Primary hyperparathyroidism (PHPT) is hypersecretion of parathormone (PTH) from the parathyroid glands, resulting in persistent hypercalcemia and usually hypercalciuria. It frequently occurs as the effect of single or multiple adenomas (80–85%); less often, it is the result of parathyroid hyperplasia (15–20%); in very rare cases it is caused by parathyroid carcinoma (<1%) [1, 2]. Even more rarely PHPT is part of genetically acquired endocrine diseases: multiple endocrine neoplasia type 1 (MEN1), MEN2A, MEN1-like syndromes, etc. [3]. PHPT is a common endocrine disorder that is still rarely taken into account by clinicians. Its prevalence varies from 1 to 4.3/1000, depending on sex, age and the screening threshold for hypercalcemia [1].
men, reaching 21/1000 in women above the age of 50 [4]. Classic PHPT is a multisystemic symptomatic disorder [5]. The most recognizable symptoms are renal and skeletal complications: nephrolithiasis, nephrocalcinosis, *osteitis fibrosa cystica* (OFC) and osteoporosis. There are also nonspecific manifestations from different organs, including cardiovascular, gastrointestinal, rheumatic and neuropsychological symptoms that often mimic other diseases [5]. A variety of symptoms appear at different times and with variable intensity, which may delay the diagnosis [6, 7]. Other manifestations are specific for PHPT (e.g. brown cell tumors), but often receive only symptomatic treatment in surgery units [8].

There is a growing amount of evidence that the presentation of PHPT has evolved in the last few decades to a less symptomatic form [9]. However, in countries where plasma calcium-phosphate tests are less popular, many symptomatic patients receive delayed diagnosis. Untreated PHPT leads to irreversible changes including skeletal deformations and renal insufficiency [6, 7, 10].

**Objectives**

The purpose of this paper is to revise the symptomatology profile of contemporary PHPT; and to facilitate early PHPT diagnosis by encouraging interdisciplinary communication among medical professionals.

**Material and Methods**

The prevalence of PHPT symptoms were analyzed retrospectively in a group of 100 consecutive patients diagnosed with PHPT in Wroclaw Medical University’s Department of Endocrinology, Diabetology and Isotope Therapy (Wroclaw, Poland) between 2002 and 2012. The group consisted of 94 women and 6 men, at the average age of 57.1 years (SD: 13.7 years) at the moment of diagnosis.

During the diagnostic process the data was analyzed thoroughly, following standard procedures. Biochemical conditions – hypercalcemia, hypophosphatemia, hypercalciuria, and elevation of serum PTH level – were analyzed. Patients were assessed by thyroid ultrasound and technetium Tc 99m sestamibi scintigraphy or, occasionally, by computed tomography.

Osteoporosis was evaluated using dual X-ray densitometry (DXA) at three sites: the lumbar spine, femoral neck and distal one-third of the radius, with individual descriptions of the trabecular and cortical bones. Fragility fractures and features of *osteitis fibrosa cystica* (OFC) were evaluated using hospital X-ray data and anamnesis documentation. The occurrence of cardiovascular symptoms was based on hospital measurements of arterial blood pressure, any history of hypotensive drug therapy and anamnesis documentation. Metabolic syndrome was assessed according to International Diabetes Federation (IDF) 2009 criteria, based on available blood test results. Gastrointestinal and renal symptoms were assessed by abdominal ultrasound imaging and anamnesis documentation, including endoscopic investigation data. The time between the first onset of the disease symptoms and the final PHPT diagnosis were also noted.

The retrospective character of the study limits its scope; only the available data has been included. Uncertain data records concerning neuropsychological symptoms were found in the analyzed group and the authors decided not to include these. For the presentation of the quantitative data, the means ± standard deviation and the median were calculated, using Microsoft Excel 2013 (Microsoft Corp., Redmond, WA, USA). The results for qualitative variables are expressed as percentages.

**Results**

In the study cohort, 96 patients (96%) were diagnosed only with PHPT, while in three cases (3%) the diagnosis was a part of MEN1, and in one case (1%) it was part of MEN1-like syndrome (with a carcinoid tumor). There was one case of parathyroid gland carcinoma; the other 99 were benign lesions of adenoma or hyperplasia. Mainly single adenomas were discovered; three cases involved multiple adenomas.

The time from discovering the first symptom and diagnosing the disease varied from under 1 year (19%), 1–10 years (46%), to over 10 years (35%).

In order to examine the presence of different symptoms, they were divided into six groups: renal, skeletal, coexisting renal and skeletal, cardiovascular, gastrointestinal and asymptomatic. The incidence of clinical symptoms in entire group of 100 PHPT patients are shown in Fig. 1.

**Renal Symptoms**

Overt renal symptoms, including detectable renal stones, nephrocalcinosis and renal colic episodes, were present in 55 patients, either on their own or along with other symptoms. Isolated renal symptoms as the only presentation of the disease were observed in 14 patients. Out of the 55 symptomatic renal patients, 53 presented typical
renal concrements. Renal papillary calcifications or nephrocalcinosis were described in 18 cases. In 49 of the symptomatic renal patients, there was precise information about the duration of the renal symptoms: In 26.5% of them renal symptoms were detected de novo during the diagnostic process of suspected PHPT; in 38.8% the previous duration of nephrolithiasis varied between one and 10 years; in 20.4% it ranged from 10 to 20 years; and in 14.3% it was more than 20 years. During the period of symptomatic renal disease multiple urological interventions were performed, some of them invasive. Lithotripsy was performed in seven cases, and in five it was repeated more than once (four times in one case, three times in three cases, twice in one case). Lithotomy was performed in seven patients (in two cases it was a double lithotomy). There were also two cases of nephrectomy due to complications of nephrolithiasis. In 41% of the patients with PHPT, renal and skeletal symptoms coexisted.

Skeletal Symptoms

Osteoporosis or osteopenia in at least one site was present in 76 patients, among whom 66 had osteoporosis (T-score < (–)2.5) and 10 osteopenia (T-score between (–)1.5 and (–)2.5) according to the WHO classification. Isolated bone symptoms were noted in 35 patients. In the current study the mean bone mass density (BMD) was lowest in the cortical bone of the radius at (–)3.0 (SD: 1.53) and in the trabecular bone at (–)2.7 (SD: 1.48). The BMD in the lumbar spine and femoral neck were (–)2.2 (SD: 1.48) and (–)2.0 (SD: 1.16), respectively. One-third of the patients reported generalized bone pain. Sixteen patients showed fragility fractures. The most frequent fracture site was the spine (eight cases) and upper limb (seven cases). Femoral neck fractures were noted in three cases; in two of them the fracture localization corresponded to the presence of OFC bone cysts. Multiple fracture sites were observed in five cases, mainly the spine and upper limb. Brown tumors were identified in 10 cases, only six of which were osteoporotic. They were mainly maxillofacial (nine), in long bones (three) and ribs (two); three patients suffered from multiple brown tumors.

Cardiovascular and Metabolic Symptoms

In the study group 58 patients presented cardiovascular disorders. Of these, 21 (21% of the whole group) had documented ischemic heart disease (IHD) (including angina pectoris, past myocardial infarction, ischemic changes in ECGs, arrhythmias) or IHD–positive anamnesis; 55 (55% of the whole group) had arterial hypertension (HA). In 94 patients the data was sufficient to expect metabolic syndrome features, which was present in 28% of the cases.

Gastrointestinal Symptoms

In the group 52 patients suffered from at least one of the following gastrointestinal symptoms: gastritis, dyspepsia, peptic ulcer, pancreatitis or cholelithiasis; 29 of the symptomatic patients had gastritis or dyspepsia, and among those seven had documented peptic ulcerous disease. There were 27 cases of documented cholelithiasis. Three patients (5.8% of 52), all women, had histories of pancreatitis, and for one of them it was the first symptom of PHPT.

Asymptomatic Primary Hyperparathyroidism

The diagnosis of 15 asymptomatic patients (without previous renal effects, and no osteoporosis/osteopenia discovered) was incidental. When
the criteria of asymptomatic history was expanded to include patients with osteoporosis or osteopenia detected only in DXA and without fragility fractures, the number of asymptomatic patients rose to 28.

**Biochemical Analysis**

The biochemical conditions in the total group of 100 analyzed patients are shown in Table 1. There were 24 patients who presented the typical biochemical profile of PHPT: hypercalcemia, hypercalciuria and hypophosphatemia simultaneously. Hypercalcemia and hypercalciuria coexisted in 45.3% of the cases. In 4.2% hypercalciuria was not accompanied by hypercalcemia, indicating normocalcemic PHPT (nPHP).

**Diagnostic Imaging**

Ultrasound (USG) of the neck and Tc99 sestamibi scintigraphy are both well-established methods of PHPT diagnostic imaging [11]. In 90% of the patients in the current study Tc99 sestamibi scintigraphy was performed, and in 60% of these patients this method revealed a parathyroid adenoma. USGs of the neck were performed on the whole group. The USGs raised the suspicion of parathyroid adenoma in only 29 cases, and in 17 of these cases (70.4%) these USG results were consistent with positive Tc99 sestamibi scintigraphy results. In 21% of the patients additional scans were performed to localize the adenoma, usually spect-CT and CT, as well as MRIs in three cases. In 34 patients no certain localization was discovered.

**Discussion**

The group of 100 consecutive PHPT patients under investigation was dominated significantly by women (96%). This reflects the fact that PHPT occurs far more often in women [4, 12]; it has been shown to increase five-fold in women above the age of 50 (like our patients) [4]. But the full reason for such a high prevalence remains unclear. It may be an effect of poorer prophylactic care among men: Men have their blood calcium levels and BMD checked less frequently, whereas women, especially around menopause, are usually monitored for osteoporosis [13].

**Laboratory Abnormalities**

PHPT is a well-known cause of hypercalcemia. The mean s-Ca level in the current study group was 2.87 mmol/L (SD: 0.35), slightly higher than in other observational data [14, 15]. In large retrospective studies conducted in Scotland on 904 PHPT patients, the mean s-Ca concentrations in hypercalcemic patients fluctuated mildly, reaching 2.62 mmol/L and 2.67 mmol/L, respectively, at 12 and 15 year intervals [14, 15]. Meanwhile, a study of Brazilian PHPT patients reported a mean s-Ca level of 2.83 mmol/L [16]. In the current study, hypercalcemia dominated significantly, affecting over 3/4 of the patients, while hypercalcemia, hypercalciuria and hypophosphatemia coincided in 1/4 of the cases. As expected, the mean PTH level was five times higher than the upper normal value. Measuring both the s-Ca and PTH levels is considered the most accurate test for PHPT [12], and the data from the present study support this. Moreover, serum PTH has been identified as the best biochemical risk factor predicting adverse outcomes in untreated PHPT [17].

**Renal Effects**

The current study was focused closely on the clinical symptomatology of PHPT. Renal symptoms were present in 55% of the patients, which was considerably less than described by Albright et al. in classic PHPT [5]. This may be an effect of the intense progress and better availability of diagnostic methods as compared with the 1930s. However, in a few patients in the current study the PHPT diagnosis was very delayed, and in these patients recurrent renal complications appeared and invasive urological treatment (lithotomy, ne-

| Table 1. Biochemical conditions in the study group of 100 PHPT patients |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
|                            | Serum Ca [mmol/L] | Serum Phos. [mmol/L] | Urine Ca [mEq/24 h] | PTH [pg/mL] |
| Mean value                  | 2.87 (SD 0.36)    | 0.81 (SD 0.23)     | 15.97 (SD 7.89)    | 324 (SD 425)      |
| Median value                | 2.8              | 0.8               | 14.3              | 192.5           |
| Normal value                | 2.1–2.6          | 0.8–1.6           | 5–15              | 11–67           |
| Biochemical symptoms        | 85% ↑CaS.        | 54% ↓PhoS.        | 49% ↑CaU.         | 100% ↑PTH      |

↑CaS – hypercalcemia; ↓PhoS – hypophosphatemia; ↑CaU – hypercalciuria.
phrectomy) was performed. The reason for this may be the low prevalence of PHPT (3%) reported among urolithiasis patients [12]. Recent retrospective studies have presented a lower incidence of nephrolithiasis in PHPT patients (18.2% to 28.6%) than observed in the current study [16, 13]. Due to the small size of the study groups, the incidence may be hard to compare [13]. There might also be differences in the features of the selected study groups. The studies mentioned above describe mainly oligosymptomatic patients with normocalcemic and mildly hypercalcemic PHPT (mean s-Ca 2.39 mmol/L and 2.82 mmol/L, respectively), whereas in the patients in the current study the s-Ca level was higher, and hypercalcemia occurred simultaneously with hypercalciuria in all but 4.2% of the group. Nephrolithiasis in PHPT is attributed mostly to extensive hypercalcemia; in the current study hypercalcuria affected 49.5% of the patients, and in that group nephrolithiasis prevailed.

**Skeletal Effects**

In the present study, 76% of the patients had bone symptoms. Osteoporosis was observed in 66% of the cases, twice as much as in a Wisconsin population study of 1309 patients with PHPT [18]. This difference may be partly related to the special features of the current study group, which was a small population dominated by postmenopausal women with a risk of osteoporosis due to estrogen deficiency, so the low BMD level may be a result of both PHPT and additional factors other than PHPT. This also concerns some other available studies [16, 19, 20]. In the present study 16 bone symptomatic patients (23.8%) had a previous history of fragility fractures, 1/3 of them with multiple fracture localizations, mainly the spine and wrist, and less frequently the femoral neck. In most cases, except one where the suspicion of PHPT was raised directly in the orthopedic unit, fragility fractures had taken place a few years before PHPT was recognized, and did not lead directly to the endocrine diagnosis. Nevertheless, in large population studies patients with PHPT show a significantly increased risk of fractures compared to the age- and sex-adjusted general population [17]. As some studies report, the prevalence of PHPT among women with osteoporosis is remarkable (8.9%), and general fractures affect from 10% to 21.4% of them [13, 16]. The observations from the present study also confirm this tendency. The mean BMD level in the current study group was lowest in the cortical bone in the distal one-third of the radius ((−)3.0; SD: 1.53) and in the trabecular bone ((−)2.7; SD: 1.48). These results are consistent with other studies, including histomorphometric analyses [19, 21, 22]. The one-third radius BMD declined by 35% in long-term observational studies evaluating the natural history of PHPT [23, 15]. In PHPT, protracted elevation of serum PTH is associated predominately with cortical bone loss, but not trabecular bone loss [22]. However, recent data suggest an alternative explanation for the preservation of the trabecular bone: PHPT causes microarchitectural remodeling in both cortical and trabecular bone; in the cortex, cortical remnants are produced, and in DXA they resemble true trabeculae [24].

In the 1930s, clinical manifestations of OFC were observed in nearly one-third of PHPT-affected individuals [5, 22]. In the current study brown tumors were identified in 10% of the cases, and in typical areas. The PHPT history of three of them was asymptomatic, while the others indicated previous nephrolithiasis in anamnesis. Two cases presented signs of OFC in multiple localizations and fragility fractures due to the presence of bone cysts. Remarkably, the coexisting osteolytic bone changes mimicked a metastatic disease of unknown origin. Nevertheless – considering that in developed countries 80% of PHPT is now recognized before the appearance of obvious skeletal symptoms, and that severe forms of PHPT are now rarely diagnosed in developed countries – the prevalence of brown tumors in the current study group was unexpectedly high [8, 22]. The problem of severe advanced symptomatic PHPT especially concerns developing countries, where younger patients often suffer from advanced OFC complications [7, 25].

It is worth noting that incidental diagnoses of PHPT in asymptomatic patients occurred in 15% of the cases, but rose to 28% after the criteria of asymptomatic PHPT were expanded to include patients with osteoporosis detected only in DXA, but without fragility fractures or OFC symptoms. These data reflect the general trend toward the less symptomatic modern phenotype of PHPT in developed countries, with rarely seen OFC, less common nephrolithiasis and sporadic gastrointestinal and rheumatic symptoms [26].

**Gastrointestinal Effects**

Many decades ago, peptic ulcer and pancreatitis were considered associated with classic PHPT [27]. In the present study, pancreatitis was found in three cases. In one case it was the first symptom of PHPT. Data gathered in other studies also reflect this tendency [28–30]. The incidence of acute pancreatitis in patients with PHPT varied from 1% to 12%, and PHPT is a confirmed risk factor for acute pancreatitis. Nevertheless, in the current study the incidence of acute pancreatitis (4%) was lower than that in other studies [19, 21, 22]. This difference may be partly related to the small size of the study groups, the incidence described by others still remains higher, at about 6% [13–15]. The reasons for such a difference may be differences in the features of the selected study groups, which were recognized, and did not lead directly to the endocrine diagnosis. Nevertheless – considering that in developed countries 80% of PHPT is now recognized before the appearance of obvious skeletal symptoms, and that severe forms of PHPT are now rarely diagnosed in developed countries – the prevalence of brown tumors in the current study group was unexpectedly high [8, 22]. The problem of severe advanced symptomatic PHPT especially concerns developing countries, where younger patients often suffer from advanced OFC complications [7, 25].
factor for this disease: The risk of pancreatitis is approximately 10 times higher in PHPT patients than in the general population. The present study also confirms that acute pancreatitis may appear in a PHPT-presenting form [28–30].

In the current study group, 29 symptomatic patients (55.7%) had gastritis or dyspepsia, but only seven (13.5%) developed endoscopically confirmed peptic ulcerous disease. This is significantly less than before proton pump inhibitors came into use, when 30% of adults with hyperparathyroidism suffered from peptic ulcer [27]. The data from the present study support the new trend not to associate peptic ulcers with PHPT too strongly [28]. Recently, however, PHPT has been associated with chronic autoimmune atrophic gastritis (CAAG) [31]. CAAG or other benign conditions could partially explain the number of dyspeptic symptoms reported by patients without a confirmed ulcerous disease.

Hypercalcemia and elevated PTH are suspected to cause cholelithiasis in patients with PHPT [32]. In the present study, cholelithiasis was observed in 27% of the patients, in agreement with other studies that have demonstrated more cases of cholelithiasis in PHPT (25.8%) compared to the general population (3.1%) [32, 33]. The present study group consisted mostly of postmenopausal women, and this might partly explain the prevalence of cholelithiasis [33].

The general incidence of gastrointestinal manifestations in the present study is quite high (52%). This may be an effect of including a wide variety of gastrointestinal symptoms, not only the severe ones described by Albright et al. [5]. As other authors have pointed out, the most frequent digestive manifestations of PHPT are non-specific symptoms consequent to smooth-muscle atony [34, 23]. The present study also confirms that nowadays the presentation of PHPT is less symptomatic than a few decades ago.

**Cardiovascular Effects**

PHPT is associated with a higher incidence of arterial hypertension than in the general population [35]. In the present study the incidence of HA was 55%. Other studies confirm this tendency, and in one report the HA incidence was even higher (81%) [35–37]. It has also been directly observed that PTH infusion results in HA in healthy subjects [38]. Still, data describing the impact of surgical PHPT treatment on HA and the circadian rhythm of blood pressure are not consistent [36, 37].

In the present study, 28% of the patients fulfilled the criteria for a diagnosis of metabolic syndrome. But there are not many observations confirming that PHPT patients suffer from metabolic syndrome more often than those with essential hypertension [37]. Is the high prevalence of metabolic syndrome a real feature of PHPT patients, or just a coincidence? This question definitely needs more investigation. Especially, in light of the fact that PHPT has been associated with an increased risk of mortality, particularly from cardiovascular diseases (CVD) [17, 39–41].

In the current study, 58% of the patients with PHPT suffered from at least one of the following CVDs: ischemic heart disease (IHD), HA or stroke, just as reported in other studies [17, 39–41]. It has been suggested that the severity of PHPT may determine the presence of cardiovascular manifestations [42]. However, a study conducted in Tayside, Scotland, showed that CVD mortality was similarly increased for patients with mild untreated PHPT and those with severe PHPT [17]. It has also been noted that elevated PTH levels have been associated with CVDs and elevated mortality in people without any known parathyroid disease as well [43–45].

Hypercalcemia is also a known cause of arrhythmias [46, 47]. One of the patients in the present study needed a cardiac pacemaker because of hypercalcemia-dependent bradycardia. After surgical treatment of PHPT, the patient’s correct heart rhythm and biochemical balance were restored. Although the incidence of CVD among patients with PHPT is high, a clinical suspicion of PHPT is hardly ever taken into account by cardiologists. The current authors suggest routine calcium-phosphorous balance tests in bradycardia patients to actively search for potential reversible causes of arrhythmia.

**Diagnosis**

In the current study, although bone symptoms were more often noted than renal symptoms (76% vs. 55%), nephrolithiasis was the patients’ main reason for seeking medical help. PHPT was most often suggested to the patients by endocrinologists (52%), family doctors/internal diseases specialists (29%) and rheumatologists at ambulatory osteoporosis care centers (10%), even though the patients had previously been treated by urologists and orthopedists. The patients were rarely directed to endocrine specialists by a urologist (2%), orthopedist (1%) or maxillary surgeon (6%). This may be because bone fractures and renal stones are poorly characteristic and are certainly more frequent in the general population than PHPT. The data from the current study indicates how great the need is
to take PHPT under consideration in the diagnostic process, especially since PHPT occurs in 3% of urolithiasis patients and in 8.9% of osteoporotic postmenopausal women [12, 13]. The authors have observed that a growing percentage of PHPT diagnostics is being performed thanks to ambulatory osteoporosis care centers, especially in menopausal women. The significant rate of PHPT suspicions raised by maxillary surgeons in the current study may be an effect of the prototypical character of the symptoms observed: brown cell tumors, gingival cysts and *epulis gigantocellularis*.

The authors have concluded that PHPT is still being diagnosed too late. Frequent particular non-specific symptoms in the general population might be partly responsible for that, as they often make the diagnosis difficult and interdisciplinary. It may also be an effect of a lack of serum calcium-phosphate balance screening. Obligatory calcium-phosphate balance screening tests in patients over 50, especially those with recurrent nephrolithiasis and osteoporosis, might be beneficial to their health. The popularization of densitometry facilitates earlier PHPT diagnosis and treatment. Promoting knowledge of PHPT symptoms and multidisciplinary diagnostic cooperation among medical professionals (especially urologists, orthopedists, gastroenterologists, rheumatologists, family doctors, dentists and maxillary surgeons) makes it more likely that patients will avoid late complications of long-lasting unrecognized disease. The current study provides evidence of the general trend, that nowadays the presentation of PHPT is less symptomatic than a few decades ago.

**References**


Address for correspondence:
Anna Jodkowska
Department and Clinic of Internal and Occupational Diseases and Hypertension
Wrocław Medical University
Borowska 213
50-556 Wrocław
Poland
Email: anna.jodkowska@umed.wroc.pl

Conflict of interest: None declared

Received: 11.03.2015
Revised: 11.04.2015
Accepted: 24.04.2015