CLINICAL STUDY

Why does depression develop in complicated osteoporosis?

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Abstract

Patients and methods: **In a prospective study we observed which female patients developed depression following an acute and painful vertebral fracture. For the statistical evaluation of questionnaires we chose randomly 32 patients with depression (out of 33 patients) aged 51–73, and 32 patients without depression (out of 44 patients) aged 52–70.**
The aim of the study: **To verify the hypothesis that the patients with more traumatic experience in the anamnesis (Questionnaire No. 1) are more depression prone following the osteoporotic vertebrae fractures and their character features are typical for subjects with higher emotional vulnerability (Questionnaire No. 2).**
Statistical analysis: **1. Questionnaires 1 and 2 were evaluated by two statistical methods: a) automatization of mathematical and statistical estimates and tests based on binomial distribution; b) ADALINE Programme. 2. Assessment of relative risk for developing depression.**
Results and conclusion: **We recommend to use questionnaires No. 1 and 2 in female patients with acute painful vertebrae fractures to select patients with the risk of depression development. These patients should be followed more frequently as outpatients and in case of first clinical symptoms of depression should be recommended for special psychiatric care. Early therapy of depression enables to accelerate the mobilisation, rehabilitation and resocialisation of patients, to improve the quality of their lives and to reduce the costs of analgetic treatment of pain, sedatives and rehabilitation *(Tab. 10, Fig. 2, Ref. 17)*.**
Key words: aetiology, depression, osteoporosis, post menopause, vertebrae fracture.

Fractures as complications of osteoporosis represent an important social and economic problem, because they increase the costs of treatment and complex care of patients. Risk factors for osteoporotic fractures are: female sex, premature menopause, age, primary or secondary amenorrhoea, primary and secondary hypogonadism in man, Asian or white ethnic origin, previous fragility fracture, low bone mineral density, glucocorticoid therapy, high bone turnover, family history of hip fracture, low bodyweight, neuromuscular disorders, smoking, excessive alcohol consumption, long-term immobilisation, low dietary calcium intake, vitamin D deficiency (1). According to Cummings et al. cohort study (2) a 50-year-old Caucasian woman has a 32 % chance of a vertebral fracture occurring in her remaining lifetime. Even more striking, women with prevalent vertebral deformities have a risk of sustaining a subsequent vertebral fracture that is five times that of women without prevalent vertebral deformities (3, 4).

Vertebral fractures lead to deformations of the chest – kyphosis, conditioning biomechanical changes in the musculoskeletal system with subsequent clinical symptomatology:

– discopathies, pseudoradicular or radicular syndrome, muscular dysbalance of the trunk musculature (chronic backache),

– ileocostal-friction syndrome (friction of costal arches with ala ossis ilii during the trunk movement),

– increase of intraabdominal pressure (loss of appetite, dyspeptic problems, diffused pain in the abdomen and under the right costal arch, obstipation),

– growth of pressure forces on pulmonary parenchyma (the disposition to infection of upper respiratory tract and lungs, the reduction of maximal breathing capacity, and the decrease of right ventricular systolic ejection fraction in combination with the increased diastolic content of the right ventricle represent a risk for the development of cor pulmonale chronicum),

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Questionnaire No. 1

For every life situation you experienced in the past insert the plus sign (+), or the minus sign (-) if such an event did not happen to you during your lifetime.

	D	NonD
1. **Wrong lifestyle – disorganised lifestyle**		
1.1. Long-term lack of sleep	18	6
1.2. Repeated overwork and exhaustion by excessive work	26	14
1.3 Lack of regular exercise	29	30
2. **Previous diseases, long-term care of gravely ill person close to you**		
2.1. Post-natal depression	6	2
2.2. Operations (give number, e.g.: 3)	12	7
2.3. Personal experience of serious illness	25	12
2.4. Long-term care of gravely ill close person who died	16	4
3. **Experience of failure or sin feeling**		
3.1. I failed in a serious situation and I still blame myself for it	15	10
3.2. I have a feeling that I sinned and I cannot come to terms with it	16	9
4. **Difficult life trials**		
I experienced:		
4.1. Death of a family member (give number)	28	29
4.2. Divorce	10	7
4.3. Disintegration of the family	11	3
4.4. Job loss	5	6
4.5. Serious financial difficulties	21	24
4.6. Loneliness, desertedness	26	7
4.7. Repeated failures in activities I felt very strongly about	23	7
4.8. Long-term conflict relations in the workplace	22	4
4.9. Nursing of physically or mentally handicapped child	1	0
4.10. I experienced an alcohol addiction	0	0

– disposition to falls mainly in leaning forward (deviating the body's centre of gravity from its normal position, disruption of skeletal statics).

Osteoporotic fracture represents for a patient a long-term stress situation, as it brings about a lifestyle change with the limitation of everyday activities and the loss of total independence. The success of the vertebral fracture therapy is often complicated by the development of depression, which is frequently diagnosed late or not at all; sometimes it is treated by sedatives as a neurasthenic syndrome, without the effect of such a treatment.

In the osteological department we were able to observe in some patients with osteoporotic vertebral fractures a very slow and unsuccessful mobilisation, rehabilitation and reconvalescence in comparison with other patients whose mobilisation was relatively quick, and they could return to their original lifestyle with some limitations. In the group of unsuccessfully mobilised patients persisted a marked vertebrogenic algic syndrome, aversion to cooperation with the physician and physiotherapist, and inability to live a normal life. These patients were prevailingly diagnosed as depressive.

The above-mentioned clinical experience brought us to the annotation of a prospective study to answer this question: Why did some women, following the clinical vertebral fracture, despite a standard therapy, develop depression and some women did not.

The aim of the study

1) To find out the confidence interval (C.I.) and median (x) for time interval of the onset of clinical symptoms of depression from the onset of osteoporotic fracture of vertebra.

2) To set up Questionnaire No. 1 focused on the anamnesis of experienced mental stress situations.

3) To compare anamnestic data (positive or negative answer) focused on experienced mental traumas, obtained by means of Questionnaire No. 1 in the group of depressed female patients with osteoporotic vertebrae fractures, with the group of female patients with osteoporotic vertebrae fractures, but without depression.

4) To compare the differences in positive and negative answers in completed Questionnaire No. 2 (characteristics of depression prone personality – according F. Flach) between the groups of depressed and non-depressed patients.

5) To evaluate validity criteria for Questionnaires No. 1 and 2:
– sensitivity,
– specificity,
– prediction values of the positive test,
– prediction value of the negative test,
– test effectiveness.

6) To calculate the relative risk (RR) for developing depression in patients with osteoporotic fracture.

Questionnaire No. 2

Depression Prone Personality Profile
If you identify with a festure fitting you in the past, insert the plus sign (+), if not, insert the minus sign (-).

	D	NonD
1. I took things very seriously, I had a feeling of a high moral responsibility for everything I did	29	14
2. I was very ambitious, I always tried to perform well	19	10
3. I was definitively a competitive person	27	22
4. I always had a feeling of having a lot of energy, that I am indefatigable, that I can work myself „into the ground“	27	4
5. I always cared too much how other people feel	18	4
6. I never wanted to hurt other people's feeling	17	5
7. I was always too much dependent on people I loved	27	19
8. I reacted too emotionally to anything that could even in a smallest way possible reduce the feeling of myself-esteem	29	13
9. Any tactlessness from other people hurt me too deeply (every humiliation or insult)	18	2
10. I was at a loss what to do in confrontation with a hostile attitude of other people, I was often helpless against attacks by other people	22	3
11. If I was verbally attacked I had troubles to pull myself together and defend myself – even in case when the defence was really justified	23	6

Characteristics of the cohort of examined female patients and methods applied

During the period of six years the study gradually included patients with one newly sustained (painful) clinical vertebral fracture, who in the past had none or at most two vertebral fractures. The patients were diagnosed with a primary or secondary osteoporosis (condition after a hysterectomy and bilateral adnexectomy, malabsorption syndrome - asymptomatic coeliacia, chronical atrophic gastritis with achlorhydria, M. Crohn). The study did not include patients with osteoporosis, induced by glucocorticoids. On the very day when the acute vertebral fracture was diagnosed, each patient filled a questionnaire No. 1 and 2.

Questionnaire 1 was set up to include the most frequent model situations of stress and mental trauma in people' s lives. Questionnaire 2 was set up according to Frederic Flach (5), including character features of persons inclined to develop depression following stressful life situations.

All patients, both in acute and chronical stage of vertebral fracture, received a standard treatment by analgesics, nonsteroid antirheumatics, myorelaxants and physical therapy:

1) in the acute stage: local application of cold, electrotherapy, tender relaxing back massage;

2) in the chronical stage: kinesitherapy directed at the removal of muscular dysbalance in the area of trunk muscles.

The choice of analgesic drug and its dosage were on individual basis, aimed at removing or minimising backache.

Depression in patients was diagnosed by means of the DSM-IV questionnaire (6).

Depressive patients were adequately treated by antidepressants. For the final evaluation of comparison of questionnaires we chose at random 32 (D) depressive patients (from the overall number of 33) and 32 (nonD) nondepressive patients (from the overall number of 44). We chose the same number of patients in both groups (observation and control) to meet the criteria for proper evaluation of qualitative features by means of questionnaires. In the depressive patients group (D) there were four patients who had already sustained one clinical vertebral fracture in the past. In the non-depressive patients group (nonD) there were four patients who had overcome a vertebral fracture and one patient had overcome two vertebral fractures. From all patients with vertebral fractures (n=64) 5 were treated with bisphosphonates (1–3 years), 4 with calcitonin (2–3 years), 6 with selective estrogen receptor modulators (1–2 years). In 49 patients were established the diagnosis of osteoporosis, when they suffered from osteoporotic vertebral fracture. These patients were not treated in the past. The age of patients in the D group ranged from 51 to 73 years, in the nonD group from 52 to 70 years.

Statistical analysis

Time for developing depression following osteoporotic fracture

We calculated the confidence interval (95 % C.I.) and median ($\tilde{x}$) for time interval (given as the number of days from the onset of vertebra fracture) characteristic for the onset of clinical signs of depression.

Evaluation of Questionnaires

In the completed questionnaires we compared:

a) presence or absence in the anamnesis of experienced stress situation,

b) presence or absence of character feature for a depression prone personality (DPP),

in the cohort of depressed and non-depressed female patients with osteoporotic vertebrae fractures.

Tab. 1. Percentage representation of parameters weights of Questionnaire No. 1 within linear combination of the whole group (alpha=0.05).

Question No.	Weights of parameters of questionnaire in %	
	D	NonD
1.1	1.93	-4.73
1.2	6.22	-0.42
1.3	5.81	8.24
2.1	-4.99	-8.35
2.2	-5.39	-4.98
2.3	4.29	-3.60
2.4	1.71	-3.15
3.1	-1.97	-3.38
3.2	0.28	-2.36
4.1	10.57	5.90
4.2	-3.65	-5.29
4.3	-1.78	-6.08
4.4	-10.07	-5.30
4.5	0.31	2.82
4.6	5.54	-2.85
4.7	5.56	-6.47
4.8	1.88	-5.15
4.9	-12.73	-10.42
4.10	-15.33	-10.42

In statistical evaluation we used two methods for the comparison of qualitative signs:

1. Automatization of mathematical and statistical estimates and tests based on binomial distribution (7, 8)

According to this statistical method the number of positive answers (x) to all questions (n) in Questionnaires No. 1 and 2 is given as a percentage of positive answers (P) from the total number of questioned patients in the D or NonD groups (n=32).

$$P = \frac{x}{n} \cdot 100\ \%$$

Differences between percentage values of positive answers in Questionnaires No 1 and 2 for D and NonD groups were evaluated by 2 (χ-square test) Statistically significant difference between answers was achieved when the following condition was met:

$$\chi^2 > 3.841$$

2. ADALINE, PC software (9)

Using ADALINE program we calculated absolute values of parameter weights in Questionnaires No 1 and 2 and their percentage expression within linear combination of the whole group. Absolute values of weights of individual parameters are given in bar diagrams. We evaluated also validity parameters of the questionnaires (sensitivity, specificity, prediction value of positive test, prediction value of negative test, effectiveness). The ADALINE program includes also the production of a recognition patterns matrix.

Recognition patterns

Every questionnaire item has a binary character (positive or negative answer). Positive answer (the presence of experience in the anamnesis, presence of DPP character feature) was indicated by the plus sign (y= +1), negative answer by the minus sign (y= −1). Recognition patterns in the form of a matrix show graphically the differences in answers to every question by every investigated patient.

Calculation of relative risk (RR)

We calculated relative risk (10, 11) for developing depression in patients with acute vertebrae fractures by means of binary association – contingency tables (Tab- K1, K2).

The risk (R1) is a ratio of the number of patients with depression exposed to risk factors (a) to the total number of observed patients exposed to risk factors (a+b). The risk (R2) is a ratio of the number of patients with depression without exposure to risk factors to the total number of patients not exposed to risk factors. Relative risk (RR) is the ratio of the risk for depression by patients with the risk factors to the risk for depression by patients without the risk factors.

$$R_1 = \frac{a}{a+b},$$

$$R_2 = \frac{c}{c+d},$$

$$RR = \frac{R_1}{R_2} = \frac{\frac{a}{a+b}}{\frac{c}{c+d}}$$

Results

Median for developing depression was the 32nd day following the onset of the osteoporotic vertebra fracture. Patients developed depression at the least after 7 days, at the most after 52 days.

$\tilde{x}$ (median) for 95 % C.I = 32 days 95 % C.I.: – upper limit 38 days
– lower limit 24 days

Evaluation of Questionnaire No. 1

Questionnaires completed by depressed patients included statistically significant higher number of positive answers to questions defining experienced stress situation in life (Tab. 1).

Differences in weights values of questionnaire parameters expressed in percentages within linear combination of the whole group are given in Table 2 (questions are numbered). Table 2 contains those questions, statistically significant for diagnosing risk patients, where the weights of answers reached positive numbers (in % or in absolute numbers) in the D group and negative numbers in the NonD group. The number of questions meeting these criteria is, at the same time, a minimum number of ques-

Tab. 2. Comparison of the number of positive answers (expressed in percentage from the overall number of questioned patients, n=32) in Questionnaire No. 1 for every question in the group of depressed patients (D) and non-depressed patients (NonD) (alpha=0.05).

Question No.	D n=32 %	NonD n=32 %	χ^2 χ-square test
1.1	56	19	10.252
1.2	84	44	12.485
1.3	88	94	0.756
2.1	22	6	3.505
2.2	38	22	1.01
2.3	78	38	11.562
2.4	50	16	9.194
3.1	44	31	1.074
3.2	50	28	3.281
4.1	88	88	0.000
4.2	34	23	1.086
4.3	34	9	6.363
4.4	16	19	0.075
4.5	66	75	0.677
4.6	78	22	22.841
4.7	72	2	17.647
4.8	72	13	27.077
4.9	3	0	0.178
4.10	0	0	0.000

tions to which the patient has to give a positive answer to be included into the depression development risk group. For Questionnaire No. 1 it is a minimum of eight positive answers.

According to validity criteria (Tab. 3) we consider Questionnaire No. 1 indicated for the recognition of depression development risk patients following an acute painful vertebra fracture.

Figure 1 brings differences in answers of depressed and non-depressed patients to individual questions by means of recognition patterns (positive answer – black field, negative answer – white field).

Evaluation of Questionnaire No. 2

Questionnaires completed by depressed patients included statistically significant higher number of positive answers for character features of depression prone persons in comparison with non-depressed patients (Tab. 4).

Differences in weights values of questionnaire parameters expressed in percentages within linear combination of the whole group are given in Table 5.

Table 5 contains the questions, statistically significant for diagnosing risk patients, where the weights of answers reached positive numbers (in % or in absolute numbers) in the D group and negative numbers in the NonD group. The number of questions meeting these criteria is, at the same time, a minimum number of questions to which the patient has to give a positive answer to be included into the depression prone person risk group. For Questionnaire No. 2 it is a minimum of six positive answers.

According to validity criteria we consider Questionnaire No. 2 indicated for diagnosing depression prone persons (Table 6).

Fig 2 brings differences in character features of depressed and non-depressed patients by means of recognition patterns (positive answer – black field, negative answer – white field).

Calculation of relative risk for Questionnaire No. 1 (Tab K1)

$$RR = \frac{R_1}{R_2} = \frac{\frac{a}{a+b}}{\frac{c}{c+d}} = \frac{\frac{28}{28+4}}{\frac{4}{4+28}} = \frac{0.875}{0.125} = 7.0$$

95% CI (6.4; 8.1)

RR for developing depression in patients with osteoporotic vertebrae fractures is 7,0 time higher for patients, which answered in Questionnaire No. 1 eight and more questions positive then in

Tab. K1. Contingency table for Questionnaire No. 1.

	Depression	
Questionnaire No. 1	Yes	No
Positive	28 (a)	4 (b)
Negative	4 (c)	28 (d)

a, b, c, d – frequencies

Tab. 3. Validity criteria of Questionnaire No. 1 (alpha=0.05).

	Validity criteria (in %)								
Group	TN	FP	FN	TP	Sensitivity	Specificty	Prediction values of the positive test	Prediction values of the negative test	Test effectiveness
D	25	7	1	31	96.88	78.13	81.58	96.15	87.50
NonD	31	1	7	25	78.13	96.88	96.15	81.58	87.50

TP – true positives, TN – true negatives, FP – false positives, FN – false negatives

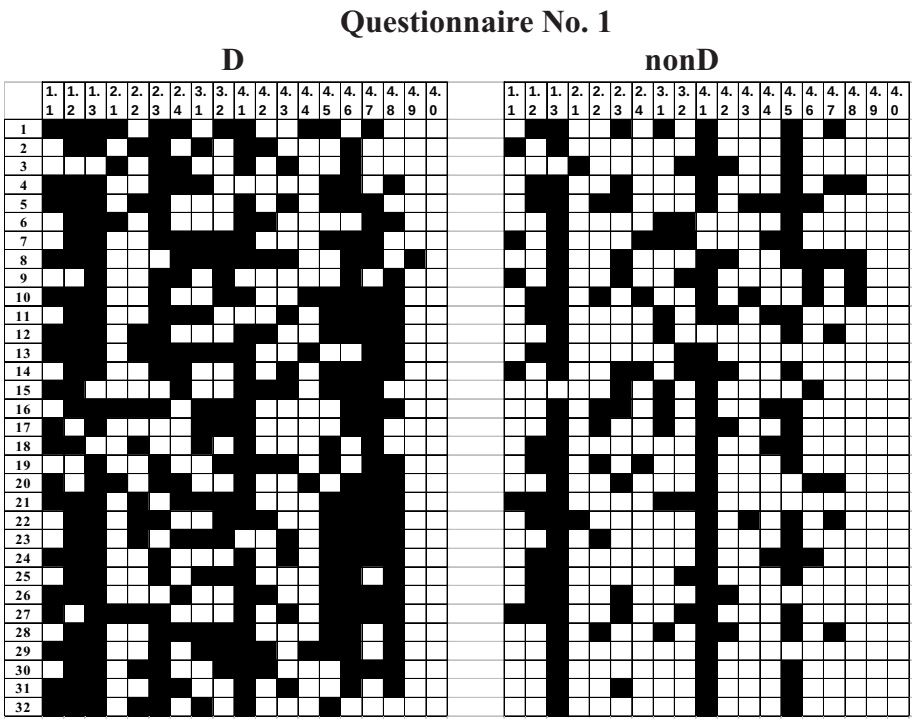

Fig. 1. Discrimination analysis of recognition patterns for Questionnaire No. 1 (columns are numbered by questions numbers in Questionnaire No. 1, the lines are numbered by serial numbers of individual patients n=32, positive answer – black field, negative answer – white field).

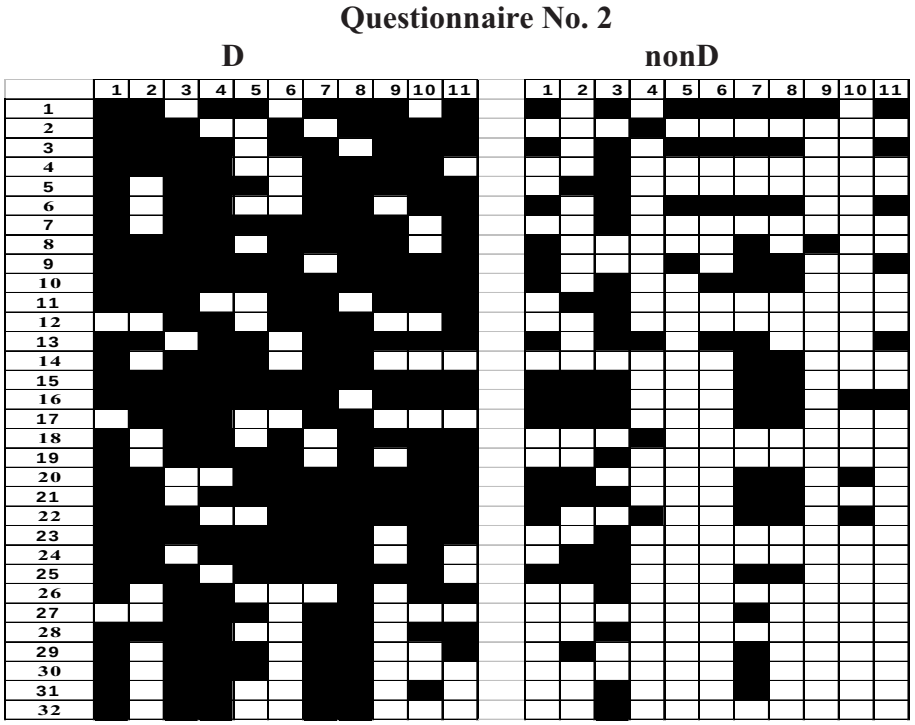

Fig. 2. Discrimination analysis of recognition patterns for Questionnaire No. 2 (columns are numbered by numbers of questions about character features of depression prone persons in Questionnaire No. 2, the lines are numbered by serial numbers of individual patients n=32, positive answer – black field, negative answer – white field).

patients with osteoporotic fractures, which answered in Questionnaire No. 1 less than eight questions positive.

Calculation of relative risk for Questionnaire No. 2 (Tab K2)

$$RR = \frac{R_1}{R_2} = \frac{\frac{a}{a+b}}{\frac{c}{c+d}} = \frac{\frac{29}{29+5}}{\frac{3}{3+27}} = \frac{0.8529}{0.1000} = 7.0$$

95% CI (7.6; 9.2)

RR for developing depression in patients with osteoporotic vertebrae fractures is 8,5 time higher for patients, which answered in Questionnaire No. 2 six and more questions positive, then in patients with osteoporotic fractures, which answered in Questionnaire No. 2 less than six questions positive.

Tab. K2. Contingency table for Questionnaire No. 2.

	Depression	
Questionnaire No. 2	Yes	No
Positive	29 (a)	5 (b)
Negative	3 (c)	27 (d)

a, b, c, d – frequencies

Discussion

We have not met a similar study in literature to compare our results with. Several studies, whose authors investigated clinical symptomatology accompanying osteoporotic vertebrae fractures, present also the reactive depression as one of the symptoms (12–17), but do not examine its reasons.

In our study we have been dealing with the reasons of the development of reactive depression in female patients in acute or chronically stage of painful osteoporotic vertebra fractures. We found out that those patients developed depression who had in their anamnesis more frequent incidence of traumatic experiences and a long-term overexertion on the job or at home. The onset of osteoporotic vertebra fracture with following vertebrogenic pain syndrome, disruption of sleep regime, limited mobility, loss of physical performance and independence represented for the patients a long-term stress situation. The median for developing depression was the 32nd day after the osteoporotic vertebra fracture. In this study we did not point out only that female

Tab. 4. Percentage representation of parameters weights of Questionnaire No. 2 within linear combination of the whole group (alpha=0.05).

Question No.	Weights of parameters of questionnaire in %	
	D	NonD
1	12.48	6.85
2	5.17	-13.64
3	19.26	4.53
4	11.08	-10.86
5	0.35	-9.45
6	-0.55	-7.98
7	18.80	8.75
8	19.00	3.83
9	1.51	-13.44
10	4.81	-16.65
11	7.00	-4.00

Tab. 5. Comparison of the number of positive answers (expressed in percentage from the overall number of questioned patients, n=32) in Questionnaire No. 2 for every question in the group of depressed patients (D) and non-depressed patients (NonD) (alpha=0.05).

Question No.	D n=32 %	NonD n=32 %	χ^2 χ-square test
1	91	44	18.447
2	59	31	5.254
3	84	69	2.234
4	84	13	41.273
5	56	13	15.160
6	53	16	10.774
7	84	59	5.188
8	91	41	20.686
9	56	6	22.687
10	69	9	28.423
11	72	19	20.356

Tab. 6. Validity criteria of Questionnaire No. 2 (alpha=0.05).

	Validity criteria (in %)								
Group	TN	FP	FN	TP	Sensitivity	Specificty	Prediction values of the positive test	Prediction values of the negative test	Test effectiveness
D	30	2	4	28	87.50	93.75	93.33	88.24	90.63
NonD	28	4	2	30	93.75	87.50	88.24	93.33	90.63

TP – true positives, TN – true negatives, FP – false positives, FN – false negatives

patients with osteoporotic vertebrae fractures in acute or chronically stage of the illness may develop reactive depression, but we tried to answer the question: Why do only some female patients develop depression? We see the contribution of our study in the finding that depression is developed more frequently in those women who have in their anamnesis a number of traumatic experiences and their character features are typical for depression prone persons (DPP).

Conclusion

Based on the result of our study we recommend the use of Questionnaires No. 1 and 2 in patients with acute painful vertebrae fractures for detecting risk patients for depression development. These patients should be followed more frequently within ambulatory care and in case of first clinical symptoms of depression should be recommended for special psychiatric care. Early anti-depression treatment by antidepressants of the 3rd and 4th generation (selective serotonine reuptake inhibitors – SSRI, serotonine and noradrenaline reuptake inhibitors – SNRI, noradrenergic and specific serotonergic antidepressants – NaSSA) could accelerates the mobilisation, rehabilitation and resocialisation of patients, could improves quality of their lives and reduces the costs of analgetic pain treatment, sedatives and rehabilitation. It has to be investigated in future studies.

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