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Relationship between diabetic neuropathy and occurrence of depression among diabetic patients

Piotr Dziemidok[1], Mariusz Dąbrowski[2], Marta Makara-Studzińska[3]

[1]Diabetology Department, Institute of Rural Health in Lublin
Head: dr n. med. P. Dziemidok

[2]Institute of Nursing and Health Sciences, Faculty of Medicine, University of Rzeszow
Head: Prof. dr hab. n. med. P. Januszewicz

[3]Department of Applied Psychology, Medical University of Lublin
Head: prof. dr hab. n. o zdr. M. Makara-Studzińska

Summary

Diabetes itself, by its nature, can aggravate the symptoms of depression. One of its main complications is peripheral diabetic neuropathy (PDN). Based on the literature the presence of the relationship between the PDN and depression is confirmed. The symptoms connected with instability while walking and reduction of everyday activities were the strongest predictors of the intensification of depression symptoms. The relationship between the neuropathic ulcers and depression is considered as ambiguous. Additional problems in diagnosis and evaluation is the polyetiologic character of the disease, damage to the nerve fibers of different thickness, variety of methods of the diagnosis and differences in the prevalence of diabetic neuropathy (26%–50%). The presence of the described differences may be connected with diagnostic methods and the fact of the modification of perceived symptoms such as pain by the depression itself. One of the results of difficulties in describing the relationships and diagnosis are problems, described in the literature, with the selection of patients requiring treatment of PDN.

Key words: depression, anxiety, diabetic neuropathy

Introduction

In Poland, as in other countries, the average life span is being extended. In Poland, according to the study NATPOL 2011, the average life span within the last 2 decades, has increased by 4 years. However, the source of this success is a growing awareness of problems related to an increase in prevalence of civilisation diseases, including

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type 2 diabetes. An increase in the number of cases of type 2 diabetes translates into a larger number of patients with diabetes complications, which is one of the major public health problems

Diabetes treatment is cost-consuming and aconsiderable part of these expenditures is associated with the necessity to treat the complications of diabetes, among which diabetic neuropathy is one of the most frequent and most costly complications [1].

Diabetic neuropathy is diagnosed with the presence of symptoms of dysfunction of the peripheral nervous system, after excluding other causes of this damage, e.g. alcohol abuse, vitamin B_{12} deficiency related with a chronic administration of metformin, demyelination diseases or uraemia [1, 2]. Metabolic control of diabetes, hyperlipidaemia, arterial hypertension, duration of diabetes, and a patient's height are closely related to the occurrence of diabetic neuropathy, while this relationship is less significant with respect to cigarette smoking and alcohol consumption [1].

Chronic hyperglycaemia is considered to be a pathophysiological basis of neuronal dysfunction and disorders in nerve conduction [3]. It leads to an activation of 4 mechanisms leading, among other things, to the following:

1. increased accumulation of sorbitol and fructose, leading to an increased osmotic pressure inside the neuron, and development of pseudohypoxia and decreased production of nitric oxide (activation of the polyol pathway) [3, 4];
2. activation of protein kinase C, or rather the group of 12 kinases which, by the activation of the PKC pathway and contraction of peripheral vessels, leads to cellular ischemia [5, 6];
3. activation of the hexosamine pathway, leading to pathological expression of the genes encoding plasminogen activator inhibitor type 1 (PAI-1), transforming growth factor type 1(TGF 1), and transforming growth factor type beta (TGF-β) [5–7];
4. activation of mechanisms leading to the formation of advanced glycation end products (AGE), and formation of irreversible connections in the mechanism of Amadori rearrangement [7, 8]. In consequence, an intensification of oxidative stress takes place (pathology of the polyol pathway decreases the amount of substances with antioxidative effect), the amount of reactive oxygen species (ROS) increases, and the enolysation of glucose occurs [6, 7].

Although hyperglycaemia is a triggering factor of neuronal dysfunction and impairment in nerve conduction, its importance and impact on clinical symptoms in the case of long-lasting diabetes and long-lasting metabolic decompensation seems to diminish and even disappear [9].

The prevalence of DN (diabetic neuropathy) among diabetic patients is estimated to be 30%–50% [10, 11]. In everyday practice, it may be presumed that the majority of patients with long-lasting type 2 diabetes have sensory disorders which may be equivalent to the diagnostic criteria of DN. In many cases the symptoms of DN were present already at the moment of diagnosing diabetes [12]. Patients with diabetic neuropathy are at high risk of amputation of a lower extremity [5]. On the basis of analyses performed in the United Kingdom it was found that 1/3 of diabetic patients complained of the symptoms of neuropathic pain [13].

Relationships between diabetes and depression

Diabetes itself is the cause of decreased quality of life of a patient. People suffering from diabetes are forced to struggle with many challenges in daily life – they must also change their life style in various ways. Beginning with the change of life style, the necessity to pay attention to the amount and caloric value of foods, as well as the content of carbohydrates in food products, they must remember about the effect of physical effort on the level of glucose, and take oral drugs and/or insulin. They must remember, at least a part of them, about self-monitoring of glucose level, which requires piercing one's own skin and pricking own finger. Despite all these efforts, many patients develop long-term complications. This may lead to the occurrence of the symptoms of depression, which frequently remains undiagnosed [14]. The prevalence of depression among patients with type 1 and type 2 diabetes is significantly higher, compared to the non-diabetic population [15–17, 18]. This relationship – between depression and diabetes – seems to be of a two-way character – depression is not only associated with the occurrence of diabetes and its complications, but also individuals with depression are more susceptible to the development of diabetes, compared to non-depressive population [18, 19]. Comorbid depression may reduce patient's capabilities for the application of dietary recommendations, taking drugs, and obeying the recommended style of life and physical effort [20, 21].

Mental disorders, especially anxiety and depressive disorders often accompany somatic diseases, especially those with a chronic course. Researchers from the Harvard School of Public Health in Boston, after summing up their ten-year observations, performed on a large population (more than 65,000 women aged 50–57), confirmed that depression may be both a consequence and cause of type 2 diabetes. Statistical analysis confirmed that women who suffered from depression were at 17% higher risk of diabetes, whereas in the case of women taking antidepressants – this risk was higher by 25%. The fact of diagnosing diabetes increased the risk of depression by 29%, and in the case of treatment with insulin – by 53%. These correlations remained statistically significant, irrespective of the presence of other disorders related to diabetes [19]. The effect of treatment – especially the effect of administration of insulin, has been confirmed in the evaluation of the Norwegian population by Berge, both in the case of insulin monotherapy, and combined therapy (insulin and oral anti-diabetics) [22].

In the Serbian study diabetes-related distress and diabetic neuropathy were predictors of depression among patients with type 2 diabetes. The severity of depressive symptoms showed correlation with the level of HbA1c [23]. Among Australian patients, a decreased quality of life (QOL) was observed in patients with diabetes and depression, compared to patients with diabetes without depression, which, in turn, was lower, compared to non-diabetic subjects [24]. In the meta-analysis by de Groot (2001), concerning reports published during the period between 1975 and 1999, a strong relationship was observed between the occurrence of depression, and the number of long-term complications of diabetes, including diabetic neuropathy [25]. In the group of patients with diabetes there are often those afflicted with diabetic neuropathy of various levels of advancement, which affects their quality of life. These patients, due

to the relationships between DN and the symptoms of depression, should, in an especially caring way, be subjected to clinical surveillance.

As it was mentioned earlier, patients with diabetes are more susceptible to develop depression compared to people without diabetes [18, 19]. In the 8-year follow-up study carried out in Japan on 2,764 patients it was observed that subjects with moderate to severe depressive symptoms had over 2-fold higher risk of diabetes compared to those without depression [26]. Findings from the NHANES follow-up demonstrated significantly higher risk of diabetes occurrence among participants reporting high number of depressive symptoms. However, elevated risk of diabetes was observed only among people with lower (lower than secondary) education level, and it was not found in population with higher educational level [27]. Among factors associated with the risk of diabetes development among people suffering from depression, use of antidepressants should be highlighted. In the prospective Black Women's Health Study, during 12-years follow-up, the relationship between the intensification of depression and the risk of the occurrence of diabetes was observed. However, use of antidepressants was also associated with significantly, 26% higher risk of diabetes [28]. In the meta-analysis published in 2013, Bhattacharjee et al. showed risk of diabetes increased by 50% among antidepressants users [29]. In another review paper considering impact of different antidepressive drugs groups Yoon et al. demonstrated similar (49%) statistically significantly elevated diabetes risk among users of antidepressants. In subgroup analyses significantly higher diabetes risk was observed among SSRI (selective serotonin reuptake inhibitors) users, RR 1.35 (95% CI; 1.15–1.58) and TCAs (tricyclic antidepressants) users, RR 1.57 (1.26–1.96) [30].

Relationships between peripheral diabetic neuropathy (PDN) and depression

On the basis of the results of studies of the population of 4,385 patients with type 1 and type 2 diabetes, Katon et al. indicate relationships between depression and various variables. One of these variables is the number of long-trem complications (≥ 3), including diabetic neuropathy, elevated BMI, insulin therapy as the method of treatment, young age, and a number of other factors [31].

The majority of reports published after 2000 confirm the presence of the relationship between diabetic neuropathy and depression. Despite the elaborated methods of evaluation of diabetic neuropathy [9, 32], due to the subjectivity of symptoms, the assessment of the relationship between depression and neuropathy is neither easy nor obvious. One of the causes is the variety of diagnostic methods of evaluation of diabetic neuropathy related to the lack of one ideal method. Another cause is the polyetiologic character of the disease – both large and small nerve fibres are affected, the damage of which may cause various clinical manifestations. In addition, typical medical interview biased towards the symptoms reported by a patient, may be misleading because the DN may be related to pain (neuropathic pain), and may also assume the form with sensory disorders [32], or the reduction of clinical symptoms to total numbness.

Loretta Vileikyte in her studies showed the relationships between the intensity of depression, and the lack of stability and predictability of the course of the disease and

the occurring complaints, lack of reliable therapy, and the reduction of daily activity. However, she did not report the relationship between the intensity of depression and neuropathic ulcers [33]. In their report of 2014,Vileikyte and Gonzales stress the fact that diabetic neuropathy is a risk factor of the occurrence of depression, emphasizing the importance of walking disorders more than the occurrence of pain as a factor affecting the severity of depression [34]. The sole problem of prevalence of neuropathy among patients with diabetes is unequivocal. Veglio and Sivieri assessed the frequency of occurrence of diabetic neuropathy to be 28.5% [35]. In the Rochester Study, the features of diabetic neuropathy were found in 54% of patients with type 1 diabetes, and in 45% of patients with type 2 diabetes [10]. Approximately a half of all the population affected with diabetes suffer from diabetic neuropathy [36]. According to Davies et al., the pain form of diabetic neuropathy occurs in 26.4% patients with type 2 diabetes [37], whereas Tamer et al. observed the occurrence of perceived symptoms of diabetic neuropathy in 48.2% of patients with type 2 diabetes [38]. In addition, the diagnostic problem may be the fact that the sensation of pain in older individuals is intensified in the case of concomitant depression [39]. The duration of diabetes and presence of diabetic neuropathy led to disorders in the quality of sleep in 156 older individuals with diabetes, and the fact of sleep disorders was positively correlated with the occurrence of depression in these patients [40].

A survey conducted among 255 patients confirms the relationships between diabetic neuropathy and intensity of the symptoms of depression and sleep disorders [41].

In individuals with diabetes, depression increases mortality risk (H = 1.46) and cardiovascular mortality risk (H = 1.39) [42].

The prevalence of depression with various intensities of symptoms (major and minor depression) among 253 patients with first foot ulcer was 24.1% and 8.1%, respectively. In this group, which had been observed for 18 months, 40 patients died. Depression was related with the risk of death in the case of mild episodes of depression (HR = 3.23), and in the case of severe episodes (HR = 2.73) [43].

No relationship was confirmed between the occurrence of depression and development of recurrent ulcers in patients with ulceration in medical history [44].

In the study by Vileikyte, in 338 patients, peripheral diabetic polyneuropathy was a strong factor of the occurrence of the symptoms of depression within the 18-month period of observation. The intensification of neuropathy was measured using the neuropathy disability score (NDS), and the symptoms related to instability while walking and reduction in activities of daily living were the strongest predictors of an increase in depression symptoms measured by means of the Hospital Anxiety and Depression Scale (HADS-D): initial 4.93 ± 3.79, after 18 months 5.31 ± 4.01, $p < 0.05$) [45].

Similarly, the study by Gonzalez and his team, did not confirm the relationship between the intensity of depression and occurrence of subsequent ulcer in 333 patients with diabetic foot syndrome in combination with diabetic neuropathy, after excluding peripheral angiopathy: HR = 0.88 (0.61–1.27). However, such a relationship was noted in the case of the occurrence of the first ulcer in patients with diabetic neuropathy: HR = 1.68 (1.20–2.35), $p < 0.01$. This relationship was also found with respect to the presence of diabetic retinopathy: HR = 4.43 (1.89–10.14), $p < 0.01$ and vibration

perception disorders (vibration perception threshold – VPT): HR = 1.07 (1.02–1.13), $p < 0.01$ [46].

In the same year, there was published a prospective 24-week study concerning patients with neuropathic and ischemic-neuropathic ulcers, while seeking the relationship between the healing of ulcers and the experienced level of stress. The healing predictor was neither the level of anxiety (OR = 0.810 (0.704–0.930), $p = 0.003$) nor depression (OR = 0.809 (0.704–0.929), $p = 0.003$). Such a relationship was observed with respect to the method of coping with stress [47].

Thus, the relationships between the occurrence of depression and its intensity, and various aspects of diabetic neuropathy, are unequivocal. A part of this relationship is undoubtedly associated with the sole fact of the occurrence of a chronic disease, which is diabetes. In addition, long-term complications, such as diabetic neuropathy, may decrease the quality of life of a patient and his/her satisfaction with own state of health.

In Polish pilot studies concerning, among other things, the feeling of quality of life in 42 patients with type 2 diabetes, statistically significant differences were noted with respect to the global feeling of the quality of life, satisfaction with life and physical sphere, compared to patients without diabetes [48]. The study was conducted using the Quality of Life Scale – abbreviated version (WHOQOL-Brief).

The subsequent aspect is the fact that depression exerts an effect on the method of treatment understood as normal health promotion behaviour of a patient [49]. However, the sole treatment of diabetic neuropathy according to type of neuropathy, affecting thick or thin fibres, may vary with respect to effectiveness. There are many pharmaceutical agents from various categories of drugs available for the symptomatic treatment of painful diabetic neuropathy; nevertheless, the choice of an agent is frequently difficult due to an excessively wide choice and lack of comprehensive recommendations. As a result, many patients remain untreated or incompletely treated [50].

Due to all the above-mentioned aspects, the relationships between the intensity of neuropathy and the occurrence of depression are difficult to assess, and are of a polyetiologic nature, and they are not a simple summing-up of the problems [49].

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Address: Piotr Dziemidok
Diabetology Department
Institute of Rural Health in Lublin
20-090 Lublin, Jaczewskiego Street 2