Risk factors of depression in type 2 diabetes mellitus with lower extremity arterial disease in China

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Research

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Abstract

Background

We aimed to evaluate the prevalence and risk factors of depression in type 2 diabetes mellitus with lower extremity arterial disease.

Methods:

Four hundred and forty-one patients with type 2 diabetes mellitus were recruited from Peking University of International Hospital. All patients completed the Self-rating Depression Scale, which includes 20 items, using a 4-point scale. Univariable and multivariable logistic regression was conducted to investigate risk factors of depression in patients with lower extremity arterial disease.

Results:

The prevalence of depression in lower extremity arterial disease group was significantly higher than that in non-lower extremity arterial disease group (25% vs 16%, P = 0.018). In lower extremity arterial disease group (n = 215), depression score (46.18 ± 7.38 vs 44.03 ± 6.53, P = 0.003) significantly increased compared with non-lower extremity arterial disease group (n = 226). Compared with male depressive patients, the proportion of female depressive patients (38% vs 15%, P = 0.003) was significantly higher in lower extremity arterial disease group. The depression score of female depressive patients (57.83 ± 3.29 vs 55.26 ± 1.59, P = 0.003) was significantly higher than that of male depressive patients. An increased risk of depression in female patients (crude OR: 2.50, 95% CI: 1.38–4.54, P = 0.003; adjusted OR: 2.34, 95% CI: 1.26–4.36, P = 0.008) and in patients with low body mass index (crude OR: 0.88, 95% CI: 0.80–0.96, P = 0.005; adjusted OR: 0.89, 95% CI: 0.81–0.97, P = 0.011) was detected.

Conclusion:

Both low body mass index and female are risk factors for depression.

1 Background

Lower extremity arterial disease (LEAD), a primary manifestation of peripheral arterial disease (PAD), is affecting over 200 million people worldwide[^1]. According to the prevention of progression of arterial disease and diabetes (POPADAD) study, 20.1% of ≥ 40-year-old patients with diabetes were associated symptoms exhibited PAD[^2]. PAD comprises a range of progressive vascular syndromes characterized by lower extremity pain and impaired walking ability, and is a frequent cause of amputations. PAD is also an independent predictor of cardiovascular and cerebrovascular ischemic events, affecting both the quality and expectancy of life. However, given that a large number of PAD patients are asymptomatic, it is assumed that more subjects with diabetes exhibit PAD. An insidious asymptomatic period typically makes PAD an under-diagnosed condition. The prevalence of LEAD was 21.2% in Chinese patients with diabetes older than 50 years[^3]. Diabetes mellitus is an established risk factor for LEAD[^1], and the
prognosis of LEAD in patients with diabetes mellitus is worse than that for those without diabetes, with greater susceptibility to stenosis and occlusion\cite{4}. LEAD is also associated with cardiovascular events, healing failure, amputation, and an increased risk of premature mortality.

Depression, which is recognized as a major chronic disease, has become the third most important cause of disability in the world\cite{5}. Depression is approximately twice as common in patients with type 1 or type 2 diabetes mellitus (T2DM) as in the general population, and is associated with poor outcomes\cite{6}. Depression typically presents in early adult life and is linked to self-neglect and low self-esteem, which might increase risk of unhealthy lifestyles and, in turn, increase risk of type 2 diabetes\cite{7}. In addition, depression is a strong risk factor for macrovascular complications in patients with type 2 diabetes. People with PAD have a higher prevalence of depressive symptoms than people without PAD. Moreover, depressive symptoms are associated with increased all-cause and cardiovascular mortality in PAD.

To date, the prevalence of depression in T2DM patients with LEAD and the risk factors related with depression are less understood. In this study, we aimed to evaluate the prevalence of depression in Chinese T2DM patients with LEAD. We further sought to identify factors that may influence the LEAD-depression association.

## 2 Methods

### 2.1 Patients and study design

The patients were recruited from both outpatients and inpatients of Peking University of International Hospital from June 2016 to January 2017. Patients were eligible if they were aged 50 years or older, had a well documented diagnosis of T2DM. Patients with type 1 diabetes or gestational diabetes were excluded from this study. This research protocol was approved by the Ethics Committee of Peking University International Hospital, and the study was conducted in accordance with the Good Clinical Practice and the International Conference on Harmonization guidelines. All participants provided written informed consent at the initial enrollment.

### 2.2 The Ankle-Brachial index (ABI) measurement

Ankle and brachial systolic blood pressures were measured by a trained physician at each site using a standardized protocol and equipment (Omron VP-1000, Omron Inc, China). Four blood pressure cuffs were applied as well as two ECG sensors to the inner aspect of wrists, and appropriate gel sensor pads were used. The physicians placed the phonocardiogram over the patients’ heart (left of the sternum, second intercostal space). The ABI results were available on printed report automatically and categorized as abnormal (ABI ≤ 0.90), borderline (ABI 0.91–0.99), normal (1.00–1.30), or non-compressible (ABI > 1.30). LEAD was defined by an ABI ≤ 0.90. Patients with non-compressible vessels (ABI > 1.30) and abnormal findings on an additional anatomic assessment (Duplex ultrasound) were also considered as having a comorbidity with LEAD. Patients with borderline or normal ABI also could be diagnosed with LEAD if they had claudication symptoms and an abnormal ultrasound assessment\cite{8}. 

Page 3/13
2.3 Depression score

The Self-rating Depression Scale (SDS) is the scale for assessing depression, which includes 20 problems respectively, using a 4-point scale ranging from 1 (none, or a little of the time) to 4 (most, or all of the time) \[^9\]. The statistical score of all questions were calculated after completion of the answers. Depression can be diagnosed if the score is greater than or equal to 53.

2.4 Statistical analysis

SAS version 9.4 was used for statistical analysis. Data were expressed as mean ± standard deviation or median (p25, p75). Statistical analysis included independent t-test, Mann-Whitney U test, chi-square test, univariable and multivariate logistic regression. P < 0.05 was considered statistically significant.

3 Results

3.1 Baseline data of patients

A total of 441 T2DM were recruited into our study. According to the diagnostic criteria, a summary of the participating patients’ characteristics in subgroups divided by LEAD (n = 215) and non LEAD (n = 226) is shown in Table 1. LEAD group had longer duration of diabetes, and high level of glycated hemoglobin A1C (HbA1C) compared with non LEAD group. In LEAD group, the disorder of blood lipid metabolism was more serious. No significant differences were detected with respect to other baseline clinical data and laboratory findings between the two groups. (Table 1)
Table 1
Baseline characteristics of T2DM patients with LEAD and non LEAD

<table>
<thead>
<tr>
<th>parameter</th>
<th>LEAD(n = 215)</th>
<th>non LEAD(n = 226)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n(%)</td>
<td>123(57%)</td>
<td>105(46%)</td>
<td>0.028</td>
</tr>
<tr>
<td>Age</td>
<td>63.38 ± 10.54</td>
<td>63.23 ± 6.86</td>
<td>0.858</td>
</tr>
<tr>
<td>Duration(year)</td>
<td>11.06 ± 8.82</td>
<td>8.61 ± 6.98</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI(kg/m²)</td>
<td>25.50 ± 3.69</td>
<td>25.15 ± 3.37</td>
<td>0.296</td>
</tr>
<tr>
<td>SBP(mmHg)</td>
<td>134.40 ± 16.48</td>
<td>133.00 ± 16.91</td>
<td>0.367</td>
</tr>
<tr>
<td>DBP(mmHg)</td>
<td>80.10 ± 10.52</td>
<td>76.91 ± 8.67</td>
<td>0.001</td>
</tr>
<tr>
<td>FBG(mmol/L)</td>
<td>8.29 ± 3.40</td>
<td>8.44 ± 2.83</td>
<td>0.632</td>
</tr>
<tr>
<td>HbAlc(%)</td>
<td>8.31 ± 4.33</td>
<td>7.38 ± 1.43</td>
<td>0.002</td>
</tr>
<tr>
<td>ALT(U/L)</td>
<td>23.75 ± 16.46</td>
<td>24.19 ± 15.92</td>
<td>0.776</td>
</tr>
<tr>
<td>AST(U/L)</td>
<td>22.75 ± 16.10</td>
<td>22.98 ± 13.00</td>
<td>0.868</td>
</tr>
<tr>
<td>Creatinine(µmol/L)</td>
<td>67.78 ± 23.24</td>
<td>66.08 ± 21.64</td>
<td>0.428</td>
</tr>
<tr>
<td>Cholesterol(mmol/L)</td>
<td>4.05 ± 1.37</td>
<td>4.45 ± 1.01</td>
<td>0.000</td>
</tr>
<tr>
<td>Triglyceride(mmol/L)</td>
<td>1.95 ± 1.52</td>
<td>1.89 ± 1.32</td>
<td>0.641</td>
</tr>
<tr>
<td>HDL-C(mmol/L)</td>
<td>1.04 ± 0.29</td>
<td>1.32 ± 2.03</td>
<td>0.047</td>
</tr>
<tr>
<td>LDL-C(mmol/L)</td>
<td>2.53 ± 0.87</td>
<td>2.81 ± 2.31</td>
<td>0.096</td>
</tr>
<tr>
<td>Depression score</td>
<td>46.18 ± 7.38</td>
<td>44.03 ± 6.53</td>
<td>0.003</td>
</tr>
<tr>
<td>Depression rate(%)</td>
<td>25</td>
<td>16</td>
<td>0.018</td>
</tr>
</tbody>
</table>

Abbreviations: LEAD: lower extremity arterial disease; BMI: body mass index; WHR: waist hip ratio; SBP: systolic blood pressure; DBP: diastolic blood pressure; FBG: fasting blood glucose; HbA1c: haemoglobin A1C; ALT: alanine aminotransferase; AST: aspartate aminotransferase; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol.

3.2 Prevalence of depression and depression score

The prevalence of depression in LEAD group was significantly higher than that in non-LEAD group(25% vs 16%, \(P = 0.018\)) (Fig. 1A). In LEAD group, depression score significantly increased compared with non LEAD group(46.18 ± 7.38 vs 44.03 ± 6.53, \(P = 0.003\)) (Fig. 1B).

3.3 Baseline data of patients with and without depression in LEAD group
Compared with male patients with depression, the proportion of female patients (38% vs 15%, \( P = 0.003 \)) with depression was significantly higher. The body mass index (BMI) of patients with depression was significantly lower than that of patients without depression (24.50 ± 3.29 in patients with depression and 25.84 ± 3.76 in patients without depression, \( P = 0.021 \)) (Table 2). The depression score of female with depression (57.83 ± 3.29 vs 55.26 ± 1.59, \( P = 0.003 \)) was significantly higher than that of male with depression (Table 3).

Table 2
Baseline characteristics of patients with and without depression in LEAD group

<table>
<thead>
<tr>
<th>parameter</th>
<th>depression</th>
<th>non depression</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/Female</td>
<td>19/35</td>
<td>104/57</td>
<td>0.003</td>
</tr>
<tr>
<td>Age</td>
<td>65.65 ± 9.65</td>
<td>62.62 ± 10.74</td>
<td>0.068</td>
</tr>
<tr>
<td>Duration(year)</td>
<td>11.87 ± 8.62</td>
<td>10.79 ± 8.90</td>
<td>0.439</td>
</tr>
<tr>
<td>BMI(kg/m²)</td>
<td>24.50 ± 3.29</td>
<td>25.84 ± 3.76</td>
<td>0.021</td>
</tr>
<tr>
<td>SBP(mmHg)</td>
<td>132.00 ± 17.74</td>
<td>135.20 ± 16.00</td>
<td>0.211</td>
</tr>
<tr>
<td>DBP(mmHg)</td>
<td>78.65 ± 10.79</td>
<td>80.58 ± 10.41</td>
<td>0.243</td>
</tr>
<tr>
<td>FBG(mmol/L)</td>
<td>7.96 ± 3.14</td>
<td>8.41 ± 3.48</td>
<td>0.410</td>
</tr>
<tr>
<td>HbA1c(%)</td>
<td>8.01 ± 1.92</td>
<td>8.41 ± 4.88</td>
<td>0.555</td>
</tr>
<tr>
<td>ALT(U/L)</td>
<td>22.50 ± 12.35</td>
<td>24.17 ± 17.64</td>
<td>0.521</td>
</tr>
<tr>
<td>AST(U/L)</td>
<td>22.94 ± 13.24</td>
<td>22.69 ± 16.98</td>
<td>0.920</td>
</tr>
<tr>
<td>Creatinine(µmol/L)</td>
<td>67.87 ± 31.70</td>
<td>67.75 ± 19.74</td>
<td>0.974</td>
</tr>
<tr>
<td>Cholesterol(mmol/L)</td>
<td>4.11 ± 1.32</td>
<td>4.03 ± 1.39</td>
<td>0.704</td>
</tr>
<tr>
<td>Triglyceride(mmol/L)</td>
<td>1.69 ± 1.37</td>
<td>2.04 ± 1.57</td>
<td>0.147</td>
</tr>
<tr>
<td>HDL-C(mmol/L)</td>
<td>1.08 ± 0.27</td>
<td>1.03 ± 0.30</td>
<td>0.279</td>
</tr>
<tr>
<td>LDL-C(mmol/L)</td>
<td>2.54 ± 1.03</td>
<td>2.53 ± 0.81</td>
<td>0.922</td>
</tr>
</tbody>
</table>

Abbreviations: LEAD: lower extremity arterial disease; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; FBG: fasting blood glucose; HbA1c: haemoglobin A1c; ALT: alanine aminotransferase; AST: aspartate aminotransferase; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol.
### 3.4 Odd ratio of depression for study outcomes

In univariable analysis, both gender (Odd Ratio (OR) = 2.50, 95% confidence interval (CI): 1.38–4.54, \( P = 0.003 \)) and BMI (OR = 0.88, 95% CI: 0.80–0.96, \( P = 0.005 \)) showed increased risk of depression, and age, duration, fasting blood glucose (FBG) and HbA1c were not associated with depression in LEAD group. Multivariable logistic regression indicated that gender (adjusted OR = 2.34, 95% CI 1.26–4.36, \( P = 0.008 \)) and BMI (adjusted OR = 0.89, 95% CI 0.81–0.97, \( P = 0.011 \)) remained significantly associated with the risk of depression in LEAD group, adjusting for age and duration. (Fig. 2)

### 4 Discussion

Among 441 patients with T2DM, we found that 25% of LEAD participants and 16% of non-LEAD participants met criteria for depression at baseline in our study. The results of multivariate analysis showed that only gender and BMI remained significantly associated with depression in LEAD group.

Our findings are consistent with prior study that people with PAD have a higher prevalence of depressive symptoms than people without PAD. The prevalence of depression among PAD patients is comparable to that found in the coronary artery disease patients\(^\text{[10]}\). Treatment for PAD emphasize improving quality of life and decreasing the risk of new cardiovascular disease events, mainly through pharmacotherapy and revascularization procedures\(^\text{[11]}\). Recently in a study of 797 consecutive patients undergoing peripheral vascular intervention across 33 Veterans Affairs centers, depressed patients had higher rates of non-fatal cardiovascular events compared to patients without depression\(^\text{[12]}\). In addition to increasing the risk of PAD, depression also appears to impact the functional status and symptoms of patients with PAD. There is evidence to suggest that depression exerts a negative influence on walking ability and physical function independently of PAD. Some reports indicated that among patients with PAD, those with depression have worse functional outcomes, greater need for revascularization, poorer quality of life outcomes following revascularization, and higher risk for adverse events after revascularization\(^\text{[13–15]}\). Two studies reported that depression has a close relationship with worse peripheral circulation in legs and less improvement in health status 1 year after undergoing a peripheral endovascular revascularization, respectively\(^\text{[15,16]}\). Cardiac research has also reported an association between depression and worse treatment outcomes, observing that depression among coronary artery disease (CAD) patients is correlated with decreased medication adherence, worse surgical outcomes, and poorer overall prognosis compared to non-depressed patients\(^\text{[17,18]}\). Significant improvements in both
depressive symptoms and vascular treatment outcomes among CAD have been proved in previous studies\textsuperscript{[19]}.

In the logistic regression we found that BMI and female gender were independent risk factors for depressive symptoms, which were in line with previous studies\textsuperscript{[20–23]}. Luo et al\textsuperscript{[20]} reported that the relationship between weight and depressive symptoms is negatively associated among females and males within the normal BMI range. Zhou et al\textsuperscript{[23]} found that there was a negative association between BMI and depressive symptoms for males. The study on BMI and depression, including 6224 males and 6883 females, indicated that the underweight subjects were more likely to be depressed compared with the normal weight people, whereas overweight and obese men and women were less likely to be depressed than people of normal weight\textsuperscript{[24]}. In a prospective cohort study of 1024 patients, depression was more common in women with PAD compared to those without PAD\textsuperscript{[25]}. It is possible that women and men have different risk factors for PAD, and that depression or other psychosocial factors might be more important in women\textsuperscript{[25]}. Women had a higher psychosocial burden than men and women in general are at a greater risk of depression than men\textsuperscript{[26, 27]}. Brostow et al\textsuperscript{[10]} found that several factors associated with PAD and depression, namely sex, age, race/ethnicity, disease severity and physical function. In addition to increasing the risk of PAD, depression also appears to impact the functional status and symptoms of patients with PAD. Depressive symptoms was associated with functional impairment\textsuperscript{[28]}, greater postoperative disability\textsuperscript{[29]}, and higher mortality rates in patients treated with percutaneous coronary intervention\textsuperscript{[30]}.

In such settings, assessing depressive symptoms is very important for T2DM patients with LEAD. A better understanding of patients’ psychological feature might identify risk factors that can be addressed to mitigate both patients’ depressive symptoms and the risk of revascularization. Future intervention studies should investigate whether mental health-focused interventions would improve LEAD-related outcomes.

5 Conclusion

Our study showed that T2DM patients with LEAD have a high prevalence of depression in China. Both low BMI and female were risk factors for depression in T2DM patients with LEAD.

Abbreviations

LEAD
lower extremity arterial disease
PAD
peripheral arterial disease
POPADAD
prevention of progression of arterial disease and diabetes
T2DM
type 2 diabetes mellitus
ABI
ankle-brachial index
SDS
self-rating depression scale
HbA1C
glycated hemoglobin A1C
BMI
body mass index
FBG
fasting blood glucose
CAD
coronary artery disease

Declarations

Ethics approval and consent to participate

This research protocol was approved by the Ethics Committee of Peking University International Hospital, and the study was conducted in accordance with the Good Clinical Practice and the International Conference on Harmonization guidelines. All participants provided written informed consent at the initial enrollment.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author contributions

Conceptualization: Linong Ji. Methodology: Linong Ji, Xiaomei Zhang, Sanbao Chai. Formal Analysis: Sanbao Chai, Xiaomei Zhang. Investigation: Sanbao Chai, Ning Yuan, Yufang Liu, Sixu, and Jianbin Sun. Data Curation: Sanbao Chai, Xiaomei Zhang. Writing-Original Draft Preparation: Sanbao Chai. Writing-Review & Editing: Sanbao Chai, Xiaomei Zhang. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

References


**Figures**

A

![Graph A](image)

B

![Graph B](image)

**Figure 1**
Prevalence of depression and depression scores in T2DM with LEAD and non-LEAD Abbreviations: A: prevalence of depression; B: depression scores; T2DM: type 2 diabetes mellitus; LEAD: lower extremity arterial disease; *p<0.05, **p<0.01 vs non LEAD

Figure 2

Odd ratio of depression for study outcomes in T2DM with LEAD Abbreviations: BMI: body mass index; FBG: fasting blood glucose; HbA1c: hemoglobin A1C; T2DM: type 2 diabetes mellitus; LEAD: lower extremity arterial disease