Coexistence of lower urinary tract symptoms (LUTS) with depressive symptoms in patients suffering from depressive disorders

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Summary

Aim. The aim of the present study was to investigate the correlation between lower urinary tract symptoms (LUTS) and severity of depressive symptoms in patients treated for depression.

Method. 102 patients (43 males, 59 females) aged 20–67 (M = 46.1) treated for depression were included in this cross-sectional analysis. Depressive symptoms were assessed with the 17-item Hamilton Depression Rating Scale (HDRS) and Quick Inventory of Depressive Symptomatology – Self Report (QIDS-SR). LUTS were examined with the International Prostate Symptom Score (IPSS). In order to analyze the impact of presented symptoms, both urological and psychiatric, on quality of life of analyzed individuals the 30-item General Health Questionnaire (GHQ-30) was used.

Results. The average IPSS score in women was significantly higher than in men (9.59 vs. 6; p = 0.04). Patients suffering from at least moderate depression assessed with QIDS-SR had significantly higher scores in IPSS (9.76 vs. 4.1; p = 0.002). Severity of all LUTS assessed with IPSS correlated with QIDS-SR score in examined men (p < 0.05). In women, the total IPSS score correlated with the QIDS-SR score (p < 0.05) and with the total GHQ-30 score (p < 0.05). A number of other significant (p < 0.05) correlations were observed between the total IPSS score and certain items' scores in the GHQ-30 both in men and women.

Conclusions. LUTS are common among patients with depression. There is a correlation between severity of depressive symptoms and LUTS. LUTS affect quality of life and well-being as well as cause marked distress in depressed patients. Comorbidity of LUTS and depression

should draw attention of both psychiatrists and urologists and enhance interdisciplinary treatment approach. Further prospective and cohort studies are essential to reveal more details of the correlation between LUTS and depression.

Key words: depression, LUTS, comorbidity, IPSS, HDRS, QIDS-SR

Introduction

Lower urinary tract symptoms (LUTS) are considered as serious and common health problem. According to the International Continence Society (ICS) definitions and findings from 2002 [1], LUTS are divided into three groups: storage symptoms (urgency, frequency, nocturia, and urgency urinary incontinence), voiding symptoms (hesitancy, straining, slow stream, intermittency, terminal dribble) and post-micturition symptoms (post micturition dribble, feeling of incomplete emptying) [2].

The multicentre studies carried out so far on large groups representative of the general population have revealed the occurrence of at least one LUTS symptom in the majority of the adults examined [3, 4]. In a population-based cross-sectional study of 19,164 adults in 5 countries – Epidemiology Urinary Incontinence and Comorbidities (EPIC) – the most commonly reported type of LUTS, in both women and men was nocturia (48.6% of men, 54.5% of women), and the other in order of frequency, there was urgency in men and urinary incontinence in women [3]. The authors of the prospective cohort study associated with the EPIC study cited above estimate that the global number of patients affected by LUTS will continue to grow and reach 2,300,000,000 by 2018 [5]. The incidence of LUTS increases with age, this applies to both women and men [3]. The presence of LUTS is not limited only to urological diseases. The occurrence of LUTS affects the course of the accompanying diseases regardless of their etiology [6–9]. LUTS may also be the prodrome of various diseases [10, 11]. Authors of many works showed a negative impact of occurring LUTS on health-related quality of life [9, 12–14].

For many years, the relationship between the occurrence of LUTS and depressive and neurotic symptoms has been observed. In a cross-sectional multicenter study epiLUTS, conducted on groups representative of the general population of the USA, UK and Sweden, the severity of symptoms of depression and anxiety was examined using the Hospital Anxiety and Depression Scale – HADS [12]. Clinical criteria for depression (HADS-D \geq 8 score) were met by 29.8% of men and 37.6% of women among those with LUTS. Predictive factors for the occurrence of depression were perceived frequency and incomplete emptying for men and weak stream, urgency and stress urinary incontinence for women. Also in the EPIC study people reporting LUTS were characterized by much greater severity of depressive symptoms (examined by the CESD Depression Scale – Center for Epidemiology Studies Depression Scale) than those not reporting LUTS [13]. Similar results were also obtained by other studies investigating the relationship between LUTS and depression [15–18]. The bi-directional nature of this relationship has been demonstrated [16–18].

Of all LUTS, the association of nocturia and the overactive bladder syndrome (OAB) with depressive symptoms has been well studied. Nocturia, which is the most common LUTS, is, according to the ICS, a discomfort forcing to wake up to urinate one or more times at night (what is important, urination is preceded by a period of sleep, which also follows) [1]. OAB, also according to the ICS definition, consists of urinary urgency often accompanied by frequency (urinating 8 or more times a day, or according to recent diagnostic trends, such a frequency that is associated with burden and a decrease in the quality of life) and nocturia with or without urgency urinary incontinence, in the absence of urinary tract infection or other obvious pathology [1]. In many studies, the bi-directional linking of both nocturia and OAB with depressive symptoms has been proved [19, 20]. In a recently published review describing the relationship between depression and anxiety and LUTS examined so far, current theories on possible pathomechanisms linking LUTS with depression are presented [21]. The authors mention inter alia emotional discomfort, stress causing activation of the hypothalamic-pituitary-adrenal axis, reduction of blood flow in the frontal cortex, changes in serotonin and noradrenaline concentrations in the CNS, use of urological and psychotropic drugs (including antidepressant, antipsychotic drugs and mood stabilizers), as well as inflammatory process and its mediators as factors that may affect the formation, maintenance and severity of both depressive symptoms and LUTS. However, the exact nature of these dependencies remains largely unknown.

So far, the relationship between LUTS and depression has not been studied in Poland. This study was carried out in a unique population of people diagnosed with depressive disorders. Recently, Polish works investigating the occurrence of LUTS in the course of neurotic disorders have appeared [22, 23]. They mainly concerned the relationship between psychological factors and LUTS and they did not examine issues related to the somatic etiology of LUTS.

Aim

The aim of the study was to assess the severity of LUTS depending on the severity of psychopathological symptoms in patients treated for depressive disorders.

Methods

Subjects

Patients who were 18 years of age or older, treated in both outpatient and inpatient departments due to depressive disorders, were included in the questionnaire cross-sectional survey. The study received the approval of the Bioethical Committee of the Jagiellonian University (approval number KBET/266/B/2013). Each participant gave informed consent for participation in the study. All subjects completed the clinical observation chart of the patient.

Diagnostic tools

To assess the severity of the occurring LUTS, *the International Prostate Symptom Score* (IPSS) was used. It is a simple tool, created in 1992 by the American Society of Urology to assess the severity of symptoms of benign prostatic hypertrophy [24]. The simplicity of its use as well as the versatility and reliability in assessing the severity of LUTS caused that it began to be used not only in men, but also in women. This also applies to papers published recently [25, 26]. The IPSS scale has already been used in earlier studies investigating the association of depressive symptoms with LUTS [15, 16, 27]. In these studies, the severity of LUTS assessed with the IPSS questionnaire correlated with the severity of depressive disorders. However, it should be emphasized that these studies were carried out mainly in the general population.

The 17-item *Hamilton Depression Rating Scale* (HDRS) and the QIDS-SR Inventory (*Quick Inventory of Depressive Symptomatology – Self Report*) were used to assess the presence and severity of depressive symptoms. The HDRS is, due to its good psychometric properties, one of the most frequently used tools of this type with sensitivity and specificity comparable with other scales investigating the severity of depressive symptoms [28–30]. In the previously published papers, higher HDRS results correlated with greater severity of LUTS [31, 32].

The QIDS-SR scale is also a simple, widely used tool with good psychometric properties [33, 34]. In contrast to the HDRS, it is a self-assessment scale and allows to get information from a patient's perspective, like the IPSS scale. To date, the QIDS-SR scale has not been used in studies investigating the relationship between depression and LUTS. *The General Health Questionnaire* (GHQ-30) is a screening tool applied to assess the mental health of adults in the general population [35, 36]. It was chosen in order to obtain more detailed assessment of issues related to the quality of life of the subjects.

Statistical methods

In the description of the studied group, the arithmetic mean, standard deviation (SD) was used. Pearson's correlation was used to assess the dependence. Also χ^2 NW tests and Student's *t*-tests for two independent variables were performed. Statistically significant results were p < or equal to 0.05. The statistical analysis was performed using STATISTICA 12 software (UJ CM license).

Results

Totally, 121 persons agreed to participate in the study. 102 people were included in the study group -43 (42.16%) men and 59 (57.84%) women. The mean age of all subjects was 46.1±11.3 years (range: 20–67 years), the mean BMI value was 26.72±5.19 kg/m², the average period of previous psychiatric treatment was 10.7±8.6 year (range: 0–38 years), the mean number of previous psychiatric hospitalizations was

 2.4 ± 3.5 (range: 0–20). 3 persons (2.94%) had primary education, 35 persons (34.31%) had secondary education, 11 persons (10.78%) – vocational education, 53 persons (51.96%) – higher education. 54 respondents were professionally active (52.94%), 28 (27.45%) were pensioners, 12 (11.76%) were unemployed, 5 people (4.9%) were during education, and 3 (2.94%) were retired.

68 people (66.66%) were married, 9 (8.82%) were divorced, 3 (2.94%) were separated, 5 (4.9%) were in informal relationships, 2 people (1.96%) were widowed, and 15 subjects (14.7%) were single persons.

32 respondents lived in the countryside (31.37%) and 70 (68.63%) in the city, of which 50 people (49.2%) lived in a city of over 500,000 inhabitants.

| Number of respondents | n = 102 (100%) |
|---|------------------|
| Mean age of the respondents | 46.1±11.3 years |
| The mean BMI value | 26.72±5.19 kg/m2 |
| The average duration of current psychiatric treatment | 10.7±8.6 years |
| The mean number of hospitalizations | 2.4±3.5 |
| Sex | |
| Men | n = 43 (42.16%) |
| Women | n = 59 (57.84%) |
| Marital status | |
| Married | n = 68 (66.66%) |
| Divorced | n = 9 (8.82%) |
| In separation | n = 3 (2.94%) |
| Informalrelationships | n = 5 (4.9%) |
| Single | n = 17 (16.66%) |
| Education | |
| Primary | n = 3 (2.94%) |
| Secondary | n = 35 (34.31%) |
| Vocational | n = 11 (10.78%) |
| Higher | n = 53 (51.96%) |
| Professional status | |
| Work | n = 54 (52.94%) |
| Pension | n = 28 (27.45%) |
| Unemployment | n = 12 (11.76%) |
| Education | n = 5 (4.9%) |
| Retirement | n = 3 (2.94%) |

Table 1. Characteristics of the studied group

table continued on the next page

| Place of residence | |
|--------------------|-----------------|
| Village | n = 32 (31.37%) |
| City | n = 70 (68.63%) |

The results of the analysis of mean values obtained in the HDRS and QIDS-SR scales in all patients were as follows: 15.3 ± 8.96 in the HDRS and 14.17 ± 6.37 in the QIDS-SR scale. The mean value among all subjects in the IPSS scale was 8.07 ± 8.76 , and on the GHQ-30 scale 61.2 ± 21.59 .

The highest mean point value (the highest severity of symptoms) in the total number of surveyed women and men of all LUTS assessed in the IPSS scale was obtained by: nocturia (1.53 ± 1.64), frequency (1.19 ± 1.48), weak stream (0.86 ± 1.28), while the lowest value was obtained by straining (0.5 ± 1.09). The highest average point value in the IPSS scale was obtained by the last question regarding the quality of life related to LUTS – 1.71 ± 1.62 . According to the score obtained in the IPSS scale, 62 subjects (60.78%) had mild (0-7 points), 31 subjects (30.39%) moderately severe (8-19 points), and 9 subjects (8.82%). significantly increased (20-35 points) LUTS.

In terms of the severity of symptoms of depression assessed with the 17-item *Hamilton Depression Scale* (HDRS), 20 subjects (19.6%) were in remission, 24 (23.52%) had mild, 27 (26.47%) moderate, 18 (17.64%) severe, and 13 (12.74%) very severe depressive symptoms.

According to the results obtained in the second scale used in the study to assess the symptoms of depression, the QIDS-SR, 12 subjects (11.76%) were in remission (0–5 points), 18 (17.64%) had mild (6–10 points), 31 (30.39%) moderate (11–15 points), 20 (19.6%) severe (16–20 points), and 20 (19.6%) very severe (21–27 points) depressive symptoms [37].

The mean point values obtained in the HDRS and QIDS-SR scales among the studied women and men were respectively: 15.3 ± 9.50 and 15.4 ± 8.27 for the HDRS and 14.44 ± 6.16 and 13.8 ± 6.71 for the QIDS-SR. The mean point value obtained in the IPSS scale in the examined women was higher (amounted to 9.59 ± 9.94) than in the men (6 ± 6.34), which was confirmed by the *t*-test for independent samples (p = 0.04).

The highest mean point value (greatest severity of complaints) in the surveyed women among all LUTS assessed in the IPSS scale was obtained by: nocturia (1.74 ± 1.69) , frequency (1.43 ± 1.62) , urgency (1.45 ± 1.62) , and intermittency (1.00 ± 1.45) , while the lowest value was obtained by straining (0.57 ± 1.14) . The highest mean point value in the IPSS scale in the surveyed women had the question regarding the quality of life related to LUTS – 1.89 ± 1.70 . In men, the highest mean point value among those assessed with the IPSS LUTS scale was obtained by: nocturia (1.25 ± 1.54) , frequency (0.81 ± 1.20) , weak stream (0.79 ± 1.10) , and the lowest by: urgency (0.39 ± 1.04) and straining (0.39 ± 1.04) . Also in men, the highest mean point value in the IPSS scale was obtained by the question regarding the quality of life related to LUTS, which amounted to 1.46 ± 1.48 .



Figure 1. Luts and gender

The sum of points obtained in the HDRS did not correlate in a statistically significant way with the intensity of none of the IPSS LUTS, or sum of points in the IPSS when the total number of examined men and women was assessed. The sum of HDRS points in women did not correlate with any of LUTS assessed in the IPSS or the sum of points in the IPSS. In the studied men the sum of points in the HDRS weakly correlated with the severity of nocturia (r = 0.24; p < 0.05), urgency (r = 0.22; p < 0.05) and straining (r = 0.21; p < 0.05).

The severity of IPSS LUTS measured in the overall study was positively correlated with the severity of depression measured with the QIDS-SR scale (r = 0.36; p < 0.05). Moreover, this relationship concerned all LUTS assessed in the IPSS, as well as the quality of life associated with them. The highest correlation was observed in the case of LUTS-related quality of life (r = 0.39; p < 0.05) as well as the feeling of incomplete bladder emptying after voiding (r = 0.36; p < 0.05), and the lowest for nocturia (r = 0.20; p < 0.05).

The studied group was divided in terms of the severity of depressive symptoms in the QIDS-SR scale. The first subgroup included people who were in symptomatic remission or with mild depression, and the second group included people with at least moderate depressive symptoms. Statistical analysis (t-test for two independent trials) showed statistically significantly higher severity of LUTS (IPSS score) in the subgroup with at least moderately severe symptoms of depression (9.76±9.60 vs. 4.10 ± 4.60 ; p = 0.002).

The χ^2 NW test was used to analyze the relationship between the severity of each of the IPSS LUTS assessed with the severity of depressive symptoms in the QIDS-SR scale (remission or mild depression vs. at least moderate severity of depressive symptoms). A statistically significant relationship was observed in the case of: incomplete emptying of the bladder after voiding (p = 0.035), frequency (p = 0.005), urgency (p = 0.039), and quality of life associated with the experienced LUTS (p = 0.004).

The obtained sum of points (r = 0.34; p < 0.05) in the IPSS scale was positively correlated with the sum of points obtained in the QIDS-SR scale in the female group. This dependence concerned the majority of women assessed in the IPSS LUTS, as well as the quality of life associated with them. The greatest correlation was observed in the case of the feeling of incomplete emptying of the bladder after voiding (r = 0.41; p < 0.05), then the quality of life associated with LUTS (r = 0.38, p < 0.05), weak stream (r = 0.29; p < 0.05), frequency (r = 0.28; p < 0.05), and straining (r = 0.26; p < 0.05). There was no correlation in this group with the sum of points obtained in the QIDS-SR scale in the case of nocturia and urgency.



Figure 2. LUTS and depression

Among men participating in the study, the sum of points obtained in the IPSS scale was also positively correlated with the score on the QIDS-SR scale (r = 0.43; p < 0.05). The severity of all IPSS-rated scales in the LUTS men group correlated with the sum of QIDS-SR points. This was mostly related to the quality of life related to LUTS (r = 0.40; p < 0.05), followed by weak stream (r = 0.33; p < 0.05), urgency (r = 0.32; p < 0.05) and feelings of incomplete emptying of the bladder after micturition (r = 0.30; p < 0.05).

The assessment of the correlation in all subjects between the score obtained in *the General Health Questionnaire* GHQ-30 and LUTS measured by the IPSS scale also brought several observations. The sum of points obtained in the GHQ-30 correlated with the quality of life associated with LUTS, assessed on the IPSS scale (r = 0.28; p < 0.05).

Despite the fact that for individual LUTS assessed using IPSS (or for the number of points obtained in it), there was no correlation with the sum of points obtained in the GHQ-30, in the case of several questions included in the GHQ-30, correlations with the IPSS were observed. The most correlated with the sum of points obtained in the IPSS were: impaired ability to be in motion and having a job (r = 0.24; p < 0.05), impaired ability to leave home as often as usual (r = 0.24; p < 0.05), difficulty in taking up activity due to concern (r = 0.24; p < 0.05), and less sleep due to worries (r = 0.23; p < 0.05). When correlations were evaluated for individual types of LUTS in the IPSS with questions included in the GHQ-30, the highest number was found for the quality of life associated with LUTS and the feeling of incomplete bladder emptying after micturition, and no correlation was observed at all in the case of urgency and straining. Neither the age of all studied men and women nor the calculated body mass index BMI correlated with scores obtained in the HDRS, QIDS-SR, IPSS, and GHQ-30 scales.

Between the score obtained in *the General Health Questionnaire* GHQ-30 and the sum of points obtained in the IPSS scale in the studied women, a correlation was found (r = 0.23; p < 0.05). The sum of points obtained in the GHQ-30 was also correlated in the group of women with the quality of life associated with LUTS (r = 0.38; p < 0.05) and the intensity of the feeling of incomplete bladder emptying after micturition (r = 0.25; p < 0.05) assessed by the IPSS.

In the group of men examined for particular types of LUTS assessed by means of the IPSS (or for the number of points obtained in it) no correlation was found with the sum of points obtained in the GHQ-30. When taking into account the scores obtained in individual GHQ-30 questions in men and the total sum of points obtained in the IPSS, correlation was observed in the case of: impaired ability to play a significant and useful role in the society (r = 0.31; p < 0.05), less sleep due to worries (r = 0.28, p < 0.05), and the occurrence of restless and disturbed sleep (r = 0.27; p < 0.05) and difficulties in taking up activities due to worries (r = 0.23; p < 0.05).

In the group of women surveyed, such correlations were greater and concerned especially the impaired ability to be in constant motion and having a job (r = 0.37; p < 0.05), impaired ability to leave the home as often as usual (r = 0.37; p < 0.05),

experiencing a continuous load (r = 0.32; p < 0.05), and difficulty in focusing on the activity (r = 0.31; p < 0.05).

Comparing the studied groups of men and women with respect to the correlation between particular types of LUTS assessed in the IPSS with the number of points scored in particular questions included in the GHQ-30, it should be stated that while in both women and in men such correlations for each of the LUTS are present, in the case of the surveyed women, the number of such correlations is definitely higher.

In the group of women surveyed, the age positively correlated with the sum of points obtained in the HDRS (r = 0.24; p < 0.05), while the body mass index BMI slightly negatively correlated with the severity of the feeling of incomplete bladder emptying after voiding assessed in the IPSS (r = -0.20; p < 0.05). In the group of men examined, age correlated negatively with the sum of points obtained in the QIDS-SR (r = -0.22; p < 0.05), positively correlated with the sum of points obtained in the IPSS (r = -0.22; p < 0.05), and among LUTS assessed on the IPSS with age, the correlation was especially observed with the feeling of incomplete emptying of the bladder after micturition (r = 0.38. p < 0.05) and weak stream (r = 0.28; p < 0.05). The BMI value of the studied men negatively correlated with the sum of points obtained in both depression rating scales used. This applies more to the HDRS (r = -0.36; p < 0.05) than to the QIDS-SR (r = -0.28; p < 0.05). The value of BMI index was also correlated in men with severity of some LUTS assessed in the IPSS. This was related to the weak stream (r = 0.23; p < 0.05) and intermittency(r = 0.21; p < 0.05).

Discussion

This study is the first in Poland to analyze the relationship between LUTS and depressive symptoms. It is also the first study in Poland assessing the prevalence of LUTS among people being treated psychiatrically due to depressive disorders. In other countries, work on this subject arose, however, other research scales were used in their course. In the examined group, the severity of LUTS was high, significantly higher among women than in men. Almost 40% of all respondents experienced at least moderately severe LUTS. Both in the studied women and men the highest severity of symptoms was observed in the case of nocturia, which is consistent with the results obtained in large, multicenter studies conducted in groups representative of the general population [3, 4].

The severity of LUTS in the examined men positively correlated with age, which makes the methodology of this study credible in the context of the results of earlier studies conducted in larger groups, representative for the general population [3]. There was a negative impact of LUTS on the quality of life and well-being of both women and men, which was also found in other studies investigating this relationship [12–14, 27, 37, 38]. The results obtained in the IPSS correlated with the results in the GHQ-30, which indicates a clinical significance of this relationship. In the studied group, greater severity of each of the LUTS types assessed in the IPSS was found in

people with more severe depressive symptoms assessed by the QIDS-SR. This is an important observation, of important clinical significance, especially when we take into account the results of a recent survey among psychiatrists pointing to their insufficient knowledge about LUTS and the lack of adequate attention devoted to the occurrence of these symptoms in their patients [39].

The results of the study indicate the need for an interdisciplinary approach to at least some patients suffering from depression and experiencing LUTS. These symptoms often co-exist and influence each other's severity. Due to the bi-directional nature of the relationship between depression and LUTS [17] and the lack of sufficient psychological awareness of psychiatrists on the occurrence of LUTS in their patients [39] the first step to improve the situation of patients could be the use of the IPSS questionnaire by psychiatrists as a screening tool to assess the severity of LUTS in people suffering from depressive disorders. Particularly important and needed it would be for older people as well as those experiencing more severe depressive symptoms. Similarly, it would be justified to use self-assessment scales by urologists for cases of suspected depression in patients treated for LUTS. In the study, the QIDS-SR showed a significant correlation with LUTS and its use could be particularly useful. This could significantly improve the detectability of depressive disorders in this group in order to treat patients more effectively.

One should also mention the significant negative impact of depressive disorders and LUTS on the patients' life comfort, indicated in this study and in other studies [21, 27, 37, 38]. The postulated actions could significantly improve this comfort and health-related quality of life. However, in order to achieve all the objectives set above, cooperation between psychiatrists and urologists both in the field of diagnosis and the treatment of depression and LUTS is needed. This seems to be the most important conclusion of this work.

The pharmacological treatment of depression may influence the severity of LUTS [40, 41]. We did not analyze the examined group in terms of pharmacotherapy, because it was heterogeneous, but the most commonly used antidepressants among the subjects were serotonin and noradrenaline reuptake inhibitors (SNRIs). It was used by 35% of respondents. The second most common in terms of frequency were selective serotonin reuptake inhibitors (SSRIs), which were used by 26% of subjects. In a previous study, the use of SSRIs doubled the relative risk of two or more micturitions overnight, both in men and women [42]. On the other hand, according to some authors, administration of duloxetine belonging to the SNRI group significantly reduces the severity of OAB symptoms in adult women compared to the placebo group [43]. The authors of the systematic review indicate the efficacy of duloxetine in the treatment of stress urinary incontinence [44]. However, the recently published meta-analysis questioned the appropriateness of using duloxetine in this indication due to its frequent and intense side effects and poor tolerance resulting in drug discontinuation [45]. In the case of the use of many antidepressant medications, including those belonging to SNRI and SSRI (and, among others, antipsychotics and benzodiazepines), incontinence was

described [46]. The above data indicate an ambiguous but clinically significant effect of the use of antidepressants on the severity of LUTS. According to the current state of the literature, it is difficult to indicate whether the decreasing or increasing intensity of LUTS prevails. It seems that this is largely an individual matter for each patient, which indicates the need for individualized planning of psychopharmacotherapy in the group of patients with LUTS.

The limitations of the described study were: its cross-sectional character, the size of the studied group, the heterogeneity of pharmacotherapy and the lack of a control group. In our study, we did not indicate a correlation between LUTS and the severity of depressive symptoms assessed using the HDRS. There is, however, a probability that such a correlation would be demonstrated in a larger group. In order to finally confirm the relationships observed in this paper, it is necessary to conduct further, cohort and prospective, multicenter studies. Despite its limitations, the study in question is one of the pioneering works in this field in Poland.

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