm.

Arterial stiffness measurement

Arterial stiffness was measured using the Sphygmocor apparatus (Sphygmocor BPAS-1; PWV Medical, Sydney, Australia). In brief, a high-fidelity micromanometer (SPC-301; Millar Instruments, Houston, TX, USA) was used to flatten but not occlude the right radial artery, using gentle pressure. When the two surfaces are flattened, circumferential pressures are equalized and an accurate pressure waveform can be recorded. Data were collected directly into a portable microcomputer. The system software allowed online recording of the peripheral waveform, which was assessed visually to ensure that the best possible recording was obtained and that artefacts from movement were minimized. After 20 sequential waveforms had been acquired, the integral software was used to generate an averaged peripheral and corresponding central waveform that was used for the determination of the Augmentation index (AI). AI was defined as the difference between the first and second peaks of the central arterial waveform, expressed as a percentage of the pulse pressure. AI is a measure of the contribution that the wave reflection makes to the arterial pressure waveform. The amplitude and timing of the reflected wave ultimately depend on the stiffness of the small vessels and large arteries, and thus, AI provides a measure of systemic arterial stiffness. To check for the reproducibility of AI, two measurements were performed on 20 subjects on consecutive days by the same observer. The mean difference in AI between the first and second measurements was 1.58, and the SD was 2.54.

Statistical analysis

Numbers are expressed as mean ± SD. Student's "*t*" test was used to compare groups for continuous variables and chi square test to compare proportions among groups. To determine the confounding effect of various risk factors on the association of IMT and AI with depression, regression analysis was done using depression as the dependent variable and IMT and AI as the independent variables. A univariate analysis was first done and adjusted models were constructed using multivariate regression analysis to determine the association of IMT with depression by adjusting for other variables like age, gender, BMI, fasting plasma glucose, cholesterol and hypertension that had a significant association on univariate analysis. A $P < 0.05$ was considered as statistically significant.

Results

The mean age of the study population [n = 1505] was 41.0 ± 13 years and 55% (n = 836) of the subjects were males. Of the 1505 subjects studied, depression was present in 16.6% ($n = 250$) subjects. Table 1 provides the clinical and biochemical characteristics of the subjects with and without depression. Subjects with depression were older [45.6 ± 14.4 vs. 39.9 ± 12.6 years, $P < 0.001$] compared to those without.

Figure 1 illustrates the mean IMT and AI among subjects with and without depression respectively. IMT (0.77 ± 0.31 mm vs 0.71 ± 0.14 mm, $P < 0.001$) and AI (24.8 ± 11.4 vs 21.9 ± 10.4, $P < 0.001$) were higher in subjects with depression compared to those without. When the subjects with depression were segregated on the basis of gender, IMT was higher in females with depression compared to

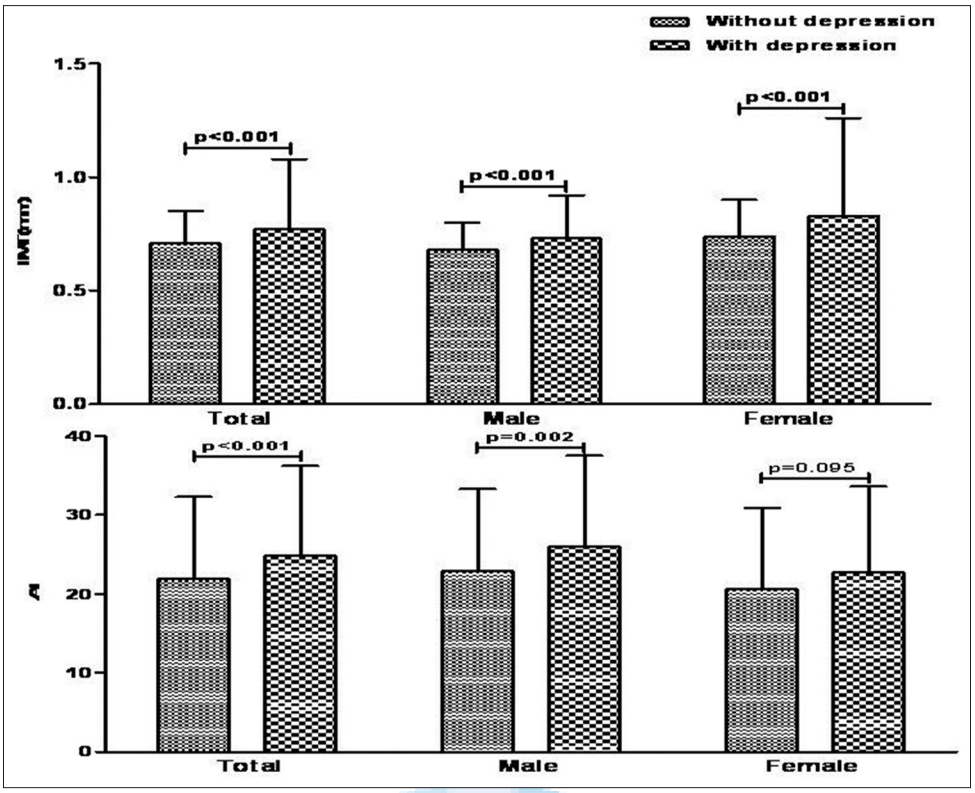

Figure 1: Mean IMT and AI among subjects with and without depression

Table 1: Age adjusted clinical and biochemical characteristics of the groups with and without depression

Variable	Subjects without depression (*n*=1255)	Subjects with depression (*n*=250)	*P*
Age (years)	40±13	45±14	<0.001
Men *n* (%)	679 (81)	157 (19)	0.007
Waist (cm)*	84±11	83±11	0.595
BMI (kg/m2)*	23±4.0	23±4.0	0.392
Systolic blood pressure (mmHg)*	120±18	119±19	0.245
Diastolic blood pressure (mmHg)*	75±11	75±11	0.504
Fasting plasma glucose (mg/dl)*	98±38	93±31	0.025
HbA1c (%)*	6.1±1.4	6.0±1.4	0.119
Total cholesterol (mg/dl)*	181±38	179±40	0.525
Serum triglycerides (mg/dl)*	127±89	117±63	0 0.074
HDL cholesterol (mg/dl)*	43±10	44±10	0.683
LDL cholesterol (mg/dl)*	113±33	113±32	0.948
Urea (mg/dl)*	21±10	20±8.0	0.144
Creatinine (mg/dl)*	1.0±0.4	1.0±0.1	0.473

*These values are presented as age adjusted mean±SD

males (0.83 ± 0.43 mm vs 0.73 ± 0.12 mm, $P < 0.001$) while AI was found to be higher in males with depression compared to females (26.0 ± 11.5 vs 22.7 ± 11.5, $P = 0.002$) respectively.

Figure 2 presents the prevalence of depression in relation to tertiles of IMT and AI. An increase in the prevalence of depression was observed with increasing tertiles of IMT (IMT < 0.63: 14.2%; 0.63-0.72: 14.4%; >0.72: 21.6%, trend $\chi^2 = 9.54$, $P = 0.02$) and AI (AI < 18: 13.6%; 18-27: 16.9%; >27: 19.8%, trend $\chi^2 = 6.52$, $P = 0.01$).

Table 2 presents the results of the logistic regression analysis using depression as dependent variable and IMT and AI as independent variable. IMT showed a significant association with depression both in the unadjusted model (OR = 4.53, CI: 2.157-9.46, $P < 0.001$) as well as in the adjusted model, which included age, gender, BMI, fasting plasma glucose, cholesterol and hypertension (OR = 2.17, CI: 1.01- 4.63, $P = 0.047$, $R^2 = 0.038$). However while AI showed a significant association with depression in the unadjusted model (OR = 1.03, CI: 1.01-1.04, $P < 0.001$, $R^2 = 0.043$) but in the adjusted model when adjusted for age, gender, BMI, fasting plasma glucose, cholesterol and hypertension, the significance was lost (OR = 1.01, CI: 0.99-1.02, $P = 0.445$).

Discussion

This paper presents the following findings. There is an association of depression with both IMT and AI. However, while the association with IMT persisted even after adjustment for possible confounders in the case of AI, the statistical significance was lost after adjusting for confounders.

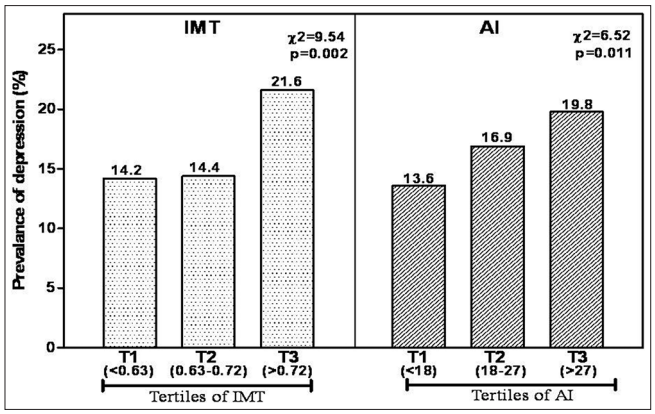

Figure 2: Prevalence of depression in relation to tertiles of intima media thickness and augmentation index

Table 2: Association of depression with IMT and AI

Variables	Odds ratio	95% confidence interval	*P*
Independent variable:			
Intima media thickness			
Unadjusted	4.53	2.17-9.46	<0.001
Adjusted for age+gender+BMI+ FPG+Cholesterol+Hypertension	2.17	1.01-4.63	0.047
Independent variable:			
Augmentation index			
Unadjusted	1.03	1.01-1.04	<0.001
Adjusted for age+gender+BMI+ FBS+Cholesterol+Hypertension	1.01	0.991-1.02	0.445

IMT: Intima medial thickness, AI: Augmentation index, BMI: Body mass index, FPG : Fasting plasma glucose

Both cardiovascular disease and depression cause a significant decrease in quality of life for the patient and impose a significant economic burden on society. There is an increasing evidence that depression per se could be an independent risk factor for cardiovascular disease but the relationship is complex as cardiovascular disease can produce depression.[29]

This study gave us an opportunity to look at association of depression with carotid intima thickness in an epidemiological setting in Asian Indians, a population with a high prevalence of premature CAD.[30] IMT represents an early stage of "structural atherosclerosis" in the artery, and is a subclinical marker for CAD.[9,17] We found that the mean IMT values were higher in subjects with depression and the prevalence of depression increased with increasing tertiles of IMT. The results of this study are in line with previous reports from western population, which found evidence for an association between depression and carotid IMT.[7,9]

Not surprisingly, IMT values also increased significantly with increasing age among subjects with depression. However, an unexpected finding was that when the subjects with depression were segregated on the basis of gender, IMT was found to be higher among females compared to males. This may be explained by the well known fact that the prevalence of depression is higher among females.[31,32] On the other hand, AI was higher among males with depression. This may be related to the higher blood pressure among males.

The exact mechanism by which depression may be associated with atherosclerosis is not known. However, those with depression may have increased cortisol or catecholamine levels or greater inflammation markers, all of which could predispose to atherosclerosis. Increased level of anxiety, which often correlates with depressive symptoms, has also been associated with faster progression of carotid IMT.[33] Studies have consistently shown that emotional problems can contribute to the development of coronary heart disease (CHD).[34]

We also found an association between depressive symptoms and Augmentation index, which is a measure of arterial stiffness. Our results are in agreement with the findings of Netherlands Study of Depression and Anxiety which showed an increased arterial stiffness in subjects with depressive symptoms.[33]

Everson and coworkers[35] examined the association between high levels of hopelessness and progression of carotid atherosclerosis in over 900 Finnish middle-aged men in the Kuopio Ischemic Heart Disease Study (a 4-year follow up study) and reported that high levels of hopelessness were associated with faster progression of carotid IMT. Agewall *et al*.[12] observed that negative feelings (discontent) were related to an increase in the common carotid IMT in a 3-year follow up of 94 hypertensive men in Sweden. Increased level of anxiety, which often correlates with depressive symptoms, has also been associated with faster progression of carotid IMT.[36] Studies have consistently shown that emotional problems can contribute to the development of Coronary Heart Disease (CHD).[37-39]

Depressive symptoms are associated with unhealthy eating habits, a sedentary lifestyle, and lack of exercise, enhanced sympathetic activity, vascular inflammation, and platelet activation. These factors contribute significantly to the pathway linking the atherosclerosis process with depressive symptoms.

The strength of the study is that this is the first from India to our knowledge, which has examined the association of depressive symptoms with functional and structural markers of atherosclerosis in a general population. One of the limitations of the study is that, this is being a cross-sectional study, no cause-effect relationships can be

drawn between depression and IMT or AI. Moreover AI is not considered as the best indicator of arterial stiffness and there are other indices like augmentation pressure which are believed to be better than AI which have not been measured in this study. However, AI is still used as a marker of arterial stiffness in several studies.[9,17]

In conclusion, we report an association between depressive symptoms and increased common carotid IMT and AI. Our study suggests that in subjects with depression, screening for atherosclerosis should be done, as it could help in earlier identification of those at potential risk of developing CAD.

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