Original Article

Association of Stress, Depression and Anxiety among Individuals with Microvascular Complications in Type 2 Diabetes

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Abstract

Background and Aims: The impact of a chronic illness like diabetes on physical and mental wellbeing has been gaining more focus in the last few decades. This study aimed to investigate the association of stress, depression, and anxiety among individuals with type 2 diabetes mellitus (T2DM) and microvascular complications. **Materials and Methods:** This cross-sectional study included 315 participants aged ≥20 years with T2DM seen at a tertiary care diabetes centre who were screened for diabetic retinopathy, nephropathy, and neuropathy and assessed for stress, depression, and anxiety using the Depression, Anxiety Stress Scale 21 (DASS 21). Diabetic retinopathy was classified according to the Early Treatment Diabetic Reinopathy Study grading system diagnosed using retinal photography [Early Treatment DR Study grading system] i.e., presence of at least one distinct microaneurysm; nephropathy, if urinary albumin excretion was ≥30 mg/µg of creatinine; and neuropathy, if vibration perception threshold of the big toe using biothesiometry was ≥20 V. **Results:** Prevalence of stress was higher in those with neuropathy (60% vs 40%, $P < 0.001$), nephropathy (61% vs 39%, $P < 0.001$) and retinopathy (57% vs 43%, $P < 0.05$) compared to those without. Prevalence of depression was also higher in individuals with neuropathy (66% vs 34%,$P < 0.001$), nephropathy (58% vs 42%, $P < 0.001$) and retinopathy (55% vs 45%, $P < 0.05$). In multiple regression analysis, stress was significantly associated with retinopathy (OR=3.13,CI:1.75–5.58, $P < 0.000$), neuropathy (OR=2.50, CI:1.42–4.39,$P < 0.001$) and nephropathy (OR=2.06,CI:1.19–3.56, $P < 0.010$),depression was also significantly associated with retinopathy (OR=1.97,CI:1.04–3.73, $P < 0.037$), neuropathy (OR=2.77,CI:1.45–5.30,$P < 0.002$) and nephropathy (OR=2.59,CI:1.42–4.70,$P < 0.002$). **Conclusions:** Individuals with microvascular complications of diabetes should be screened for stress, depression,and anxiety so that proper counselling can be given.

Keywords: Anxiety, depression, microvascular complications, stress, type2 diabetes mellitus

Introduction

Non-communicable diseases (NCDs) such as diabetes and cardiovascular diseases are chronic, have a high mortality rate, and are more prevalent in low and middle-income countries.[1] Amongst the NCDs, diabetes shows the strongest association with mental health disorders.[2] Generally, 20–25% of individuals living with a chronic illness develop psychological or mental health issues.[3] The global prevalence of diabetes is 463 million, with India ranking second in the world with 77 million, and having an overall prevalence of 7.3%.[4,5] The health costs incurred by individuals suffering from diabetes are 2.3 times higher than those without diabetes.[6] Thus, the

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financial burden is very high in a country like India with its huge diabetic population.[7]

Psychosocial factors such as stress, interpersonal problems, unhealthy food habits, and lack of physical activity are some of the risk factors for poor glycaemic control and also possibly contribute to diabetic complications.[8] Although it has been recognized that depression and anxiety lead to poor metabolic control, subclinical levels of stress and distress also may have an adverse effect on glycaemic control.[9]The stress response should, however, be differentiated from depression and anxiety.[10]

Individuals with diabetes and mental health issues show lower medication adherence, poorer compliance with their treatment regimen, and, hence are at greater risk for disabilities than those without.[11] There are very few studies that have investigated the association between the tripartite aspects of stress, depression, and anxiety along with microvascular complications of diabetes, in India. This study was undertaken to study the prevalence of stress, depression, and anxiety among adults with type 2 diabetes mellitus (T2DM) attending a tertiary diabetes care centre in Chennai and to look at their association with microvascular complications.

Materials and Methods

A total of 315 participants aged ≥20 years with T2DM who were seen during the period 2017 to 2019, at a tertiary diabetes centre and also screened for microvascular complications, namely, retinopathy, nephropathy, and neuropathy, were included in the study. Inclusion criteria were males and females with T2DM who were willing to participate in the study and give written informed consent.

Exclusion criteria were individuals who were on medication for any major psychiatric disorders such as schizophrenia, major depressive disorder, bipolar disorder, or obsessive-compulsive disorder. Patients with gestational diabetes mellitus, secondary diabetes, type 1 diabetes, or those with any other significant illness were also excluded.

All participants were briefed regarding the study and assured of strict confidentiality and the procedure of measuring stress, depression, and anxiety using a questionnaire was explained to them. A written informed consent was obtained from all the participants. This study was approved by the Ethics Committee of MDRF.

Anthropometric and clinical measurements

Demographic information such as current age, education, income status, duration of diabetes etc., were collected. Anthropometric measurements were obtained using standardized techniques according to the Anthropometric Standardization Reference Manual.[12] Height, weight and waist circumference were measured using standard techniques. Body mass index (BMI) was calculated using the formula: weight (in kg) divided by height (in m) squared. Blood pressure was recorded in the sitting position in the right arm to the nearest 1mmHg using the electronic Omron machine-HEM-8712 (OmronCorprn, Tokyo, Japan). Age, education and income were categorized with Kuppuswamy's socioeconomic scale as the basis.[13]

Biochemical investigations

Participants arrived at the centre after an overnight fast of at least 8 hours to estimate the fasting venous blood glucose, glycated haemoglobin (HbA1c) and serum lipid levels. All measurements were performed in the laboratory of Dr.Mohan's Diabetes Specialities Centre (DMDSC), which regularly participates in external quality assurance programs from Bio-rad Laboratories, Hercules, CA, USA.Plasma glucose, serum cholesterol, triglyceride and high density lipoprotein(HDL) cholesterol were measuredusing auto analyzer. Low-density lipoprotein (LDL) cholesterol was calculated using Friedewald formula.[14] Microalbuminuria was measured in fasting urine samples.

Data collection instrument for depression, anxiety, and stress (DASS- 21)

The DASS-21, which is a validated tool developed by Lovibond and Lovibond (1995) is widely used in clinical and non-clinical populations. It is designed to measure the states of stress, depression, and anxiety and comprises 7 items each, divided into subscales. The DASS 21 has a high degree of reliability for all the scales, namely, stress, depression, and anxiety, and has been validated in the Indian population.[15,16] The Stress scale, which measures a state of constant tension and inability to relax has a cut-off of ≥15, while the Depression scale which measures low mood, despair, and poor self-esteem has a cut-off of ≥10. Finally, the Anxiety scale which measures Irrational fears, somatic complaints, and symptoms of panic, has a cut-off of ≥8.

Definitions

Type 2 diabetes

Defined as fasting plasma glucose (FPG) ≥126 mg/dl or a 2 Hr post glucose value (2Hr PG) of ≥200 mg/dl or a past medical history of diabetes and not on insulin for at least 2 years after the diagnosis.[17]

Diabetic retinopathy

All participants underwent a complete detailed ocular examination. Dilated fundus examination was done using Zeiss Digital Camera and graded by an ophthalmologist. Retinopathy was graded as level 10 represents no retinopathy, level ≥20 non-proliferative diabetic retinopathy and level ≥60, proliferative diabetic retinopathy.[18]

Neuropathy

Biothesiometer (Biomedical Instrument Co., Newbury, Ohio,USA) was used to assess neuropathy. As previously reported, a single observer examined the vibratory perception threshold (VPT) of the great toes in a standardised manner. Neuropathy was diagnosed if VPT was ≥ 20 V.[19]

Nephropathy was diagnosed if there was either:

Microalbuminuria

Albumin excretion between 30 – 299 µg/mg of creatinine[20] or

Macroalbuminuria

If albumin excretion was ≥ 300 µg/mg of creatinine.[20]

Statistical analyses

Statistical analyses were done using Statistical Package for Social Sciences (SPSS IBM version 25). Continuous variables are expressed as mean ± SD and categorical variables as frequencies and percentages. Pearson chi-square test was used to compare variables. Multivariate analysis using logistic regression analysis was used to test the effect of variables associated with complications after adjusting for confounding variables, $P < 0.05$ was considered statistically significant.

Results

The characteristics of the study population based on stress, depression and anxiety are shown in [Table 1]. The mean age of the study participants was 50 ± 12 years, 59% were males and the mean duration was 10.6 ± 7.5 years. Individuals with stress (45 ± 12 vs 52 ± 12, $P < 0.001$), depression (46 ± 12 vs 51 ± 12, $P < 0.05$), and anxiety (44 ± 11 vs 52 ± 12, $P < 0.001$) were younger compared to those without stress, depression and anxiety, respectively. Similarly, individuals with stress (28 ± 6 vs 26 ± 5, $P < 0.05$) and depression (28 ± 5 vs 26 ± 5, $P < 0.05$) had significantly higher BMI compared to those without stress and depression. Individuals with stress (8 ± 7 vs 10 ± 7, $P < 0.05$) and anxiety (8 ± 7 vs 10 ± 8 $P < 0.05$) had shorter duration of diabetes compared to those without stress and anxiety. The mean HbA1c was elevated in individuals with depression (9 ± 2 vs 8 ± 2, $P < 0.05$).

[Figure 1] Shows the gender-wise prevalence of stress, depression, and anxiety among the 315 individuals with T2DM. Females had a higher prevalence of stress

Table 1: Clinical and biochemical characteristics of individuals based on stress, depression and anxiety

Variables	Without Stress (n=179)	With Stress (n=136)	Without Depression (n=233)	With Depression (n=82)	Without Anxiety (n=181)	With Anxiety (n=134)
Age (years)	52 ± 12	45 ± 12*	51 ± 12	46 ± 12$	52 ± 12	44 ± 11^
Duration of diabetes (years)	10 ± 8	8 ± 7#	10 ± 8	9 ± 7	10 ± 8	8 ± 7£
BMI (kg/m²)	26 ± 5	28 ± 6#	26 ± 5	28 ± 5$	26 ± 5	27 ± 6
Waist circumference (cms)	93 ± 17	97 ± 14#	94 ± 16	96 ± 16	94 ± 16	95 ± 16
Hip (cms)	97 ± 18	101 ± 14#	98 ± 17	101 ± 16	98 ± 16	100 ± 17
Systolic blood pressure (mmHg)	128 ± 15	126 ± 13	127 ± 15	126 ± 14	127 ± 15	126 ± 14
Diastolic blood pressure (mmHg)	78 ± 7	79 ± 7	78 ± 7	78 ± 7	78 ± 6	78 ± 8
Fasting plasma glucose (mg/dl)	158 ± 61	157 ± 56	156 ± 60	166 ± 56	156 ± 62	160 ± 53
Glycated haemoglobin (%)	8 ± 2	8 ± 2	8 ± 2	9 ± 2$	8 ± 2	8 ± 2
Serum total cholesterol (mg/dl)	167 ± 45	168 ± 44	168 ± 43	167 ± 50	167 ± 46	169 ± 40
Serum Triglycerides (mg/dl)	158 ± 101	165 ± 113	151 ± 90	157 ± 109	158 ± 101	165 ± 113
Serum HDL cholesterol (mg/dl)	42 ± 13	39 ± 9	43 ± 13	37 ± 9	45 ± 13	35 ± 7
Education n (%)@						
Non -Graduates	102 (43)	80 (41)	130 (44)	51 (37)	101 (44)	80 (40)
Graduates	77 (57)	55 (59)	102 (56)	30 (63)	79 (56)	53 (60)
Occupation n (%)@						
Unemployed	95 (47)	70 (48)	123 (47)	44 (46)	97 (46)	68 (49)
Skilled and semi-skilled	98 (45)	80(41)	128 (45)	48 (41)	99 (45)	79 (41)
Professionals	164(8)	121(11)	214 (8)	71 (13)	164 (9)	120 (10)
Income (INR) n (%)@						
≤ 13880	143 (20)	114 (16)	186 (20)	69 (15)	145 (20)	111 (17)
13881- 37014	120 (33)	77 (43)	153 (34)	48 (41)	114 (37)	89 (33)
≥37015	95 (47)	80 (41)	126 (46)	46 (44)	103 (43)	67 (50)

Data presented as Mean (±SD),

*p<0.001 compared to T2DM without stress, # p<0.05 compared to T2DM without stress, $p<0.05 compared to T2DM without depression, ^p<0.001 compared to T2DM without anxiety, £p<0.05 compared to T2DM without anxiety

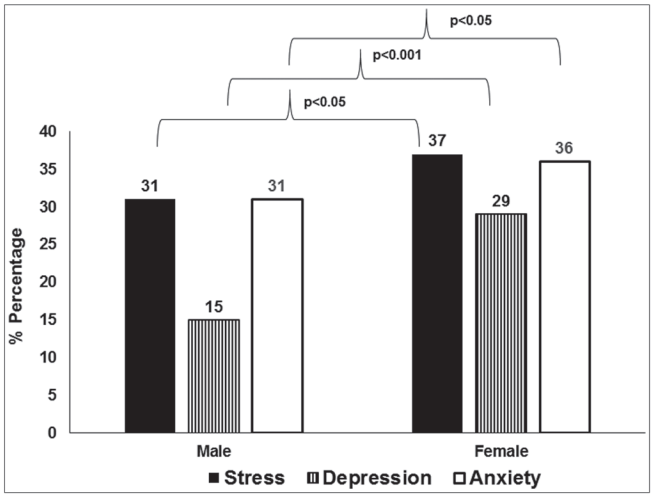

Figure 1: Gender wise prevalence of stress, depression and anxiety among individuals with type 2 diabetes

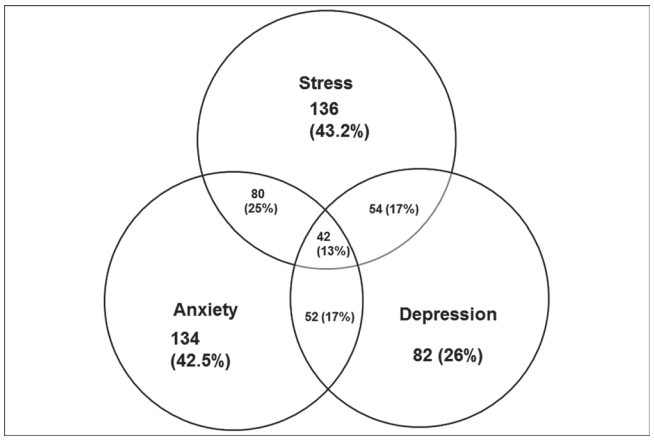

Figure 2: Venn diagram showing the overlapping of stress, depression and anxiety among the study population

(females-37% vs males- 31%, $P < 0.05$), depression (females-29% vs males-15%, $P < 0.001$) and anxiety (females-36% vs males-31%, $P < 0.05$).

[Figure 2] shows that of the 315 individuals, 136 (43.2%) had stress alone, 82 (26%) had depression alone and 134 (42.5%) had anxiety, while 42 individuals (13%) had stress, and depression and anxiety.

[Figure 3] presents the prevalence of stress, depression, and anxiety among those with and without microvascular complications. The prevalence of stress was significantly higher in those with neuropathy (60%) followed by nephropathy (61%) and retinopathy (57%) compared to the respective complications. Prevalence of depression was significantly higher in individuals with neuropathy (66%), followed by those with nephropathy (58%) and retinopathy (55%) compared to those without the complications.

We then carried out a multivariate analysis. Various factors associated with microvascular complications were included as independent variables. Stress was significantly associated with retinopathy (OR=3.13, CI:1.75–5.58, $P < 0.000$), neuropathy (OR=2.50, CI:1.42–4.39, $P < 0.001$), and nephropathy (OR=2.06, CI:1.19–3.56, $P < 0.010$) after adjusting for age, duration of diabetes and HbA1c. Similarly, depression was significantly associated with retinopathy (OR=1.97, CI:1.04–3.73, $P < 0.037$), neuropathy (OR=2.77, CI:1.45–5.30, $P < 0.002$), and nephropathy (OR=2.59, CI:1.42–4.70, $P < 0.002$) even after adjusting for the above-mentioned variables. However, anxiety was significantly associated with neuropathy (OR=2.37, CI:1.31–4.29, $P < 0.004$) [Table 2].

Discussion

This study reports on the prevalence of stress, depression, and anxiety in individuals with T2DM and their association with microvascular complications. The study shows the following findings: Firstly, females had a higher percentage of stress, depression, and anxiety compared to males. Secondly, individuals with microvascular complications showed a higher prevalence of stress and depression. Finally, there was an association between retinopathy, nephropathy, and neuropathy with stress and depression, while anxiety was associated with neuropathy alone.

This study confirms earlier studies that showed that females have higher levels of stress, depression, and anxiety.[21,22] Stress was higher in females, having a family history of chronic illnesses, and an HbA1c >8.5%.[21,23,24] Depression was associated with females, older age, complications and anxiety, whereas anxiety was associated with females, chronicity of the disease, poor sleep quality and depression.[25] A study in Saudi Arabia showed a higher prevalence of stress, depression, and anxiety (57% vs 58% vs 54%) among females compared to our study (37% vs 29% vs 36%) (21). The prevalence of depression was 15.1% in the Chennai Urban Rural Epidemiological Study (CURES) compared to 26% in this study; the percentage was also higher in females compared to males (16.3% vs 13.9%) in contrast to our study (29% vs 15%).[26] Some of the reasons cited for the higher prevalence of emotional distress in women was interpersonal relationships, greater domestic responsibilities, and fear of complications.[27]

Generally, individuals with diabetes show much higher stress levels compared to the general population, as shown in our earlier study.[28] Exposure to chronic stress due to living with diabetes has a direct impact on average sugar levels.[29] Higher HbA1c and glucose levels lead to higher levels of anxiety, although in our study, those with depression showed higher HbA1c.[30] The chronic nature of diabetes can lead to microvascular complications, especially in those with a long duration of diabetes and if diabetes is uncontrolled. Earlier studies reported that individuals with poor glycemic control, comorbidities, and microvascular complications showed higher levels

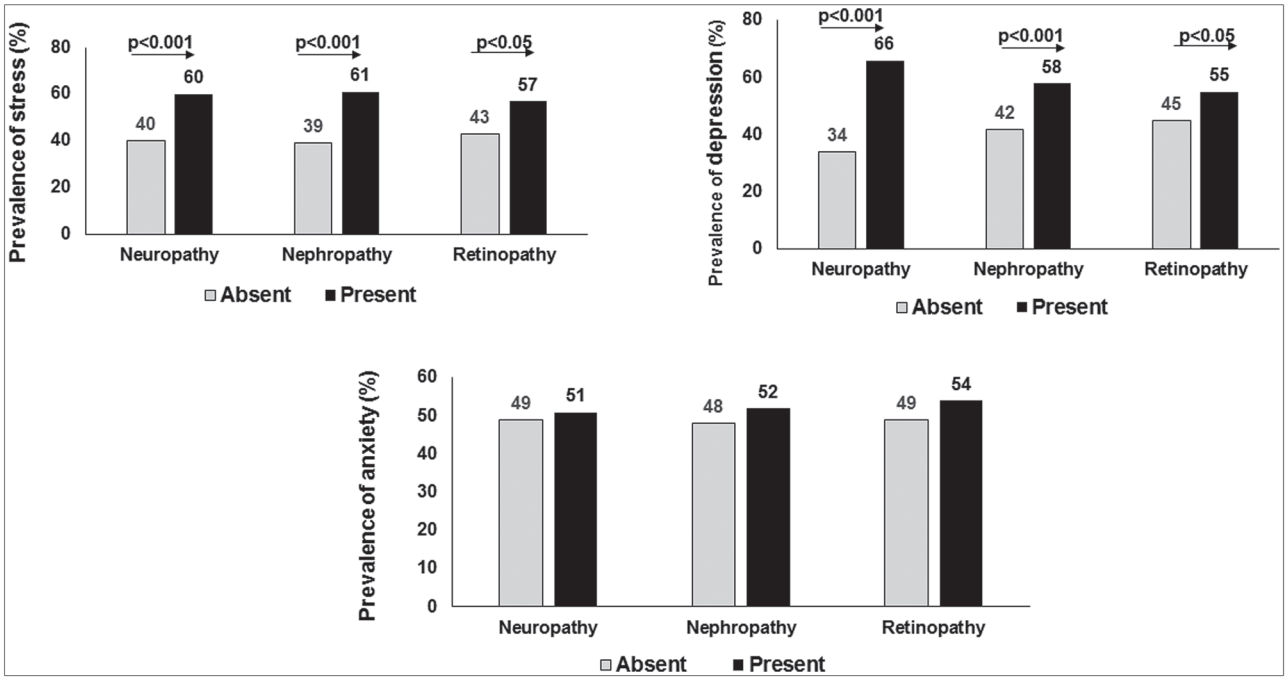

Figure 3: Prevalence of stress, depression and anxiety in relation to microvascular complications

Table 2: Association of Depression, Stress and Anxiety with microvascular complications of diabetes

		Stress				Depression				Anxiety			
		OR	95% C.I.for EXP(B)		p value	OR	95% C.I.for EXP(B)		p value	OR	95% C.I.for EXP(B		p value
			Lower	Upper			Lower	Upper			Lower	Upper	
Retinopathy	Model-1	2.66	1.65	4.28	0.000	2.01	1.19	3.40	0.009	1.01	0.62	1.64	0.967
	Model-2	3.27	1.97	5.44	0.000	2.53	1.45	4.41	0.001	1.22	0.72	2.04	0.447
	Model-3	3.13	1.75	5.58	0.000	1.97	1.04	3.73	0.037	1.30	0.72	2.35	0.380
Neuropathy	Model-1	1.61	1.02	2.55	0.038	1.89	1.12	3.17	0.016	1.09	0.68	1.75	0.700
	Model-2	2.80	1.63	4.83	0.000	3.29	1.77	6.13	0.000	2.22	1.25	3.94	0.006
	Model-3	2.50	1.42	4.39	0.001	2.77	1.45	5.30	0.002	2.37	1.31	4.29	0.004
Nephropathy	Model-1	2.23	1.33	3.74	0.002	3.02	1.74	5.26	0.000	0.98	0.57	1.68	0.962
	Model-2	2.28	1.34	3.86	0.002	3.21	1.81	5.69	0.000	0.97	0.56	1.71	0.941
	Model-3	2.06	1.19	3.56	0.010	2.59	1.42	4.70	0.002	0.99	0.55	1.76	0.972

Model-1: Unadjusted, Model-2: Adjusted for age and gender, Model-3: Model 2+HbA1c and duration of diabetes

of not only stress but also anxiety and depression.[21,31,32] We confirm these findings. However, in the absence of complications, poor 'perceived' glycaemic control increased the risk of depression and anxiety.[33] There appears to be a bi-directional relationship between depression and stress and microvascular complications. Thus, those suffering from depression and stress were more likely to develop complications, and conversely, the presence of microvascular complications results in increased depression levels as well as stress.[34,35]

A meta-analysis looking at the association between neuropathy and depression has shown that individuals with neuropathy were twice as likely to suffer from depression.[36] Those suffering from neuropathy showed a composite score of 51.4% for anxiety and depression, while 26% had overlapping symptoms of both.[37] Retinopathy and nephropathy were both predictors for depression in a study done in India[38] and our study confirms these findings. Neuropathic pain leads to debilitation and depression. Perception of pain is greater in those with high-stress levels, while pain itself causes increased stress.[39,40] A recent study also showed neuropathy was significantly associated with depression.[41]

In the Chennai Urban Rural Epidemiological Study (CURES), we earlier showed a significant association between depression with neuropathy (28% with neuropathy vs 16% without neuropathy), retinopathy (35% with retinopathy vs 21% without retinopathy), and nephropathy (35% with nephropathy vs 25% without nephropathy) compared to those without complications.[42] Neuropathy and nephropathy were strong predictors of depression and these findings are similar to this study.[31] The Fremantle

study also showed that patients suffering from depression had a higher prevalence of nephropathy.[43]

In an earlier study, there was an association between severe diabetic retinopathy and depression.[44] Individuals suffering from sight-threatening retinopathy showed severe stress which also affected interpersonal relationships.[45] Although visual impairment which interferes with daily activities leads to mental stress, one theory suggests that stress itself maybe a causative factor for the onset and progression of retinopathy due to dysregulation in the brain, eye, and autonomic system, as a result of the activation of stress hormones.[46]

Since stress may pose a challenge to self -care and glycaemic control, it could also be a predictor and end result of diabetes complications.[34,47] Therefore, identification of high-risk patients with poor glycemic control and emotional distress could help avoid complications and improve quality of life. Assessment of mental health disorders among those with complications should be given priority.[48] A collaborative care model combining screening and treatment of depression in several diabetes centres showed a significant reduction of depressive symptoms and improvement in cardiometabolic markers after simultaneous treatment of depression and diabetes.[49]

One of the strengths of this study is that it focuses on the impact of diabetic complications on three common mental health disorders, stress, depression, and anxiety.

One of the limitations of the study is that being cross-sectional; a cause-effect relationship could not be established. Generalizability to the whole population was also not possible as the participants were drawn from a single tertiary diabetes center. Other limitations are that we do not have a history of depression in the family or of pre-morbid depression, before the onset of diabetes.

From the study, it seems prudent to suggest that regular assessment of mental health disorders, particularly in those with diabetes complications is necessary. Early psychosocial interventions may help to reduce the prevalence of these mental health disorders in those with diabetes.

Author contributors

JV, VM, RMA, RP, and TAP were responsible for the study design and execution of the entire project. TAP, UV, and SJ helped in data collection, statistical analysis, and providing valuable input. JV wrote the first draft of the paper and carried out the analysis. VM, RP, SP and ST helped in analysis and interpretation of data, and revised all drafts of the article. All authors approved and read the manuscript.

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Conflicts of interest

The authors have no conflict of interest to disclose.

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