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Depressive and anxiety disorders in patients with primary hyperparathyroidism

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Summary

Aim. The objective of the study was to evaluate the prevalence and severity of anxiety and depression in patients with primary hyperparathyroidism (PHPT), and to determine a relationship between the severity of these disorders and the serum calcium ion and parathyroid hormone level, as well as to evaluate the usefulness of self-rating scales in screening for depressive disorders in PHPT patients.

Method. Using the 17-item *Hamilton Depression Rating Scale* (HAM-D), *Beck Depression Inventory-II* (BDI-II) and *Hospital Anxiety and Depression Scale* (HADS), study was performed on a group of 101 patients with PHPT. A control group included 50 patients diagnosed with non-toxic thyroid goiter.

Results. The HAM-D indicated higher prevalence and severity of depressive symptoms in the whole population of patients and in women with PHPT. Such a relationship was not observed in men. The BDI-II indicated higher prevalence and severity of depressive symptoms in the whole population of patients and in women with PHPT. Such a relationship was not observed in men. The HADS did not show significant differences in the prevalence of depressive and anxiety symptoms between the study and control groups in the whole population and after taking into account the gender division.

Conclusions. A relationship between PHPT and depression was confirmed. Such a relationship was not confirmed for anxiety. A relationship between the severity of depression and the serum calcium ion and parathyroid hormone level was also not confirmed. A statistically significant negative correlation between the severity of anxiety and the serum calcium ion level in the whole population of patients, and an additional positive correlation between the serum parathyroid hormone level and the severity of anxiety in

women were confirmed. Self-rating tests are not sufficient for screening for depressive disorders in PHPT patients.

Key words: primary hyperparathyroidism, depression, anxiety

Introduction

Parathyroid glands are small glands that are typically located on the back of the thyroid gland. They can also be located in the thyroid parenchyma, thymus, pericardium and anterior or posterior mediastinum [1–3]. The basic function of parathyroid glands is to maintain the calcium homeostasis in the extracellular fluid and blood serum by secreting parathyroid hormone (PTH), which is the main regulator of the calcium balance [4].

Primary hyperparathyroidism (PHPT) is characterized by excessive secretion of parathyroid hormone which is caused by overproduction of PTH which is insensitive or poorly sensitive to the suppressive effect of hypercalcemia. Primary hyperparathyroidism is one of the most common endocrine disorders [1]. It is believed that only diabetes, thyroid diseases and polycystic ovary syndrome are more common than PHPT [1, 5]. The incidence rate depends on gender, with PHPT occurring much more often in women [6, 7].

Typical symptoms of primary hyperparathyroidism result from skeletal lesions, such as subperiosteal bone resorption, acroosteolysis, brown tumor and osteoporosis, as well as renal disorders, such as bilateral, recurrent kidney stone disease [8, 9]. Full-blown PHPT occurs only in 20% of cases; the remaining 80% is of subclinical (asymptomatic) course [8–13]. In this form of PHPT, the symptoms take the form of the so-called masks: nephrological, rheumatological, gastroenterological, endocrinological, cardiological, and hematological one [3, 5, 14].

In the course of PHPT, somatic symptoms can be accompanied by psychopathological symptoms [3, 5]. At the early stage of PHPT patients rarely report any somatic symptoms, while complaining of apathy, weakness, malaise, sleep disorders, lack of appetite, cognitive disorders (especially memory deterioration), and affective and anxiety disorders [7, 15, 16]. The most common psychopathological symptoms that occur in the course of PHPT are depressed mood, sleep disorders, emotional lability, neurasthenic symptoms, irritability, cognitive disorders and deterioration in daily activities [6–8, 10, 11, 15, 17–26]. More severe forms of PHPT involve psychotic symptoms, such as delusions, hallucinations and disorders of consciousness [24].

A relationship between the severity of psychopathological symptoms and the level of calcium in serum has already been described. However, what must be taken into account is that sensitivity to hypercalcemia varies significantly from patient to patient [15, 27]. According to another theory, the severity of mental disorders in PHPT is not associated with the level of calcium ions, but rather may result from other factors, such as personality traits before the illness occurred or social and cultural factors [20].

The occurrence of depressive and anxiety disorders in PHPT patients is the subject of studies published in recent years. Most of these studies focused on evaluating the severity of these disorders in patients before and after parathyroidectomy. The results generally indicate higher occurrence of depressive and anxiety disorders in PHPT patients, and alleviation of symptoms after the surgical procedure [28–37]. Still, the etiology of mental disorders in PHPT patients remains unclear. A handful of studies show there is a relationship between the severity of anxiety disorders and the level of parathyroid hormone [38], and between the level of calcium ions in serum and the severity of neuropsychological symptoms [30]. A detailed overview of sources touching upon this issue is provided in a separate publication [14].

Aim of the study

We predetermined the following study aims:

(1) Evaluate the prevalence and severity of anxiety and depressive disorders in PHPT patients.
(2) Determine a potential relationship between the severity of these disorders and the level of calcium ions and parathyroid hormone in serum.

Self-rating depression scales (which are less time-consuming [39–43]) are generally considered useful in screening tests in patients with somatic illnesses, thus we predetermined the third aim — namely evaluating *the Beck Depression Inventory – II* (BDI-II) and *the Hospital Anxiety and Depression Scale* (HADS) as suitable tools for screening of depressive disorders in PHPT patients. The choice of tools was based mainly on their availability for physicians rather than for psychiatrists.

Material and methods

The study was conducted from 1 March 2014 to 30 March 2016 at the Chair and Department of General Surgery, Medical University of Silesia, Bytom. During this period 130 patients were admitted in order to undergo parathyroidectomy. 29 of them were excluded due to lack of consent or meeting the exclusion criteria: renal failure, bipolar disorder, schizophrenia, schizotypal and delusional disorders, mental impairment, dementia or cognitive disorders that would prevent an individual from filling out questionnaires, and taking psychotropic medications at the time of the study and 3 months preceding it. Eventually 101 patients diagnosed with PHPT were screened. The control group consisted of 50 patients who were hospitalized during the same period due to a non-toxic thyroid goiter.

After giving consent to take part in the study, all patients filled out a personal questionnaire and underwent a basic psychiatric assessment. Then the 17-item *Hamilton Depression Rating Scale* (HAM-D) was used to evaluate depressive symptoms. After the assessment, each participant filled *the Beck Depression Inventory – II* (BDI-II)

and *the Hospital Anxiety and Depression Scale* (HADS) on their own. Diagnosis of depression or anxiety disorders was confirmed on the basis of ICD-10 criteria [44].

Next stage involved the analysis of correlation between the results obtained through HAM-D, BDI and HADS methods and the laboratory test results – measuring the level of calcium and parathyroid hormone in serum. Evaluation of calcium and parathyroid hormone levels in serum was based on data obtained from hospital records. No additional laboratory tests were performed.

The Bioethics Committee at the Medical University of Silesia decided that conducting the study entitled *Evaluation of mental state in patients diagnosed with hyperparathyroidism* does not require the Committee's approval.

Statistical analysis

Among the results features marked for the treatment and the control group, only the age variable is represented in the ratio scale. Hence the normality test was performed for this particular feature. The result of the Shapiro–Wilk test showed a significant deviation from the normal distribution. The results obtained using the HAM-D, BDI and HADS scales are represented in the ordinal scale. Considering the deviation from the normal age distribution in both groups, the values of median and quartile 1 and 3, as well as an interquartile range were determined for each variable. The nonparametric Mann–Whitney *U* test was used to compare both groups.

In terms of gender and normative values both groups were compared using the test of independence, which was complemented by Fisher's exact test in cases where sample size was small. For data gathered from the treatment group the Spearman's rank correlation coefficient was calculated along with a significance test for this coefficient. The reason for choosing the Spearman's rank correlation coefficient was that in each case one of the correlated features is represented in the ordinal scale.

Results

The study involved 101 patients in the treatment group and 50 patients in the control group. Both groups were similar in terms of age and gender. A detailed characteristics of both groups is provided in Table 1.

Table 1. **Group characteristics**

Parameters	Treatment group	Control group
Women	85	16
Men	42	8
Age range	20–86 years of age	25–75 years of age
Median age	60.0	58.0

Depressive and anxiety disorders

The Hamilton Depression Rating Scale (HAM-D) was used to evaluate the prevalence and severity of depressive symptoms. The cut-off point was set at 7 points.

The analysis of the obtained results showed a significantly higher prevalence and severity of depressive symptoms in the group of patients diagnosed with PHPT (Figure 1).

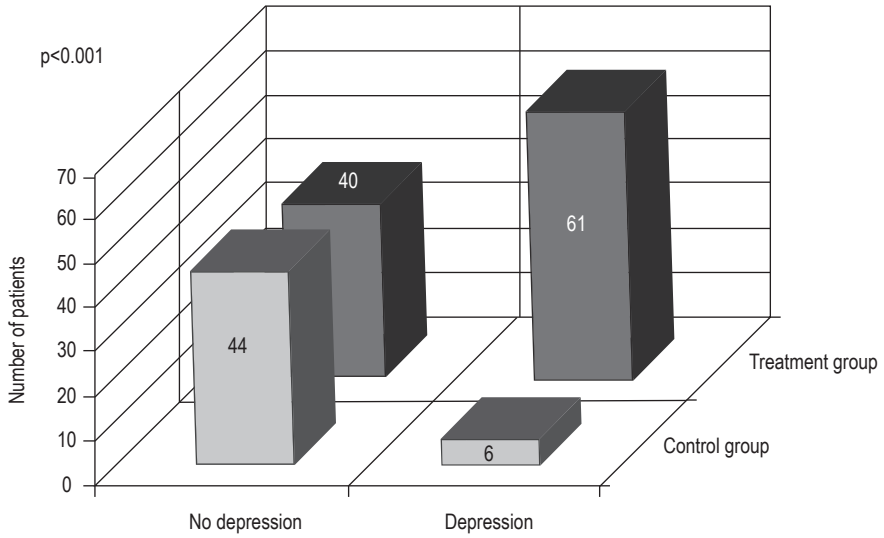

Figure 1. **The comparison of groups in terms of the number of people showing the presence of depressive disorders in the study using the Hamilton Depression Rating Scale (HAM-D)**

Similar results were observed in women ($p < 0.001$) (Figure 2).

Such dependence was not observed in men ($p > 0.05$). Detailed results are provided in Table 2.

Table 2. **Results in the Hamilton Depression Rating Scale (HAM-D)**

Hamilton Depression Rating Scale	Treatment group	Control group	Statistical significance
Median	9	2	p < 0.001
Presence of disorders	61 (101)	6 (50)	p < 0.001
Median (women)	9	2	p < 0.001
Presence of disorders (women)	53 (85)	4 (42)	p < 0.001
Median (men)	2.5	4	p > 0.05
Presence of disorders (men)	5 (16)	2 (8)	p > 0.05

The treatment group showed higher severity of depressive symptoms than the control group ($p < 0.001$) (Figure 3).

Similar results were observed in women ($p < 0.001$) (Figure 4).

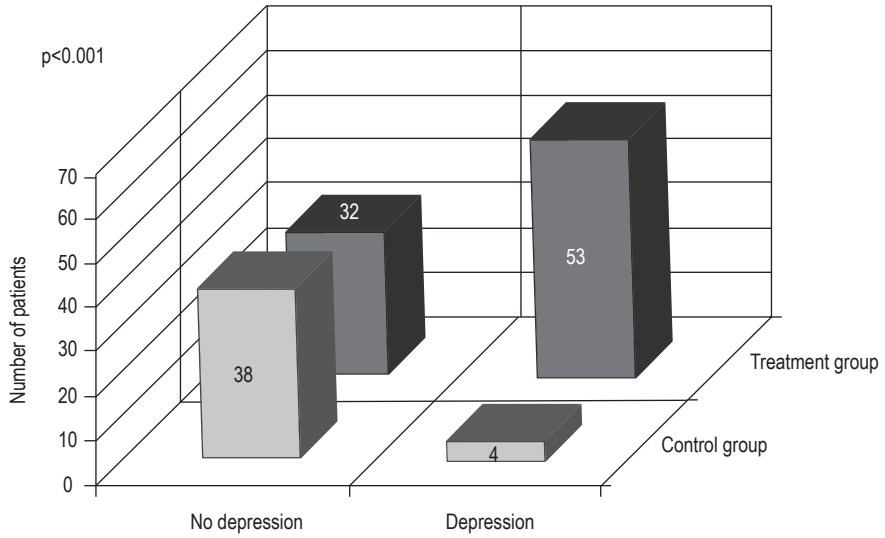

Figure 2. **The comparison of groups in terms of the number of people showing the presence of depressive disorders in the study using the Hamilton Depression Rating Scale (HAM-D) (women)**

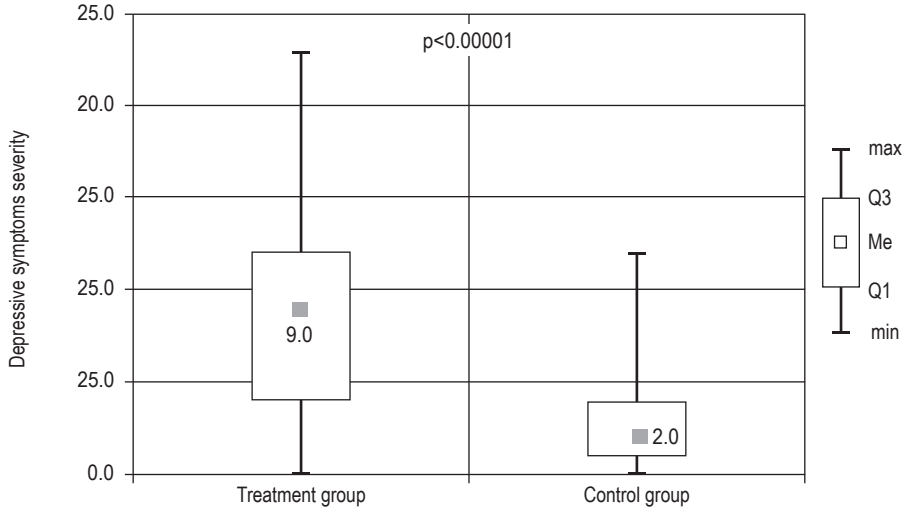

Figure 3. **Severity of depressive symptoms in the Hamilton Depression Rating Scale**

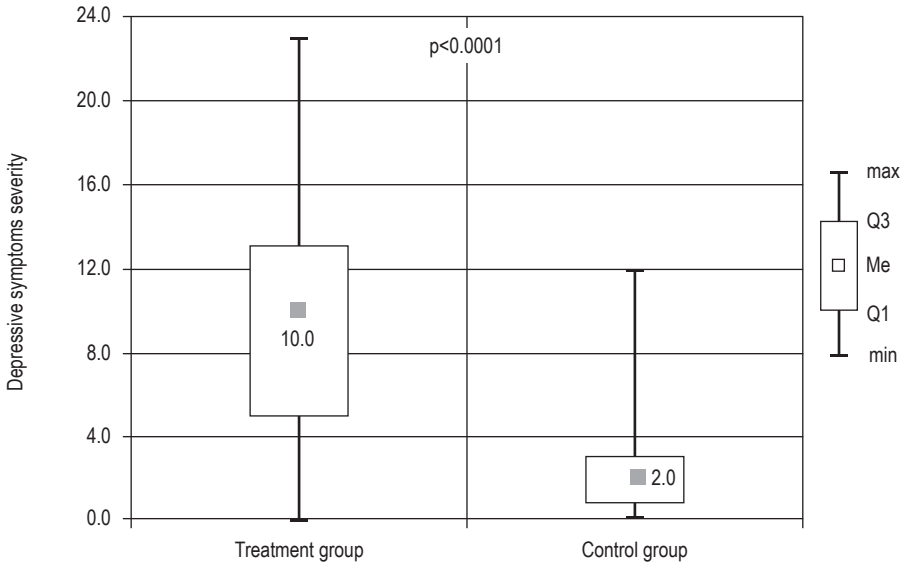

Figure 4. **Severity of depressive symptoms in the Hamilton Depression Rating Scale (women)**

Such dependence was not observed in men ($p > 0.05$).

Table 3 illustrates the distribution of the severity of depressive symptoms taking into account the division of the groups. Interpretation of the results was as follows: 8–13 points indicating mild symptoms, 14–18 points indicating moderate symptoms, 19–22 points indicating severe symptoms, 22 points and more indicating very severe depressive symptoms.

Table 3. **The size of groups, including the division into severity of symptoms based on the results obtained on the Hamilton Depression Rating Scale (HAM-D)**

Severity of depressive symptoms		Treatment group (n)			Control group (n)		
		Women	Men	Total	Women	Men	Total
Hamilton Depression Rating Scale	no depression	32	11	43	38	6	44
	mild	30	4	34	4	2	6
	moderate	16	1	17	0	0	0
	severe	7	0	7	0	0	0
	very severe	0	0	0	0	0	0

The results of *the Beck Depression Inventory – II*-based test (BDI-II) were also statistically compared. The cut-off point was set at 13 points. The analysis of the results showed a significantly more frequent exceeding of the cut-off point and higher severity of depressive symptoms in the group of patients diagnosed with PHPT (Figure 5).

Similar results were observed in women ($p < 0.05$) (Figure 6).

Such dependence was not observed in men ($p > 0.05$).

Detailed data concerning the number of patients is provided in Table 4.

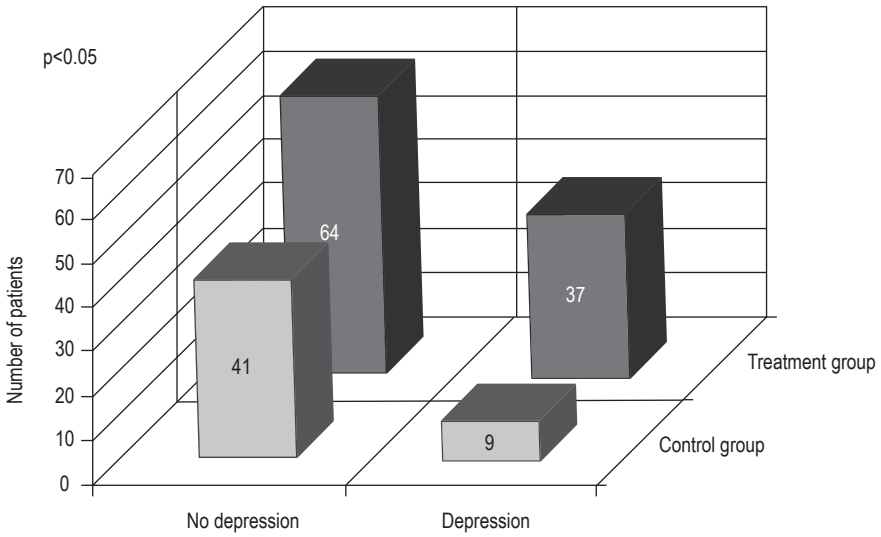

Figure 5. **The comparison of groups in terms of the number of people showing the presence of depressive disorders in the study using the Beck Depression Inventory – II (BDI-II)**

Table 4. **Results of the Beck Depression Inventory – II (BDI-II)**

Beck Depression Inventory	Treatment group	Control group	Statistical significance
Median	10	5.5	$p < 0.01$
Presence of disorders	37 (101)	9 (50)	$p < 0.05$
Median (women)	10	5	$p < 0.01$
Presence of disorders (women)	33 (85)	7 (42)	$p < 0.05$
Median (men)	2.5	4	$p > 0.05$
Presence of disorders (men)	3 (16)	2 (8)	$p > 0.05$

The next analysis involved disorder severity measured using the BDI-II. The treatment group showed higher severity of depressive symptoms than the control group ($p < 0.05$) (Figure 7).

Similar results were observed in women ($p < 0.05$) (Figure 8).

Such dependence was not observed in men ($p > 0.05$).

Table 5 illustrates the distribution of the severity of depressive symptoms taking into account the division into groups. Following interpretation of the results was used: 14–19 points: mild symptoms, 20–28 points: moderate symptoms, 29 points and more: severe symptoms.

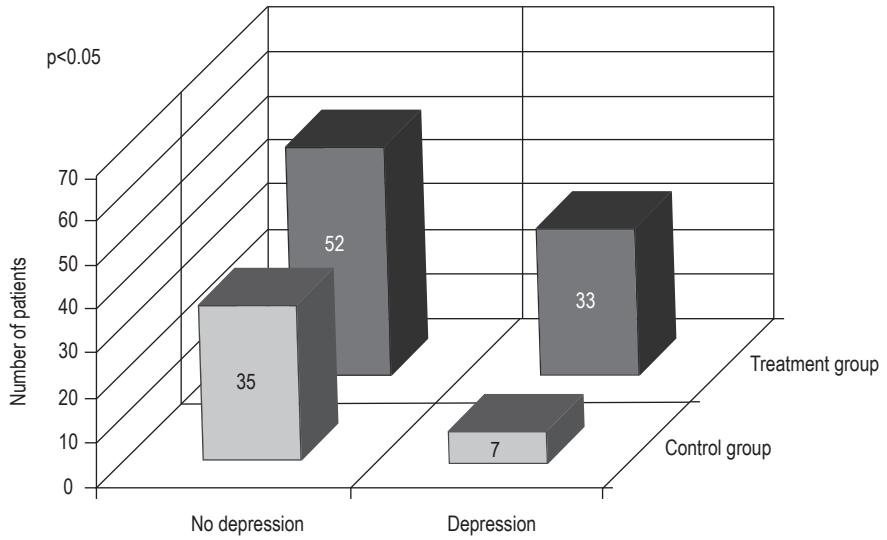

Figure 6. **The comparison of groups in terms of the number of people showing the presence of depressive disorders in the study using the Beck Depression Inventory – II (BDI-II) (women)**

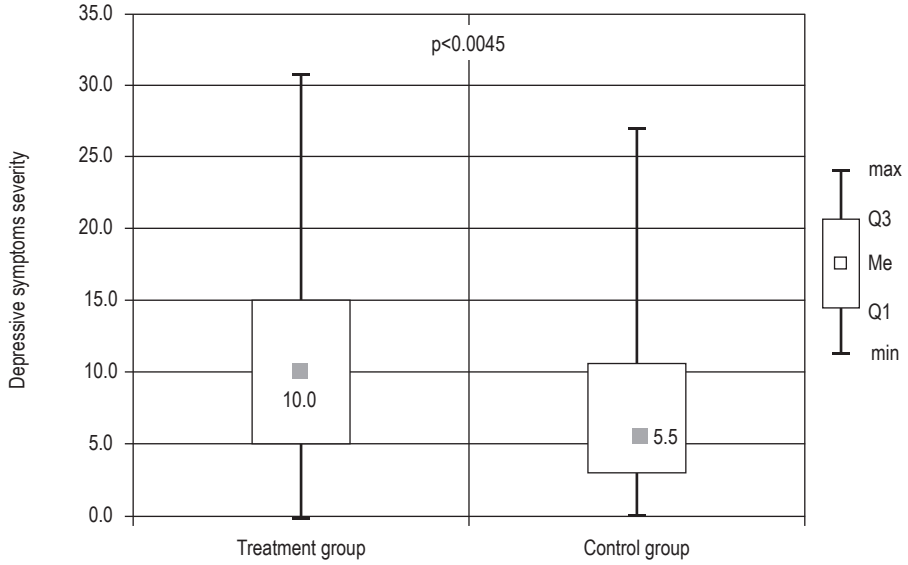

Figure 7. **Depressive symptoms severity in the Beck Depression Inventory – II**

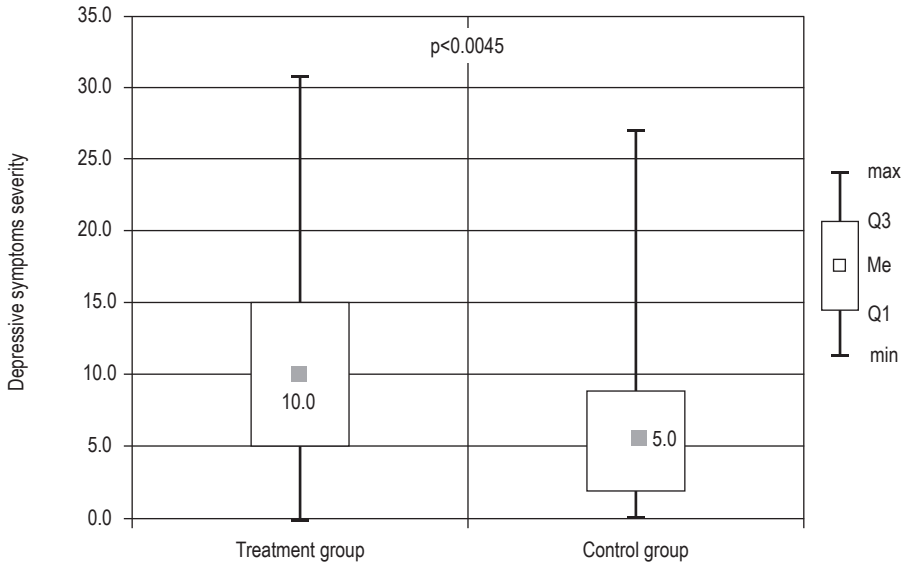

Figure 8. **Depressive symptoms severity in the Beck Depression Inventory – II (BDI-II) (women)**

Table 5. **The size of groups, including the division into severity of symptoms based on the results obtained in the Beck Depression Inventory – II (BDI-II)**

Severity of depressive symptoms		Treatment group (n)			Control group (n)		
		Women	Men	Total	Women	Men	Total
Beck Depression Inventory	no depression	52	13	65	35	6	41
	mild	23	2	25	4	1	5
	moderate	10	1	11	3	1	4
	severe	0	0	0	0	0	0

In order to compare both groups in terms of the occurrence of depressive and anxiety symptoms, *the Hospital Anxiety and Depression Scale* (HADS) was also used. The cut-off point was set at 7 points for both the depressive and anxiety symptoms subscales. Detailed results are provided in Tables 6 and 7.

Table 6. **Results obtained in the HADS-D subscale**

HADS-D scale	Treatment group	Control group	Statistical significance
Median	5	2	$p < 0.01$
Presence of disorders	21 (101)	6 (50)	$p > 0.05$

table continued on the next page

Median (women)	5	2.5	p < 0.01
Presence of disorders (women)	19 (85)	5 (42)	p > 0.05
Median (men)	4	2	p > 0.05
Presence of disorders (men)	2 (16)	1 (8)	p > 0.05

Table 7. **Results obtained in the HADS-A subscale**

HADS-A scale	Treatment group	Control group	Statistical significance
Median	6	6	p > 0.05
Presence of disorders	39 (101)	17 (50)	p > 0.05
Median (women)	7	6	p > 0.05
Presence of disorders (women)	36 (85)	15 (42)	p > 0.05
Median (men)	5	6	p > 0.05
Presence of disorders (men)	3 (16)	2 (8)	p > 0.05

Correlations

The results were analyzed with the use of Spearman's correlation coefficient. Statistically significant correlation between the severity of depression symptoms (HAM-D, BDI-II, HADS) and the serum calcium and parathyroid hormone level was not observed in the group of all examined patients, also after taking into consideration the division into groups according to sex. However, it was proved there is a slight negative correlation between the severity of anxiety symptoms evaluated using the HADS and the level of calcium ions in serum in patients diagnosed with primary hyperparathyroidism ($rs = -0.1863$; $p < 0.05$). If gender division is taken into account, in the group of women such relationship was also confirmed ($rs = -0.2404$; $p < 0.05$) together with a positive correlation between the severity of anxiety symptoms and the level of parathyroid hormone ($rs = 0.1797$; $p < 0.05$). In the group of men, a relationship between the severity of anxiety symptoms and the level of calcium ions and parathyroid hormone in serum was not confirmed.

Discussion

So far there are not many studies that analyze the occurrence of depressive and anxiety disorders in the population in question. Most of these studies involve small study groups (we have managed to find only one study that involved a group that was bigger than our own) with researchers focusing typically on comparing mental state before and after the surgical procedure. Only White et al. [38] conducted a similar study

and failed to find significant differences between the PHPT patients and the control group in terms of the severity of depressive and anxiety symptoms.

Control group was decided to consist of patients suffering from nontoxic goiter who were being prepared to operation. The reasons in favor of such choice were similarities in terms of lesions location and the course of the surgical procedure, as well as rare cases of hormonal imbalance [45]. Similar choice of the control group was made by Pasieka and Parsons [46], Dotzenrath et al. [29] and Weber et al. [32]. Babińska et al. [31] chose patients undergoing other surgical procedures. However, it appears that potential differences between particular surgical procedures are substantial enough so that obtained results may not be completely objective.

The results obtained by our team indicate significantly more frequently occurrence and higher severity of depressive disorders in patients with primary hyperparathyroidism when compared to general population. The HAM-D-based test showed higher prevalence and severity of depressive symptoms both in the whole population and in women who underwent the examination. The difference was highly statistically significant. The analysis of the results obtained by male participants did not show significant differences in both groups. However, this group was much smaller. Although it is in accordance with the prevalence of PHPT in general population [6, 7], it might have affected the results. The question of whether statistical significance would be obtained after enlarging the male group remains open, but the literature review shows that studying a larger group is difficult.

Results obtained from the BDI-based examination also showed a considerably higher prevalence of depressive symptoms and their higher severity both in the whole population and in the group of female patients with primary hyperparathyroidism when compared with the control group. However, the significance level was substantially lower than in the case of results obtained using the HAM-D scale. The analysis involving male participants did not show a statistically significant difference in terms of prevalence and severity of depressive symptoms in the treatment group and the control group.

The analysis of results of the HADS-based evaluation of depressive disorders did not show significant differences in the prevalence of depressive symptoms between the treatment group and the control group – both in the whole evaluated population and after gender division. However, the median amount of points scored by PHPT patients was significantly higher than in the control group – both in female and male participants and for the whole evaluated population.

The second aim of the study was to compare the sensitivity of commonly used self-rating depression scales (BDI-II, HADS) with the objective scale (i.e., the HAM-D scale) in the population of PHPT patients. The difference between the results obtained through the self-rating scales and those from the objective scale indicates higher sensitivity of the latter. It suggests that using self-rating scales for screening of depressive disorders in PHPT patients may be insufficient. Moreover, the study results indicate the need for performing thorough, depressive disorder-oriented routine diagnostic

procedures in PHPT patients, and in many cases providing those patients with full psychiatric care.

The analysis of the results concerning anxiety disorders did not show any significant differences between the treatment group and the control group both for the whole population and by gender division. However, the study circumstances need to be taken into account. Patients from both the treatment group and the control group awaited for the surgical procedure, which could intensify anxiety and thus distort the results. Another factor that could affect the results was the fact that anxiety disorders were evaluated only using the self-rating scale. This calls for conducting a study on anxiety disorders in PHPT patients using the objective scale. This is where the analogy to the interlinkages of mental disorders in cardiovascular diseases overlaps. The negative impact of depression on the prognosis of the cardiovascular diseases was clearly confirmed, however, the impact of anxiety on the course of these diseases is still questionable [47].

In the study we failed to find a statistically significant correlation between the occurrence and severity of depressive disorders and the parameters routinely evaluated in PHPT. The analysis of publications showed that there was lack of convincing evidence of significant relationship between the severity of depressive symptoms and biological indicators of the disease, and the summary is in the consensus of experts presented by Bilezikian in 2014 [29, 31, 48, 49]. In the PubMed and MEDLINE databases, no later reports were found that would significantly change this view. This indicates the need for conducting further studies concerning this population of patients in order to determine a possible relationship between PHPT and the occurrence of depressive disorders.

Statistically significant slight negative correlation was found between the severity of anxiety symptoms and the serum calcium ions level. In the group of women, it was also found that the serum parathyroid hormone level correlated positively with the severity of anxiety symptoms, what was in agreement with earlier researches [8, 30, 38, 50]. We failed to find similar relationships in men. This suggests the need for conducting further studies on the population of PHPT patients, and indicates the direction of such studies.

Conclusions

1. Significant relationship between primary hyperparathyroidism and depressive symptoms were found in the research. Such relationship was not proved for anxiety symptoms.
2. Significant relationship between the severity of depressive symptoms and the serum calcium ions and parathyroid hormone level was not observed. Slight significant negative correlation was found between the severity of anxiety symptoms and the serum calcium ions level. In the group of women, it was also found that the serum parathyroid hormone level correlated positively with the severity of anxiety symptoms.

3. Self-rating tests are not sufficient for screening of depressive disorders in PHPT patients. Evaluation has to be conducted using the objective scale.

Practical conclusion: PHPT patients should be screened for depressive and anxiety disorders.

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