Diabetic Peripheral Neuropathy and Depression: Dancing with Wolves? - Mini-Review and Commentary on Alghafri et al. “Screening for depressive symptoms amongst patients with diabetic peripheral neuropathy”

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Abstract

The co-existence of diabetic peripheral neuropathy (DPN) and depression in subjects with diabetes is being increasingly recognized. The interaction of these two serious comorbidities may increase morbidity and mortality. An emerging thought is that persistent depression, along with stroke and cognitive dysfunction, may represent a cluster of potential microvascular injuries affecting the brain, which shares a common risk factor with DPN. Current evidence highlights metabolic and clinical covariates, which may interact in subjects with DPN and depression. However, there is a lack of rigorous enquiry into the confounding effect of cognitive dysfunction and vascular brain disease. Furthermore, high-quality longitudinal studies exploring the direct impact of these comorbidities on diabetes course and on the progression of the comorbidities themselves are lacking. Improved insights into comorbid DPN and depression may help to improve screening for and treatment of both these conditions.

Keywords: comorbidities · complications · depression · diabetes mellitus · diabetic neuropathy

1. Introduction

The association between diabetes mellitus and depression has long been recognized, particularly in type 2 diabetes (T2D). A diagnosis of T2D may increase the risk of incident clinical depression by approximately 25-52%, after adjusting for covariates and comorbidities [1, 2]. Indeed, a recent meta-analysis of epidemiological studies concluded that subjects with T2D had a 2-fold increased risk of major depressive disorder [3]. Conversely, individuals with depression exhibited an up to 1.5 times increased risk of developing T2D [4]. Likewise, depression in type 1 diabetes (T1D) is 3 times more prevalent than in the general population [5], with adolescents and younger adults with T1D tending to have disproportionately higher risk [6]. Importantly, comorbid diabetes and depression have been confirmed to increase the risk of mortality [7, 8].

In T2D, depression is linked with poor glycemic control and clinically significant micro- and macrovascular disease [8, 9]. In T1D, depression is associated with poor treatment adherence, higher diabetes distress scores [10], suboptimal glycemic control, and recurrent diabetic ketoacidosis [11, 12]. Diabetes-specific risk factors, such as micro- and macrovascular complications [13, 14], act in concert with traditional risk factors for depression, including female gender, lower levels of education, and psychosocial factors (e.g. childhood trauma and social deprivation), thereby creating a complex web of interactions [15].

2. Diabetic peripheral neuropathy and depression

Diabetic peripheral neuropathy (DPN) is a common complication of diabetes, affecting up to 50% of subjects with diabetes over their lifetime [16, 17]. Older age,
longer diabetes duration, poor glycemic control, height, male gender, hypertension, dyslipidemia, and certain ethnicities represent the major risk factors for DPN [16, 17]. Sensory-predominant, length-dependent distal symmetrical sensorimotor neuropathy is the most common presentation, with an insidious onset and gradual clinical progression [18]. DPN can negatively impact on physical function secondary to neuropathic pain, Charcot osteoarthropathy, unsteadiness, and lack of postural control [18, 19]. However, when severe DPN with loss of protective sensation (LOPS) develops, the foot becomes particularly vulnerable to ulcerations, and amputations are its ultimate risk [16-19].

Given the high prevalence of both depression and DPN in combination, it is not surprising that these two comorbidities are closely associated. Clinical measures of DPN, such as the neuropathy disability score (NDS) and the vibration perception threshold (VPT) have been shown to be independently associated with the Hospital Anxiety and Depression Scale (HADS), a 7-item scale measuring the absence of positive affect and pleasure [19]. Recently, an association between another depression screening instrument, the Patient Health Questionnaire 9 (PHQ-9), and sudomotor dysfunction has been reported [20]. Symptoms of DPN, including reduced foot sensation, pain, and unsteadiness, are also related to depression, with more severe symptoms being associated with more marked depression scores [5, 19]. These observations have been confirmed in a recent large meta-analysis demonstrating that depression was independently associated with DPN (p = 0.002) with a moderate effect size (r = 0.28) [21].

3. The impact of the study by Alghafri et al.

The study by Alghafri et al. is of particular interest in the context of an association between DPN and depression [22]. Subjects with diabetes were examined for DPN and completed the PHQ-9 depression screening questionnaire. Diagnosis of DPN was based on abnormal 10g monofilament test or 128 Hz tuning test [22]. Subjects with DPN exhibited significantly higher mean PHQ-9 scores than those without DPN (6.09 ± 4.80 vs. 2.24 ± 2.63, p < 0.0001) [22]. Furthermore, a greater proportion of subjects with DPN had higher severity of depression (PHQ-9 ≥ 10) than those without DPN (26.6% vs. 2.0%) [22]. Interestingly, subjects with a history of diabetic foot ulcer (DFU) or peripheral arterial disease were excluded, which is an important strength of the study [22]. This new study adds to the growing appreciation that DPN and depression are closely associated.

Nevertheless, there are a few important limitations in the study by Alghafri et al. [22]. Firstly, the study sample was very small. Secondly, as duly acknowledged by the authors, the diagnostic criteria for DPN, in particular the 10g monofilament, are suitable to detect advanced DPN with LOPS, but are not sensitive enough for milder, incipient DPN [22]. To detect the latter reliably, clinical examination scores (notably the Neuropathy Disability Score or the Toronto Clinical Neuropathy Score) would have been more suitable [16, 18]. Admittedly, there is a lack of uniformity in the diagnostic criteria used for DPN in the studies evaluating both DPN and depression, making it difficult to compare them. Thirdly, the mean age of participants was 77 years [22]. While the diagnostic accuracy of PHQ-9 in the elderly has been confirmed, measures of DPN such as those used in the study by Alghafri et al. are intrinsically and inversely related to age and, therefore, less reliable in such old populations [16, 18]. Finally, the authors did not adjust for confounding factors, especially co-existent neuropathic pain [23].

A recent systematic review of comorbid DPN and depression identified a triad of clinical characteristics in such individuals: Older age (often >65 years of age), frailty (often with neuropathic pain and other diabetes complications), and poor glycemic control despite insulin treatment [24]. The presence of depression does not simply increase the risk of incident neuropathic DFU by two-fold [25, 26], it even negatively impacts the clinical outcome and may increase mortality [27]. An important message from the study by Alghafri et al. is that it reinforces the clinical need to screen for depression in subjects with LOPS [22]. This may also have economic ramifications. Indeed, it is estimated that subjects with DPN and depression have 50% higher healthcare costs than those with DPN only [28].

4. Association of cognitive dysfunction and vascular brain disease

One emerging concept is the recognition that depression, stroke, and cognitive dysfunction may be representations of cerebral microvascular disease [29]. Pivotal risk factors for the latter include hyperglycemia, insulin resistance, dyslipidemia, and hypertension [29], which are also the main risk factors for DPN [16-18]. Indeed, cognitive dysfunction is commonly present in subjects with DFU [30], who, in turn, frequently have DPN. Therefore, a major limitation in the current literature on comorbid DPN and depression is the lack of information on cognitive dysfunction and vascular brain disease.

5. Clinical practice for diabetic peripheral neuropathy and depression

At present, there are no specific screening or treatment recommendations for depression in DPN. In a recommendation paper focusing on primary care physicians, the American Diabetes Association has emphasized that all subjects with diabetes and DPN should be regularly screened for depression [31]. This is in accordance with evidence from interventional trials that treating depression may lead to simultaneous improvement in both diabetes and depression [32]. Nonetheless, we certainly need to know more about the clinical and biochemical characteristics as well as the sociodemographic factors in comorbid DPN and depression. New information should come from large and adequately powered prospective cohort studies. Last but not least, we need a consensus on the diagnostic...
criteria of DPN and depression to interpret reliably and compare future interventional trials.

6. Inhibition of RAS in diabetic nephropathy

In conclusion, DPN may co-exist with depression and vice versa. It is evident that the two conditions share common risk factors, mainly those classically associated with cardiovascular disease in diabetes. However, they also share certain clinical characteristics, in particular older age, frailty, neuropathic pain, and diabetes complications. While this constellation may be considered the equivalent of “birds of the same feather flocking together” [33], its clinical impact can be as fierce as a wolf pack. In everyday practice, subjects with LOPS should be evaluated for depression early, with the aim of avoiding resultant impoverishment in the quality of life [17, 25, 27, 34].

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References
1. Pan A, Lucas M, Sun Q, van Dam RM, Franco OH, Manson JE, Willett WC, Ascherio A, Hu FB. Bidirectional association between depression and type 2 diabetes mellitus in women. Arch Intern Med 2010. 170(21):1884-1891.
2. Golden SH, Lazo M, Carnethon M, Bertoni AG, Schreiner PJ, Diez Roux AV, Lee HB, Lyketsos C. Examining a bidirectional association between depressive symptoms and diabetes. JAMA 2008. 299(23):2751-2759.
3. Wang F, Wang S, Zong QQ, Zhang Q, Ng CH, Ungvari GS, Xiang YT. Prevalence of comorbid major depressive disorder in Type 2 diabetes: a meta-analysis of comparative and epidemiological studies. Diabet Med 2019. 36(8):961-969.
4. van Sloten T, Schram M. Understanding depression in type 2 diabetes: a biological approach in observational studies. F1000Res 2018. 7:F1000 Faculty Rev-1283.
5. Barnard KD, Skinner TC, Peveler R. The prevalence of comorbid depression in adults with Type 1 diabetes: systematic literature review. Diabet Med 2006. 23:445-448.
6. Hood KK, Huestis S, Maher A, Butler D, Volkening L, Lafel LM. Depressive symptoms in children and adolescents with type 1 diabetes. Association with diabetes-specific characteristics. Diabetes Care 2006. 29(6):1389-1391.
7. Petrak F, Baumeister H, Skinner TC, Brown A, Holt RI. Depression and diabetes: treatment and health-care delivery. Lancet Diabetes Endocrinol 2015. 3(6):472-485.
8. Darwisch L, Beroncal E, Sison MV, Swordfager W. Depression in people with type 2 diabetes: current perspectives. Diabetes Metab Syndr Obes 2018. 11:333-343.
9. Lin EH, Rutter CM, Katon W, Heckbert SR, Ciechanowski P, Oliver MM, Ludman EJ, Young BA, Williams LH, McCulloch DK, Vor Koff R. Depression and advanced complications of diabetes: a prospective cohort study. Diabetes Care 2010. 33(2):264-269.
10. Snoek FJ, Bremmer MA, Hermans N. Constructs of depression and distress in diabetes: time for an appraisal. Lancet Diabetes Endocrinol 2015. 3:450-460.
11. Ciechanowski PS, Katon WJ, Russo JE. Depression and diabetes: impact of depressive symptoms on adherence, function, and costs. Arch Intern Med 2000. 160:3278-3285.
12. McGrady ME, Lafel L, Drotar D, Hood KK. Depressive symptoms and glycemic control in adolescents with type 1 diabetes. mediational role of blood glucose monitoring. Diabetes Care 2009. 32(5):804-806.
13. Peyrot M, Rubin RR. Levels and risks of depression and anxiety symptomatology among diabetic adults. Diabetes Care 1997. 20:585-590.
14. Holt RI, de Groot M, Golden SH. Diabetes and depression. Curr Diab Rep 2014. 14:491.
15. Ciel B, Pantoon U, Willaing I, Holt RI. Diabetes and depression in Denmark 1996–2010: national data stratified by occupational status and annual income. Diabet Med 2017. 34(1):108-114.
16. Papanas N, Ziegler D. Risk factors and comorbidities in diabetic neuropathy: an update 2015. Rev Diabet Stud 2015. 12:48-62.
17. Ziegler D, Papanas N, Vinik AI, Shaw JE. Epidemiology of polyneuropathy in diabetes and prediabetes. Handb Clin Neurol 2014. 1263-22.
18. Vas PR, Sharma S, Rayman G. Distal sensorimotor neuropathy: improvements in diagnosis. Rev Diabet Stud 2015. 12:29-47.
19. Vileikyte L, Leventhal H, Gonzalez JS, Peyrot M, Rubin RR, Ulbrecht JS, Garrow A, Waterman C, Cavanagh PR, Boulton AJ. Diabetic peripheral neuropathy and depressive symptoms: the association revisited. Diabetes Care 2005. 28(10):2378-2383.
20. Ji L, Zhang Y, Zhang Q, Zheng H, Sun W, Zhu X, Zhang S, Lu B, Su L, Shi H, et al. Self-reported depressive symptoms might be associated with sudomotor dysfunction in Chinese T2DM patients. Exp Clin Endocrinol Diabetes 2019. In press.
21. de Groot M, Anderson R, Freedland KE, Clouse RE, Lustman PJ. Association of depression and diabetes complications: a meta-analysis. Psychosom Med 2001. 63(4):619-630.
22. Alghafri RM, Gatt A, Formosa C. Screening for depressive symptoms amongst patients with diabetic peripheral neuropathy. Rev Diabet Stud 2020. In press.
23. D’Amato C, Morganti R, Greco C, Di Gennaro F, Cacciotti L, Longo S, Mataluni G, Lauro D, Marfìa GA, Spallone V. Diabetic peripheral neuropathic pain is a stronger predictor of depression than other diabetic complications and comorbidities. Diab Vasc Dis Res 2016. 13(6):418-428.
24. Zafeiri M, Tsiositou C, Kleinnaki Z, Manolopoulos P, Ioannidis I, Dimitriradis G. Clinical characteristics of patients with co-existent diabetic peripheral neuropathy and depression: a systematic review. Exp Clin Endocrinol Diabetes 2021. 129(2):77-85.
25. Iversen MM, Tell GS, Espenhaug B, Midtjøl K, Graue M, Rokne B, Berge LI, Østbye T. Is depression a risk factor for diabetic foot ulcers? 11-years follow-up of the Nord-Trøndelag Health Study (HUNT). J Diabetes Complications 2015. 29(1):20-25.
26. Williams LH, Rutter CM, Katon WJ, Reiber GE, Ciechanowski www.diabeticstudies.org

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P. Heckbert SR, Lin EH, Ludman EJ, Oliver MM, Young BA, Von Korff M. Depression and incident diabetic foot ulcers: a prospective cohort study. *A J Med* 2010. 123(8):748-54.e3.

27. Ismail K, Winkley K, Stahl D, Chalder T, Edmonds M. A cohort study of people with diabetes and their first foot ulcer: the role of depression on mortality. *Diabetes Care* 2007. 30(6):1473-1479.

28. Boulanger L, Zhao Y, Bao Y, Russell MW. A retrospective study on the impact of comorbid depression or anxiety on healthcare resource use and costs among diabetic neuropathy patients. *BMC Health Serv Res* 2009. 9:111.

29. van Sloten TT, Sedaghat S, Carnethon MR, Launer LJ, Stehouwer CD. Cerebral microvascular complications of type 2 diabetes: stroke, cognitive dysfunction, and depression. *Lancet Diabetes Endocrinol* 2020. 8(4):325-336.

30. Natovich R, Kushnir T, Harman-Boehm I, Margalit D, Siev-Ner I, Tsali Chin D, Volkov I, Givon S, Rubin-Ashe D, Cukierman-Yaffe T. Cognitive dysfunction: part and parcel of the diabetic foot. *Diabetes Care* 2016. 39(7):1202-1207.

31. American Diabetes Association. Standards of medical care in diabetes - abridged for primary care providers. *Clinical Diabetes* 2018. 36:14-37.

32. Atlantis E, Fahey P, Foster J. Collaborative care for comorbid depression and diabetes: a systematic review and meta-analysis. *BMJ Open* 2014. 4:e004706.

33. Vas PR, Papanas N. Depression and diabetic peripheral neuropathy: birds of a feather, but when do they flock together? *Exp Clin Endocrinol Diabetes* 2020. 128:347-349.

34. Ziegler D, Papanas N, Schnell O, Nguyen BD, Nguyen KT, Kulkrantrorn K, Deerochanawong C. Current concepts in the management of diabetic polyneuropathy. *J Diabetes Investig* 2020. In press.