Original Article

Association of Depression with Complications of Type 2 Diabetes – The Chennai Urban Rural Epidemiology Study (CURES- 102)

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Abstract

Objective: The aim of the study was to assess the relationship between depression and diabetic complications among urban south Indian type 2 diabetic subjects [T2DM].

Methods: T2DM subjects [n= 847] were recruited from the Chennai Urban Rural Epidemiology Study [CURES], a population based study in Chennai (formerly Madras) in South India. A previously validated depression questionnaire [PHQ-12 item] was administered. Four field stereo retinal colour photography was done and diabetic retinopathy [DR] was classified according to the Early Treatment Diabetic Retinopathy Study grading system. Neuropathy was diagnosed if the vibratory perception threshold of the right great toe, measured by biothesiometry, was ≥20. Nephropathy was diagnosed if urinary albumin excretion was ≥300 µg/mg creatinine. Peripheral vascular disease [PVD] was diagnosed if an ankle-brachial index was <0.9. Coronary artery disease [CAD] was diagnosed based on a past history of documented myocardial infarction and/or electrocardiographic evidence of Q wave and/or ST segment changes.

Results: Of the 847 T2DM studied, 198 (23.4%) were found have depression. The prevalence of depression was significantly higher among diabetic subjects with DR (35.0% vs 21.1%,p<0.001), neuropathy (28.4% vs15.9%,p=0.023), nephropathy (35.6% vs 24.5%,p=0.04) and PVD (48.0% vs 27.4%,p<0.001) as compared to subjects without these complications. DR, neuropathy, nephropathy, and PVD were associated with depression even after adjusting for age, gender, duration of diabetes and glycated haemoglobin. DR (Odds ratio [OR] =2.19, Confidence interval [CI]:1.45-3.51,p<0.001) was associated with depression even after adjusting for neuropathy and nephropathy. There was also a significant association between depression and neuropathy, after adjusting for retinopathy and nephropathy (OR=2.07,CI:1.41-3.04,p<0.001). There was a significant association of depression with nephropathy but this was lost (OR=1.71, CI: 0.87-3.35,p=0.119) after adjustment for retinopathy. PVD (OR=3.52,CI:1.94-6.40,p<0.001) remained significantly associated with depression even after adjusting for CAD. However, there was no significant association of depression with CAD (OR=0.73, CI:0.42 -1.27, p=0.264).

Conclusion: Among Asian Indians, the prevalence of depression is higher in T2DM subjects with retinopathy, neuropathy, nephropathy and PVD compared to those without the respective complications.

Introduction

Depression is twice as common in patients with diabetes as in the general population, and its prevalence appears to increase with the number of diabetic complications.[1] Earlier studies have examined the association of depression with micro- and macrovascular complications of diabetes and there is evidence to suggest that the long-term complications of diabetes are associated with depressive symptoms.[2,3] A meta-analysis of 27 studies conducted by de Groot et al[2] to determine whether an association existed between depression and diabetes complications reported that depression was associated with retinopathy, neuropathy, nephropathy and macrovascular disease.

There is limited data on depression in relation to diabetic complications from India, which has over 50 million people with diabetes.[4] Hence this study was undertaken to examine the association between depression and diabetes related complications in an urban south Indian population.

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Subjects and Methods

The Chennai Urban Rural Epidemiology Study (CURES) is a large ongoing epidemiological study conducted on a representative population of Chennai using systematic random sampling . The details of the sampling and methods of the study are published elsewhere.[5,6]

Briefly, in Phase I, 26,001 subjects were randomly selected from 46 of 155 corporation wards of Chennai. Self reported type 2 diabetes was diagnosed if subjects gave a history of diabetes diagnosed by a physician and/or if they were on treatment with anti-diabetic drugs. These individuals were classified as 'known diabetic subjects (KD).

In Phase II, all the known diabetic (KD) subjects (n=1529) identified in Phase I of the study, and those who were diagnosed to have diabetes on screening with an oral glucose tolerance test (OGTT), termed as newly detected diabetes (NDD) (n=371) were invited to Dr.Mohan's Diabetes Specialties Centre, a tertiary referral centre for diabetes for detailed studies on various vascular complications. In a subset of 900, randomly selected T2DM (KD and NDD) subjects a depression questionnaire was administered. The Institutional ethics committee approval was obtained for the study and informed consent was obtained from all the study subjects.

For this study, a total of 847 (Response rate:94%) T2 DM (KD: 579 and NDD: 268), who had information on all test parameters

[gradable retinal photographs, biothesiometry, ECG and doppler studies and microalbuminuria estimations] and who had completed PHQ 12 item questionnaire were included.

Anthropometric measurements including weight, height, waist and hip measurements were obtained using standardized techniques.[5] The body mass index (BMI) was calculated using the formula: weight (kg) / height (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 2mm Hg from the top of the mercury meniscus. Systolic pressure was recorded at the first appearance of sound and diastolic pressure at the disappearance of the sound (Korotkoff's phase V). A mean of two readings taken 5 minutes apart was recorded as the blood pressure. Hypertension was diagnosed in subjects who were on antihypertensive medication or had a systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg.[7]

The 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. Glycated hemoglobin (HbA1c) was estimated by the high pressure liquid chromatography using the Variant machine (BIORAD, Hercules, California,USA). Serum cholesterol and serum triglycerides were measured by CHOD-PAP method and GPO-PAP method respectively. High-density lipoprotein (HDL) cholesterol was estimated by the 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.

Urine samples were collected after an overnight fast. Microalbumin concentration was measured using an immunoturbidometric assay (Hitachi 902 autoanalyser, Roche Diagnostics, Mannheim, Germany). Subjects in whom the microalbumin level was above the upper limit of detection (>450 mg/l) were assigned a value of 450 mg/l. The diagnostic criterion for macroalbuminuria or overt nephropathy was albumin excretion ≥300 µg/mg of creatinine.[8]

The ocular fundi were photographed using four-field stereo color retinal photography [Zeiss FF 450 plus camera] by trained and certified retinal photographers as described earlier.[9] Photographs were graded by an ophthalmologist using the early treatment Diabetic retinopathy Study [ETDRS] grading system.[10] The minimum criterion for diagnosis of DR was the presence of at least one definite microaneurysm in any field. Briefly, according to the ETDRS grading, level 10 represents no retinopathy, level ≥20 non-proliferative DR (NPDR) and level ≥ 60, proliferative DR (PDR).[10] Diabetic Macular Edema (DME) was defined as retinal thickening at or within 1 disc diameter of the center of the macula or the presence of definite hard exudates.

Resting twelve-lead electrocardiogram (ECG) was performed using Myocard R electrocardiograph (Marks Electronics, Chennai, India). CAD was diagnosed based on positive medical history (documented myocardial infarction (MI), angina pectoris and coronary artery bypass graft) and/or ischemic changes on a conventional 12-lead ECG which included ST-segment depression (Minnesota codes 1-1-1 to 1-1-7) or Q-wave changes (Minnesota codes 4-1 to 4-2).[5]

Doppler studies were performed by a single observer, which included recording of pressure tracings using the KODY Vaslab Machine (Kody Labs, Chennai, India). The ankle/brachial pressure index (ABI) was calculated in every subject. An ABI of less than 0.9 was the criteria used for the diagnosis of peripheral vascular disease.[11]

A biothesiometer (Biomedical Instrument Co., Newbury, Ohio, USA) was used to assess vibratory perception threshold (VPT) of the great toes in a standardized fashion. Neuropathy was diagnosed if VPT of the great toe exceeded mean +2 SD of healthy non-diabetic study population aged 20-45 years (cut point ≥20V).[6]

A modified version of the Patient Health Questionnaire (PHQ)- 9 item was used to assess depression. It was modified for local conditions into a 12 item questionnaire (PHQ-12 item as previously described.[12] The modified -12 item was developed with yes or no response by using the same version of PHQ-9 item; however, three of the questions in the PHQ-9 item were split into two thus accounting for 12 items. The response categories were also made dichotomous (yes/no), such that the subject would be asked whether they had any of the twelve depressive symptoms and, if yes, their frequency, during the pervious two weeks would be recorded. The modified PHQ-12 item was then validated and shown to be a reliable instrument for screening of depression in the general population with a score > 4 being the best to identify depression in south Indian population.[12] It took 10 minutes to administer the questionnaire.

Statistical Analysis

All statistical analyses were performed using SAS statistical package (version 9.0; SAS Institute, Inc., Cary, NC). Numbers are expressed as mean ± standard deviation. Student's "t" test was used to compare groups for continuous variables. Chi square test was used to compare proportions among groups. Logistic regression model was used to determine whether age, gender, duration of diabetes and glycated haemoglobin were independently associated with depression and its complications. For all statistical tests, p value <0.05 was considered as the level of significance.

Results

Of the 847 type 2 subjects included in this study, (KD: 579 (68.4%) and ND: 268 (31.6%), depression was seen in 198 subjects (23.4%). Table 1 depicts the characteristics of diabetic subjects with and without depression. Subjects without depression were older (51.5 ± 10.8 years) compared to those with depression (49.1 ± 12.2 years) [p=0.009]. None of the other characteristics were significantly different between the two groups.

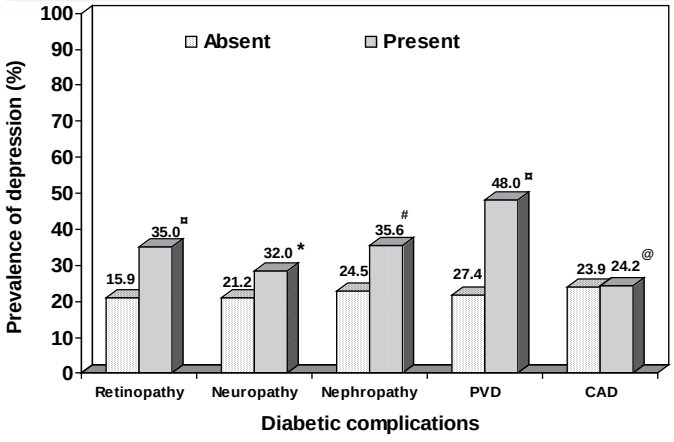
Figure 1 presents the prevalence of depression among subjects with and without diabetic complications. Prevalence of depression was higher in subjects with retinopathy (35%) compared to subjects without DR (21.1%, p<0.001). In addition, when analyzed with respect to severity of diabetic retinopathy, the prevalence of depression was highest among subjects with proliferative diabetic retinopathy [PDR] (39.1%) followed by those with non proliferative diabetic retinopathy [NPDR] (33%) and lowest among subjects without diabetic retinopathy (21.1%) and the trend was significant [Trend chi χ^2: 12.263, p =0.002]. The prevalence of depression in subjects with neuropathy (28.4% vs 21.1%, p=0.023] and nephropathy (35.6% vs 22.7%, p=0.0.04) was also significantly higher compared to subjects without these respective complications. Prevalence of depression in subjects with PVD was significantly higher compared to those subjects without PVD (48% vs 21.8%, p<0.001).

Figure 2 presents the prevalence of depression in relation

Table 1: General characteristics of diabetic subjects with and without depression

Variables	Diabetic Subjects		p Value
	Without Depression (n=649)	With Depression (n=198)	
Age (years)	51.5±10.8	49.1±12.2	0.009
Male n (%)	303(46.7)	80(40.4)	0.122
Waist (cms)	91±10	89.3±10.2	0.057
Hip (cms)	98±10	97±11	0.264
Height (cms)	158±9	157±9	0.129
Weight (kg)	63.4±11.3	61.5±12.2	0.043
Body mass index (kg/m^2)	25.3±4.1	24.9±4.5	0.215
Fasting blood sugar (mg/dl)	159.8±63.9	160.3±71.7	0.943
Duration of diabetes (Years)*	4.4 ± 0.2	4.6 ± 0.4	0.687
HbA1c %	8.6±2.1	8.6±2.2	0.869
Serum cholesterol(mg/dl)	199±41	203 ±43	0.300
Serum triglycerides(mg/dl)**	151.5±5.1	156.7±9.8	0.093
Serum HDL cholesterol(mg/dl)	42.4±8.9	43.6±9.5	0.922
Serum LDL cholesterol (mg/dl)	124.3±33.7	124.6±34.0	0.928
Creatinine (mg/dl)	0.9±0.2	0.9±0.2	0.118
Smoking n (%)	109 (16.8)	39 (19.7)	0.338
Alcohol n (%)	124 (19.1)	41 (20.7)	0.610

Data presented as mean ± standard deviation (S.D) or number (%) subjects; *Standard error of mean (SEM); **Geometric mean



PVD-Peripheral vascular disease ; CAD-Coronary artery disease

¤ p<0.001; * p=0.023; # p= 0.04; @ p=0. 263

Fig. 1 : Prevalence of depression in relation to diabetic complications

to the number of diabetic complications. The prevalence of depression in subjects without any complication was 16.2% and in those with one complication it was 29.2%, while in those with two or more complications, it was 33.1% [Trend chi χ^2: 22.43, p<0.001].

To evaluate the association of depression with various complications, models were developed based on logistic regression using depression as the dependent variable. Various factors associated with microvascular complications were first included as independent variable and later the complications themselves were included in the model (Table 2). Depression

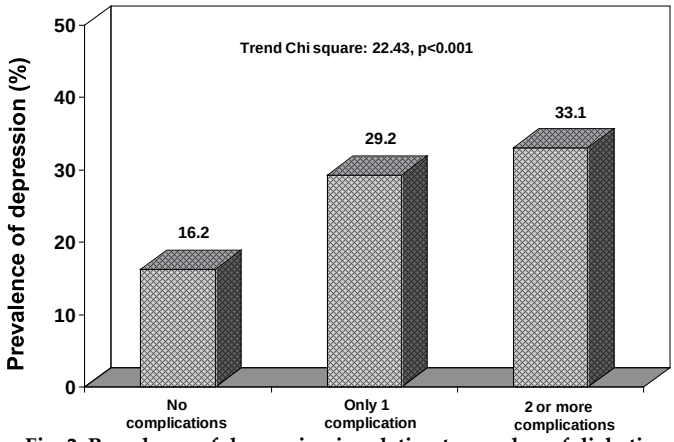


Fig. 2: Prevalence of depression in relation to number of diabetic complications (micro and macrovascular)

Table 2: Association of depression with microvascular complications of diabetes

Variables	Odds ratio	95% confidence interval	p value
Retinopathy (No =0, Yes = 1)			
Model 1: Unadjusted	2.017	1.363- 2.983	<0.001
Model 2 :Model 1 + age	2.226	1.492-3.321	<0.001
Model 3 :Model 2 + gender	2.289	1.530-3.424	<0.001
Model 4: Model 3 + HbA1C	2.373	1.571-3.583	<0.001
Model 5: Model 4 + duration of diabetes	2.266	1.483-3.464	<0.001
Model 6: Model 5 + neuropathy	2.285	1.488-3.507	<0.001
Model 7: Model 6 + nephropathy	2.185	1.417-3.371	<0.001
Neuropathy (No =0, Yes = 1)			
Model 1: Unadjusted	1.483	1.064-2.067	0.020
Model 2: Model 1 + age	2.074	1.424-3.023	<0.001
Model 3: Model 2+gender	2.052	1.407-2.992	<0.001
Model 4: Model 3+ HbA1C	2.059	1.412-3.004	<0.001
Model 5: Model 4 + duration of diabetes	2.060	1.411-3.007	<0.001
Model 6:Model 5 + retinopathy	2.071	1.415-3.031	<0.001
Model 7:Model 6 + nephropathy	2.072	1.414-3.035	<0.001
Nephropathy (No =0, Yes = 1)			
Model 1: Unadjusted	1.879	0.999-3.537	0.050
Model 2: Model 1 + age	2.017	1.066-3.818	0.031
Model 3: Model 2+gender	2.018	1.066-3.818	0.031
Model 4: Model 3+ HbA1C	2.069	1.083-3.956	0.028
Model 5: Model 4 + duration of diabetes	1.973	1.029-3.784	0.041
Model 6: Model 5 + neuropathy	2.007	1.040-3.873	0.038
Model 7: Model 6 + retinopathy	1.708	0.872-3.345	0.119

was significantly associated with retinopathy even after adjusting for age, gender, glycated haemoglobin, duration of diabetes, neuropathy and nephropathy. (OR=2.19, CI: 1.45-3.51, p<0.001). There was significant association of depression with neuropathy even after adjusting for age, gender, glycated haemoglobin, duration of diabetes, retinopathy and nephropathy (OR=2.07, CI: 1.41-3.04, p<0.001). There was an association of depression with nephropathy but the association was lost after adjusting for retinopathy (OR=1.71, CI: 0.87-3.35, p=0.119).

Depression was significantly associated with peripheral

Table 3: Association of depression with macrovascular complications of diabetes

Variables	Odds ratio	95% confidence interval	p value
Peripheral Vascular Disease (No =0, Yes = 1)			
Model 1: Unadjusted	3.305	1.851-5.901	<0.001
Model 2: Model 1 + age	3.560	1.974-6.419	<0.001
Model 3: Model 2 + gender	3.453	1.910-6.243	<0.001
Model 4: Model 3 + HbA1C	3.444	1.904-6.228	<0.001
Model 5: Model 4 + duration of diabetes	3.520	1.938-6.394	<0.001
Model 6 Model 5 + CAD	3.524	1.940-6.403	<0.001
Coronary artery disease (No =0, Yes = 1)			
Model 1: Unadjusted	0.730	0.420-1.269	0.264
Model 2: Model 1 + age	0.839	0.476-1.478	0.544
Model 3: Model 2 + gender	0.835	0.474-1.472	0.534
Model 4: Model 3 + HbA1C	0.834	0.473-1.471	0.532
Model 5: Model 4 + duration of diabetes	0.810	0.459-1.432	0.469
Model 6:Model 5 + PVD	0.804	0.452-1.430	0.458

vascular disease (PVD) in the unadjusted model (OR: 3.305, 95% CI: 1.851-5.901, p <0.001), and the which retained significance was retained even after adjusting for age, gender, glycated hemoglobin duration of diabetes and CAD (OR= 3.52, CI: 1.94-6.40, p<0.001). There was no significant association with depression and CAD (OR= 0.73, CI: 0.42 -1.27, p = 0.264) (Table 3).

Discussion

In this study, we report that the prevalence of depression is higher among T2 DM subjects with retinopathy, neuropathy, nephropathy and PVD. Biological, psychological or behavioral responses to stressors facing patients with diabetes may all play a role in increasing the prevalence of depression in patients with diabetes.[2] Functional impairment in diabetic patients with neuropathy or retinopathy, may also increase prevalence of depression as shown by the increasing depression with increasing severity of retinopathy in our study.

Conversely, it has been reported that individuals with depression are at increased risk of developing clinically significant micro and or macro vascular complications of diabetes.[2] Thus, patients with major depression and diabetes have a 36% higher risk of developing advanced microvascular complications, such as end stage renal disease or blindness and 25% higher risk of developing macrovascular complications.[13]

Yoshida et al,[14] reported that the presence of microvascular complications, specifically neuropathy, was associated with depression independent of age, gender, marital status, social support, pain, perception of general health, diabetes type, duration of diabetes, glycated hemoglobin and insulin requirement. Other studies have also demonstrated that presence of diabetic complications particularly diabetic neuropathy[15] and retinopathy[16] was associated with depression. In our study, depression was associated with retinopathy and neuropathy even after adjusting for age, gender, glycated hemoglobin and duration of diabetes and other microvascular complications.

Depression has been linked with dysregulation of hypothalamic-pituitary-adrenal axis, over activity of the sympathetic nervous system and with pro-inflammatory and pro coagulation markers in patients with coexisting cardiovascular disorders.[17] Studies have shown that neuro-endocrine and inflammatory responses accompanying depression also play similar roles in the progression of microvascular and macrovascular complications among patients with type 2 diabetes. It is known that subjects with depression are less willing to start insulin therapy or take regular treatment for their diabetes.[18] Ours is a cross sectional study was based on ECG findings. This could also contribute to the higher HbA1c levels and increased risk for diabetic complications. However, in this study we did not find any significant difference in the HbA1c levels among diabetic subjects with and without depression.

Depression and ischemic heart disease are the two strongest contributors to the global burden of disease. An association between depression following acute coronary syndrome and subsequent adverse events like Myocardial Infarction, stroke, coronary heart failure and death has been observed.[19] In our study we did not find any significant association with depression and coronary artery disease. Most of the earlier studies were on post myocardial infarction patients[20] and were longitudinal in nature. This could explain the differences between these studies and the current study.

One of the limitations of our study is that, being a cross-sectional study, definite conclusions about cause and effect relationships between diabetic complications and depression cannot be made. Secondly, depression was only measured at one point in time. However, this is unlikely to affect the study results as depression runs a chronic or recurrent course among patients with co-existing diabetes. Moreover these findings are generally consistent with those of other studies and also with the meta-analysis studies done by de Groot et al.[2]

In conclusion, this study shows that there is a significant association between depression and various diabetes complications in type 2 diabetic subjects. Although further research is needed to clarify the underlying mechanisms for this association between depression and diabetes complications, this study emphasizes the importance of intervening when patients with diabetes present with depression as treatment of our condition can benefit the other.

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