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Pathology of the Gastrointestinal Tract in Patients with Primary Hyperparathyroidism

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Aim. To present data of Russian and foreign studies on the prevalence, pathogenesis and clinical picture of gastrointestinal tract (GIT) pathology in patients with primary hyperparathyroidism (PHPT).
Key point. At the beginning of the 20th century PHPT was considered a severe endocrine disease with specific bone and kidney complications, however in 1957 W.T. St Goar proposed a mnemonic triad to recognize this pathology as “diseases of stones, bones and abdominal groans”. A high frequency of gastrointestinal complaints, peptic ulcer, pancreatitis, cholelithiasis in patients with PHPT has been reported. Hyperparathyroidism has been shown to cause smooth muscle atony with specific upper and lower GI symptoms such as nausea, heartburn and constipation. The prevalence of peptic ulcer in patients with PHPT, according to studies of the 50s–60s of the last century, ranged from 10 to 25 %. However, studies linking PHPT to peptic ulcer development were performed before the advent of proton pump inhibitors, did not include large-scale prospective studies, and produced contradictory results. Currently, this association remains likely only in the presence of Zollinger-Ellison syndrome in case of multiple endocrine neoplasia syndrome type 1 (MEN-1). On the other hand, the development of pancreatitis in PHPT is one of the most studied pathologies. In developing countries its frequency can reach 10–20 % due to the absence of routine screening for blood calcium. Some authors report the impact of elevated parathyroid hormone levels on the formation of gallbladder stones by inhibiting of gallbladder emptying, hepatic bile secretion and mobility of the sphincter Oddi, and changing of the bile composition. A number of studies have found an increased risk of developing malignant neoplasms of the intestine, especially the colon, in patients with PHPT.
Conclusion. The digestive manifestations of parathyroid dysfunction in patients can often be overlooked, and serum calcium levels should be included in the routine examination in the presence of abdominal symptoms.
Key words: primary hyperparathyroidism, gastrointestinal tract, peptic ulcer, pancreatitis, cholelithiasis
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Патология желудочно-кишечного тракта у пациентов с первичным гиперпаратиреозом

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Цель обзора: представить данные отечественных и зарубежных исследований о распространенности, патогенезе и клиническом течении патологии желудочно-кишечного тракта (ЖКТ) у пациентов с первичным гиперпаратиреозом (ПГПТ).
Основные положения. ПГПТ в начале XX века считался тяжелым эндокринным заболеванием с наличием только характерных костных и почечных осложнений, однако в 1957 году W.T. St Goar предложил мнемоническую триаду для распознавания этой патологии как «болезни камней, костей и абдоминальных жалоб» (“stones, bones and abdominal groans”). Сообщалось о высокой частоте жалоб со стороны органов ЖКТ, язвенной болезни, панкреатита, желчнокаменной болезни (ЖКБ) у пациентов с ПГПТ. Было показано, что гиперпаратиреоз вызывает атонию гладких мышц с появлением таких характерных симптомов со стороны верхних и нижних отделов ЖКТ, как тошнота, изжога и запор. Частота язвенной болезни на фоне ПГПТ, по данным исследований 50–60-х годов прошлого века, составляла от 10 до 25 %. Однако исследования, выявившие связь ПГПТ и развития пептических язв, были выполнены до появления ингибиторов протонной помпы, не включали крупномасштабные проспективные исследования и привели к противоречивым результатам. В настоящее время эта ассоциация остается вероятной только в случае сочетания ПГПТ и синдрома Золлингера – Эллисона при синдроме множественных эндокринных неоплазий 1-го типа (МЭН-1). С другой стороны, развитие

панкреатита на фоне ПГПТ является одной из наиболее изученных патологий. В развивающихся странах, где отсутствует рутинный скрининг на кальций крови, его частота может достигать 10–20 %. Некоторые авторы сообщают о влиянии повышенного уровня паратгормона на образование камней желчного пузыря путем замедления его опорожнения, снижения секреции печеночной желчи и подвижности сфинктера Одди, а также изменения состава желчи. В ряде исследований был выявлен повышенный риск развития злокачественных новообразований кишечника, особенно толстой кишки, у пациентов с ПГПТ.

Заключение. Пищеварительные проявления при нарушении функции паращитовидных желез у пациентов часто могут быть упущены из виду, и уровень кальция в сыворотке крови необходимо включать в рутинное обследование при наличии редких и/или неспецифических абдоминальных симптомов.

Ключевые слова: первичный гиперпаратиреоз, желудочно-кишечный тракт, язвенная болезнь, панкреатит, желчнокаменная болезнь.

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Primary hyperparathyroidism (PHPT) in recent years has attracted increasing attention from both Russian and foreign health professionals. PHPT was first described about 90 years ago almost simultaneously in Europe and the USA [1], and until the mid-1970s it was considered as a rare pathology of phosphorus-calcium metabolism with the development of severe bone and kidney complications [2]. The presence of abdominal manifestations of hyperparathyroidism was described by W.T. St Goar (1957) and, summarizing the known clinical symptoms of PHPT, a mnemonic triad for recognizing this pathology as "diseases of stones, bones and abdominal complaints" ("stones, bones and abdominal groans") [3] was proposed. Among the main complaints from the gastrointestinal tract (GIT), patients most often reported constipation, intestinal atony, nausea or vomiting, loss of appetite, anorexia, weight loss, and abdominal pain [4]. Some earlier studies have established an association between PHPT and gastric ulcer (GU) or duodenal ulcer (DU) [4–9], acute pancreatitis [10–12], pancreatic calcifications [12], cholelithiasis [5, 6, 13], oncological diseases of the intestine [14, 15].

After the introduction of routine analysis of blood calcium levels in the 1970s, the clinical picture of PHPT changed dramatically towards the predominance of mild and asymptomatic forms of the disease. According to the latest data, the frequency of detection of a characteristic complication in PHPT such as fibrous osteitis reaches less than 2 %, and the frequency of nephrolithiasis is less than 20 % in the USA, Western Europe and Turkey [1]. More recent studies, which investigated the gastrointestinal tract pathology in case of PHPT, have shown conflicting results and did not confirm the direct relationship of PHPT with some of the diseases described earlier.

Complaints

The most common gastrointestinal complaints described in patients with PHPT are constipation, heartburn, nausea, loss of appetite, anorexia or weight loss, and abdominal pain of various localizations. According to a study by A.K. Chan et al., complaints of constipation were observed in 33 % of patients with PHPT, heartburn — in 30 %, nausea — in 24 %, loss of appetite — in 15 %. After parathyroidectomy (PTE), a significant decrease in the number of symptoms was observed [16]. E.C. Gardner and co-authors have also reported high frequency of complaints from the gastrointestinal tract in patients: nausea was noted in 28 % of cases, vomiting — in 19 %, abdominal pain — in 29 %, constipation — in 33 % [4]. In Russia, according to a study by N.G. Mokrysheva (2011) among 394 patients with PHPT, epigastric pain was observed in 18 % of cases [17]. The exact pathophysiological mechanisms of gastrointestinal symptoms in PHPT are unknown. High concentrations of calcium ions (Ca) interfere with the transmission of afferent stimuli and reduce efferent signals from parasympathetic ganglia in the presence of a constant amount of perfused acetylcholine [4]. The rising concentration of Ca ions reduces neuromuscular excitability. The combination of these effects in hypercalcemia may lead to a decrease in the tone of the GIT. The presence of constipation in patients is most likely due to atony of the colon, while gastric atony causes the appearance of dyspepsia (nausea, vomiting and anorexia) [4].

Gastric ulcer

The relationship between PHPT and peptic ulcer disease (PUD) was first established by H.M. Rogers in 1946 [8]. According to studies from the middle of the last century, PHPT was associated with an increase in the incidence of PUD [9, 18], an increase in gastric juice secretion [19, 20] and plasma gastrin levels [21, 22]. The prevalence of PUD in patients with hyperparathyroidism in earlier publications ranged from 10 to 25 % [23]. B.M. Black (1956) et al. showed that among 207 cases of PHPT observed at the

Mayo Clinic (Rochester, USA), 17 % had evidence of PUD or surgical operation due to ulcer in anamnesis [18]. J. Hellstrom et al. (1954) observed 50 patients with PHPT, of whom duodenal ulcer was observed in 14 % of cases [9]. Among patients with DU, a 10-fold increase in the incidence of PHPT was found [24]. According to the results of Russian studies, ulcer in case of hyperparathyroidism was observed in 4–18 % of patients (A.Yu. Tsurkan, S. Zografsky, S.I. Ismailov), with predominance of women among them, the course of ulcer was characterized as severe, with severe pain syndrome, and the development of frequent exacerbations, as well as complications such as bleeding, incoercible vomiting, without significant improvement from antiulcerous therapy [5, 6, 25]. PTE resulted in permanent healing of ulcers and relief of symptoms in the majority of patients.

The mechanisms of development of PUD in PHPT have remained unclear for a long time. One of the key points of pathogenesis is considered hypercalcemia, which contributes to an increase in the production of hydrochloric acid and pepsin, as well as an increase in the motor function of the stomach, which predisposes to ulcer formation. In one of the cases described by R.F. Barreras and R.M. Donaldson, in a patient with hyperparathyroidism and coexisting PUD and with significant basal gastric hypersecretion, the concentration of Ca and gastric secretion decreased to normal values after surgical treatment and removal of three parathyroid adenomas [20].

More recent studies have questioned the existence of a direct relationship between PUD and PHPT. J.D. Ostrow and co-authors (1960) investigated 429 histologically confirmed cases of hyperparathyroidism and noted that the prevalence of PUD in PHPT and in the general population had little difference, the clinical picture of ulcer did not differ in any unusual characteristics, symptoms of ulceration were often present in the absence of ulcer visualization. The authors concluded that PUD cannot be directly related to hyperparathyroidism, since the symptoms of ulcers and the severity of PHPT had no direct association, PUD could persist, and its course often worsened after surgical treatment of PHPT [26]. D.A. Linos et al. (1978) evaluated 46 cases of PHPT in combination with PUD and noted that its course with coexistent PHPT had no characteristic differences. Among 16 cases with a complicated course of PUD, only 44 % of patients showed improvement after surgical treatment. None of the studied factors (age, gender, serum levels of Ca and PTH, location of the ulcer, and duration of the disease) had any effect on the clinical course of this gastrointestinal pathology after PTE performed. According to the results of the study, it was suggested that the relationship between PHPT and PUD is nothing more than an coincidence [27]. In another study, it was shown that the incidence of PUD detected at autopsy reached 5 % of cases [28], however, after the appearance and widespread distribution of proton pump inhibitors, a decrease in its incidence in the general population was noted. It has also been shown that only 1 % of patients with PUD had confirmed hyperparathyroidism [24, 28]. One of the most likely causes of hypersecretion of gastric juice in patients with PHPT is currently considered to be the presence of hypergastrinemia in case of a combination of Zollinger-Ellison syndrome and hyperparathyroidism (in MEN-1 syndrome).

Recently, there are not so many studies addressed to investigation of the clinical course of PUD in PHPT. The literature data describes several cases of manifestation of PHPT in the form of gastrointestinal bleeding in case of GU perforation [29, 30]. In a study of A. Jodkowska et al. (2016) among 100 patients with PHPT who had mostly symptomatic PHPT (bone, visceral or mixed), 52 % of patients had complaints from the GIT, 7 % had GU [31]. In a study conducted in the Czech Republic, there was a significantly higher incidence of PUD in patients with PHPT (n = 1750) compared with the control group (n = 2520) (15,28 % vs 4,3 %, respectively) [32], however, it is worth noting that most of the patients already had complications of PHPT. In developed countries, where mild and asymptomatic forms of PHPT currently predominate, cases of PUD in PHPT are rare.

Pancreatitis

For the first time, the development of acute pancreatitis in case of PHPT was described by O. Cope et al. in 1957 [12]. In the literature data of earlier years, the incidence of acute pancreatitis in PHPT was high and in some studies was up to 12 % of cases [11], and in hypercalcemic crisis it reached 25–34 % of cases [33]. In the case of hereditary hyperparathyroidism, 3 out of 6 affected family members had recurrent pancreatitis [34]. Jacob J.J. et al. revealed a 28-fold increase in the risk of pancreatitis in patients with PHPT compared with its incidence in the general population [10]. However, the association of PHPT and acute pancreatitis was questioned for a long time, until PHPT was finally recognized as the etiological factor in pancreatitis [35].

The pathophysiological mechanism leading to the development of pancreatitis is mostly associated with an increase in serum Ca levels. Several studies have found that hypercalcemia due to other causes, such as malignancy or administration of Ca gluconate solution, can also lead to pancreatitis [36]. It was experimentally confirmed that Ca ions contribute to the deposition of stones in the pancreatic ducts,

followed by the development of obstruction and inflammation [37]. Moreover, Ca ions promote the conversion of trypsinogen into trypsin, triggering the mechanism of pancreatitis development [35]. Also, certain genetic or environmental factors may increase the susceptibility to pancreatitis in patients with hyperparathyroidism. A strong association with the presence of a mutation in the gene of serine protease inhibitor Kazal type 1 (SPINK1) and in the gene of the cystic fibrosis transmembrane regulator (CFTR) in patients with PHPT and pancreatitis was noted [38].

Acute pancreatitis may be the first symptom in manifestation of PHPT [39, 40] and is associated with the development of complications such as recurrent acute pancreatitis, pancreatic pseudocysts and chronic pancreatitis with or without calcification, usually in the parenchyma and less often in the ducts [41]. Some authors reported a significant improvement in the clinical symptoms of acute pancreatitis, including pseudocyst resorption, after surgical treatment of hyperparathyroidism [10, 42, 43], and noted that treatment of PHPT should precede invasive treatment of pancreatic pseudocysts. However, improvement in symptoms of pancreatitis was not observed in all patients after PTE [44].

In developing countries, where routine screening for blood Ca is absent, the incidence of pancreatitis in case of PHPT reaches 10–20 % of cases [45]. R.A. Misgar et al (2020) reported revealed 6.19 % cases of pancreatitis among 242 patients with PHPT in India, of which 93.3 % had acute pancreatitis and one patient had chronic pancreatitis with calcifications. More than half of patients with acute pancreatitis had at least two episodes of pancreatitis in anamnesis. Additional risk factors for pancreatitis were not identified in any of the cases [46].

The results of some studies and clinical cases indicate an association of PHPT and chronic pancreatitis with a frequency of 1 % to 15 % of cases. Bhadada et al. examined cases of chronic pancreatitis associated with PHPT and compared it with cases of pancreatitis from other causes. In patients with pancreatitis and PHPT, higher levels of PTH and blood Ca were observed, while in the case of other causes of pancreatitis, elevated levels of PTH were secondary to maintaining normocalcemia. There were no significant differences in the incidence of steatorrhea, diabetes, pseudocysts, or pancreatic calcifications in chronic pancreatitis associated with PHPT compared with chronic pancreatitis from other causes [42].

In general, the incidence of pancreatitis associated with hyperparathyroidism tends to decrease, due to the earlier diagnosis of PHPT through the widespread screening of blood Ca levels [33]. In asymptomatic PHPT, the incidence of pancreatitis is comparable to general population [41].

Cholelithiasis

The results of some studies have shown a high prevalence of cholelithiasis in case of symptomatic PHPT [5, 6, 13, 47, 48]. P.D. Broulik et al. observed 645 patients with PHPT, cholelithiasis was detected in 30.3 % of women (157/518) and was significantly higher than in women in the control group (260/1505) (17.27 %, $p < 0.001$). Among men, there was no significant difference in the incidence of cholelithiasis (8.66 % (11/127) vs 10.58 % (54/510)) [47]. S.K. Bhadada et al. showed a high prevalence of cholelithiasis (25.8 %) in PHPT compared with the general population (3.1 %) [49]. According to data of Russian studies, cholelithiasis was established in 9 to 50.9 % of cases in patients with PHPT (Slesarenko S.S., 2000; Tsurkan A.Yu., 2006; Ismailov S.I., 2002) [5, 6].

The formation of stones in the gallbladder is associated with various etiological factors and a number of diseases. Although the pathogenesis of cholelithiasis in PHPT is still not entirely clear, the following factors may play an important role: hypercalcemia, increased PTH levels, impaired contractility of the gallbladder, modification of bile composition, estrogen intake, genetic factors, biliary tract infection, and some others. One study showed that an elevated PTH level is an inhibitor of the contractility of smooth muscles in cardiovascular system, GIT, and other tissues such as the trachea and uterus [50]. The mechanism of cholelithiasis associated with an increase in PTH may include a slowing in gallbladder emptying, a decrease in hepatic bile secretion and mobility of the Oddi sphincter, as well as changes in bile composition [47]. Gallbladder stasis can contribute to an increase in the amount of bile, the precipitation of cholesterol and calcium salts, the retention of biliary sediment and the maturation of stones. Some authors report that gallstones in PHPT consist mainly of Ca bilirubinate [41].

However, not all studies confirm the development of cholelithiasis as a complication in symptomatic PHPT [51], and there are no data on the prevalence of cholelithiasis in case of a mild form of PHPT.

Oncological diseases

A number of studies report an association between PHPT and the development of malignant neoplasms, especially in the colon [14, 15, 35, 52]. According to Farr et al., the incidence of gastric and colon cancer associated with PHPT was 10 % and 6 %, respectively [14]. In another study, in a prospective follow-up of 9782 patients with PHPT for 40 years, an increased risk of developing colon cancer, kidney cancer, and squamous cell skin cancer was found [15]. There is evidence that Ca is a potential anticarcinogenic

factor [53], and it has also been shown that Ca inhibits the activity of free fatty acids and bile acids in the process of colorectal carcinogenesis [54]. On the other hand, Ca regulates the proliferation of colon cells [55], and a decrease in Ca levels can lead to hyperproliferation of its mucosa. In patients with PHPT, an increase in the level of the active form of vitamin D accelerates the absorption of Ca from the intestine, leading to a decrease in the concentration of intra-intestinal Ca. Therefore, patients with PHPT are at high risk of developing intestinal neoplasms, and further research is required.

Conclusion

Specialists of different medical specialties should be aware of the characteristic complaints and diseases of the gastrointestinal tract observing in patients with PHPT, for timely diagnosis and adequate treatment. Studies have shown that PHPT can cause non-specific gastrointestinal symptoms that are a consequence of smooth muscle atony. The association of peptic ulcer with PHPT is not as clear-cut as has been reported in earlier literature, with the exception of Zollinger-Ellison syndrome in MEN-1. On the other hand, PHPT is a confirmed risk factor for acute pancreatitis, which may be one of the manifestations of its symptomatic form. The development of chronic pancreatitis and oncological diseases in case of PHPT requires further studies. In the presence of rare and/or non-specific abdominal symptoms in gastroenterological patients, a routine study of the level of Ca in the blood serum is recommended.

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