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MINIREVIEWS

Biliary atresia and congenital disorders of the extrahepatic bile ducts

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Abstract

Biliary atresia (BA) and choledochal cysts are diseases of the intrahepatic and extrahepatic biliary tree. While their exact etiopathogeneses are not known, they should be treated promptly due to the potential for irreversible parenchymal liver disease. A diagnosis of BA may be easy or complicated, but should not be delayed. BA is always treated surgically, and performing the surgery before the age of 2 mo greatly increases its effectiveness and extends the time until the need for liver transplantation arises. While the more common types of choledochal cysts require surgical treatment, some can be treated with endoscopic retrograde cholangiopancreatography. Choledochal cysts may cause recurrent cholangitis and the potential for malignancy should not be ignored.

Key Words: Bilier atresia; Choledochal cyst; Cholestasis; Conjugated hyperbilirubinemia

Core Tip: Biliary atresia (BA) and choledochal cysts are diseases that cause obstructive cholestasis. While the diagnosis of BA can be rather complicated, it should be made as early as possible and treated with a Kasai hepatoportoenterostomy before the age of 2 mo for a good prognosis. All patients with persistent acholic stool and elevated gamma-glutamyl transferase should be evaluated for BA, although normal ultrasonography will not rule out BA, and such patients are candidates for intraoperative cholangiography. Choledochal cysts can present symptoms at any age, and as recurrent cholangitis attacks will lead to chronic liver disease with potential malignancy, treatment and long-term follow-up are essential.

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INTRODUCTION

Jaundice develops as a result of excessive bilirubin production, a decrease in its excretion, or both. An increase in the conjugated bilirubin fraction is observed in cholestatic patients. Conjugated and direct bilirubin are often treated as synonyms, although direct hyperbilirubinemia is the sum of conjugated bilirubin and delta bilirubin, and an increase in both results in jaundice[1]. Conjugated (direct) hyperbilirubinemia is defined as serum conjugated bilirubin > 1 mg/dL when total bilirubin is < 5 mg/dL, or when serum conjugated bilirubin accounts for > 20% of the total bilirubin when the total bilirubin is > 5 mg/dL. All infants with direct bilirubin levels of > 1 mg/dL, however, should be evaluated for cholestasis[2]. Biliary atresia (BA) and choledochal cysts are known to cause obstructive jaundice, and conjugated hyperbilirubinemia will be observed. Jaundice develops in the first weeks of life in BA, whereas in choledochal cysts, it may develop at any time during infancy or childhood, or may be recognized incidentally. In both cases there is an indication for surgery or endoscopic retrograde cholangiopancreatography (ERCP)[3,4]. The present study opens a discussion on BA and choledochal cysts.

BILIARY ATRESIA

BA is characterized by progressive fibro-obliteration and destruction of the intrahepatic and/or extrahepatic bile ducts in the neonatal period, and is the most common cause of cholestasis in infants. If left untreated, it quickly advances to biliary cirrhosis and death[3]. In the 1950s, with the development of Kasai portoenterostomy by Dr. Morio Kasai, it became possible to treat BA surgically, although early diagnosis and treatment increase the effectiveness of surgery[5]. BA is the most common indication for liver transplantation (LT) in childhood, which can be performed successfully if surgical treatment fails or decompensated cirrhosis develops[6].

Epidemiology

Different frequencies of BA have been reported in different geographical regions, reported as 22371 live births in North America[7], 17049 live births in the United Kingdom[8], 18400 live births in France[9], 1.06 cases *per* 10000 live births in Korea[10], 9640 live births in Japan[11] and 1.7–1.85 *per* 10000 live births in Taiwan[12], with a greater incidence in rural locations than in urban areas reported. The reason for the higher incidence in the East than in the West is unknown, although different studies have suggested that ethnicity may play a role and that an association with human leukocyte antigen (HLA) molecules exists, suggesting that the dominant HLA molecule in a population is correlated with BA[13].

Clinical phenotypes

BA has been identified in embryonic or syndromic, and perinatal or non-syndromic forms, the latter of which accounts for more than two-thirds of all cases. The perinatal, or non-syndromic, type is generally not accompanied by other anomalies, although the association of the embryonic or syndromic type with multiple anomalies is more common (Table 1)[14]–the most common being situs inversus and intra-abdominal vascular anomalies, in addition to BA with splenic malformation (BASM) syndrome. In an earlier study by the author involving 59 BA patients, BASM was identified in seven (11%) cases, with the most common associated anomalies being midgut malrotation (in all patients), polysplenia/asplenia (in four and one patient) and preduodenal portal vein (in five patients)[15].

In a third clinical form or variant of BA, an extrahepatic cyst similar to a choledochal cyst accompanied by a fibrosing obstruction has been described, which has been reported in studies to account for 5%–10% of the total BA[16]. In all forms, bile duct proliferation and portal fibrosis are common histological features and are not distinctive[17], although a cholangiogram may reveal features specific to each form[18].

Clinical features

BA with extrahepatic cysts can be identified early with antenatal ultrasonography. Indirect findings can also be observed through antenatal ultrasonography in species with BASM[19], with the first symptom being jaundice (conjugated hyperbilirubinemia)[20]. In the embryonal type, jaundice is noticeable at birth, that is, there is no jaundice-free interval, while in the postnatal type, the physiological jaundice is followed by conjugated hyperbilirubinemia. Jaundice lasting more than 2 wk is always pathological and should be investigated. A greenish-yellow color is observed in conjugated hyperbilirubinemia, and is unlikely to occur after 8 wk. Acholic stool and dark urine usually accompany jaundice, with acholic stool usually presenting at 2 wk of age that is almost indisputable at one month of age[21]. The color of the stool may sometimes be light and not definitely acholic, and the recognition of acholic stool by parents may be delayed if the diaper is stained with dark urine.

Familial transmission is unlikely in BA. In our case series, we found the rate of consanguineous marriage to be higher in cholestatic cases not linked to BA (mostly idiopathic neonatal cholestasis) than in those with BA (56% *vs* 24%)[22]. Babies with BA are usually term and of normal birth weight. In the most common perinatal type, weight gain is normal in the first weeks, but begins to decrease in

Table 1 Associated anomalies of embryonic or syndromic biliary atresia

Origin of anomaly	Description
Splenic anomalies	Asplenia, double splen, polysplenia
Cardiovascular anomalies	Interrupted/absent inferior vena cava, dextrocardia, left atrial isomerism, other cardiac anomalies (pulmonary stenosis, ASD, VSD, PDA, total anomalous pulmonary venous return, coarctation of the aorta, TOF, hypoplastic left heart syndrome)
Portal vein and hepatic artery anomalies	Preduodenal portal vein, anomaly originated hepatic artery
Abdominal anomalies	Situs inversus, midgut malrotation, intestinal atresia (esophageal, duodenal or jejunal), anular pancreas, short pancreas
Renal anomalies	Renal agenesis, hypoplastic or polycystic kidneys
Other uncommon anomalies	Primary ciliary dyskinesia, caudal regression syndrome

ASD: Atrial septal defect; PDA: Patent ductus arteriosus; TOF: Tetralogy of Fallot; VSD: Ventricular septal defect.

untreated patients. Bleeding may occur due to vitamin K malabsorption; hepatomegaly and splenomegaly are signs of cirrhosis and portal hypertension, and ascites will be observed in decompensated cases[20].

Pathogenesis

The pathogenesis of BA is not yet fully known, although it has been suggested that it may stem from abnormalities in the duct morphogenesis, or genetic or postnatal factors that lead to progressive fibro-obliteration in the duct morphology (while the bile duct tree is present at birth)[23].

Defect in morphogenesis

The coexistence of other organ anomalies in the embryonal type of BA suggests the presence of an abnormality in the embryonal development process. Bile ducts emerge as a result of a series of processes in which the fetal ductal plate is remodeled at the level of the intrahepatic bile ducts of the porta hepatis. If there is a failure in the remodeling, a ductal plate malformation (DPM) develops with fetal configurations in the intrahepatic bile ducts. DPM has also been described in extrahepatic BA[24], with suggestions that ducts are present in morphogenesis, but lack periductular mesenchymal tissue support, with bile leakage causing inflammation and progressive ductal fibro-obliteration. Whether inflammation is a cause or an effect, however, is unknown.

Viral infections

Previous data indicating that diagnoses of BA in infants are seen more frequently in the autumn and spring suggest that a viral agent may be behind the development of BA in the perinatal period. No association has been identified with hepatitis A, B or C, or Rubella. Cytomegalovirus (CMV), Reovirus and Rotavirus are the most studied viruses. In a study conducted in a developed nation, the high CMV seroprevalence of mothers of infants with BA and the detection of CMV DNA in the hepatocytes suggested that CMV may play a role in the pathogenesis[25], while a further study identified no CMV DNA in the porta hepatis specimens of a group of patients with BA[26], meaning that further studies of the role of CMV are required.

Reovirus type 3 and group C rotavirus have been shown to cause fibro-obliterative cholangiopathy in several experimental studies, although any relationship between these viruses and BA in humans has yet to be proven[27,28].

Environmental toxins

After an outbreak of BA in lambs and calves in Australia, it was concluded that BA had developed in the offspring of pregnant animals exposed to certain environmental toxins. In experiments, an isoflavonoid named biliatresone, isolated from the Dysphania plant in the epidemic region of Australia was found to cause a loss of cilia in cholangiocytes, and was associated with bile duct injury[29]. BA in pregnant women has not been linked to any known environmental toxin exposure.

Maternal microchimerism

Previous studies have associated immunodysregulation with BA, and it has been suggested that maternal microchimerism plays a role in its pathogenesis. There have also been studies specifying an increased number of maternal cells in the sinusoids and portal areas of patients with BA, and another suggesting the presence of a graft-versus-host disease caused by engrafted maternal effector T lymphocytes[30]. There may be particular factors causing the second hit, however further studies will be needed to clarify this issue.

Genetic factors

The absence of Mendelian inheritance in the postnatal type and the presence of an unaffected sibling by BA in monozygotic twins suggest an absence of genetic origin in this type. It has been suggested, however, that genetic factors may play a role in the etiology of the embryonal type, accompanied by other congenital anomalies. Studies have identified different gene loci, although it cannot be said with any certainty that they cause BA alone. The *CFC1* gene encodes the cilium-associated protein inversin and the cryptic protein that provide signaling during embryonic development. PKD1L1 encodes Polycystin 1 Like 1 and regulates cilier functions, and both gene defects are associated with visceral heterotaxy. Heterozygous CFC1 and PKD1L1 mutations have been determined in some patients with BASM[31,32]. XPNPEP1 (mediates the metabolism of inflammatory mediators in epithelial cells) and ADD3 (plays a role in the spectrin-actin network in the biliary tract) mutations have been observed in some patients with BA[33]. The genes associated with other diseases have also been found in patients with BA, including JAG1 (Alagille syndrome), MYO5B (microvillus inclusion disease), ABCC2 (Dubin-Johnson syndrome), ABCB11 (PFIC type 2), UG1A1 (Crigler-Najjar syndrome), MLL2 (Kabuki syndrome), RFX6 (Mitchell-Riley syndrome), ERCC4 (Fanconi anemia) and KCNH1 (Zimmermann-Laband syndrome)[34].

Diagnosis

The early recognition of BA is important for the effectiveness of surgery, although centers follow different diagnostic algorithms based on their own experience. Diagnosing the disease as early as possible and performing the Kasai procedure before 2 mo of age (especially before 30–45 d) increases the effectiveness of the procedure and delays LT[5]. The average age at which the Kasai procedure is performed, however, usually exceeds 2 mo. In an earlier study by the author, the parents of patients diagnosed with BA noticed jaundice on the postnatal 11th day, although the average age at which patients are referred to us as a tertiary hospital is 58 d[35], due primarily to the similarity of the symptoms to common benign causes, such as physiological jaundice or breast milk jaundice. It may also be missed in well-baby visits, as jaundice may not be visible in the first days of life. The European Society for Paediatric Gastroenterology Hepatology and Nutrition and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) recommend the evaluation of total and direct serum bilirubin in newborns whose jaundice persists after 2 wk of age, and the referral of those with high serum direct bilirubin levels (direct bilirubin levels > 1.0 mg/dL or > 17 mmol/L) to a pediatric gastroenterologist or hepatologist[2]. A physical examination can thus be considered an important screening test, and so looking for signs of cholestatic jaundice during well-baby and vaccination visits by primary healthcare givers is advised.

Being a common disease, BA screening tests have been developed to extend the transplant-free period through early diagnosis and treatment. BA meets the requirements for inclusion in the newborn screening program[35]. One screening method involves the use of a stool color card, with a card carrying photos of normal and pale stools being given to the parents who are advised to contact their healthcare providers upon encountering an abnormal stool color. Stool color may also be discussed with healthcare providers during the 1st-month well-baby visit. Stool color tests were first applied in Japan and Taiwan. In Japan, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the test have been reported to be 76.5%, 99.9%, 12.7% and 99.9%, respectively, in the 1st month[21]; while in Taiwan, the sensitivity, specificity, PPV and NPV of the test at 2 mo is reported to be 89.7%, 99.9%, 28.6% and 99.9%, respectively[12]. Since the age of performing a Kasai operation with the screening test in these two countries has shortened significantly when compared to the pre-screening test (59.7 d *vs* 70.3 d in Japan, and 48.2 d *vs* 59.9 d in Taiwan) countries[35] such as Germany, Canada, Switzerland and Brazil have also started to implement this screening program. The main advantage of the stool color card method is its non-invasive nature. In a few studies in which a serum/plasma conjugated bilirubin measurement approach is applied, as an alternative method, the sensitivity and specificity of high conjugated bilirubin levels in predicting BA have been reported as 100% and 99.9%, respectively[36,37]. While this method can also facilitate the early diagnosis of other liver diseases associated with direct bilirubinemia, there are such disadvantages as its invasive nature, and uncertainties of its cost-effectivity and which thresholds to use. There have been studies identifying cholic acid and chenodeoxycholic acid in dried blood specimens[38,39] and urinary oxysterols[40] as potential markers in the screening of BA, although these metabolic products need to be tested in prospective studies.

There is no single test for the diagnosis of BA. As in all diseases, family history and birth characteristics should first be questioned as a family history of cholestasis and preterm birth suggest neonatal hepatitis rather than BA. Unlike metabolic diseases, infants with BA appear well unless cirrhosis develops, and vomiting/feeding intolerance is not expected. Despite conjugated hyperbilirubinemia, pruritus is uncommon in BA. Acholic stool may initially be absent and some stools may contain bile pigment, although acholic stool may also be observed in neonatal hepatitis, but as fibroobliteration progresses in BA, acholic stool persists. Persistent pigmented stool is not an expected finding in BA[20]. Transaminases and gamma-glutamyl transferase (GGT) are almost always elevated in BA, and GGT is disproportionately higher than transaminases, while this is opposite in neonatal hepatitis. GGT

continues to rise over time. In one study, the mean GGT levels in infants aged < 2, 2–3 and 3–4 mo were recorded as 371.6, 600.5 and 697.2 respectively[41].

Ultrasound is widely used for the evaluation of the biliary tract and liver, and the sonographic findings of patients with BA are gall bladder absence, hypoplastic gall bladder, triangular sign, absence of gallbladder contractility after feeding, and polysplenia and vascular anomalies in syndromic types [42]. Most, but not all of those with BA have a hypoplastic or absent gallbladder, and so normal ultrasonography does not exclude BA. Absence of gallbladder results are variable and may occur in 0%–53% of cases. Previous studies have reported a triangular sign to be more sensitive (58%-100%) and specific (83%-100%) for the prediction of BA, while others say report gallbladder abnormalities (short, lack of lumen) to be more sensitive (50%–100%) and specific (82%–95%)[43]. There are reports of 100% sensitivity and NPV in the identification of BA together with gallbladder anomalies and GGT[44]. In our series, GGT, pale stool and abnormal ultrasonography had maximum sensitivity and PPV (sensitivity and PPV were both 95%, diagnostic accuracy 70%)[22].

Hepatobiliary scintigraphy has been used for the diagnosis of BA. The passage of the radionuclide into the intestine is a good finding in excluding BA, although an absence of intestinal transit in hepatobiliary scintigraphy can also be seen in intrahepatic cholestasis besides BA. In a recent meta-analysis, the sensitivities and specificities of hepatobiliary scintigraphy were reported to be 84%–100% and 35%–93%, while PPV was 64.5% and NPV was 97.2%[45]. In some centers, phenobarbutal is used for 5 days prior to examination to increase the sensitivity, although hepatobiliary scintigraphy may delay a diagnosis, leading some centers to exclude hepatobiliary scintigraphy from their BA diagnostic algorithm[20].

Magnetic resonance cholangiopancreatography (MRCP) is a non-invasive imaging method that is used for selective biliary imaging. In the diagnosis of BA, the sensitivity and specificity of MRCP have been reported as 85%–100% and 36%–96%, respectively. Previous studies have reported that MRCP and ultrasonography had better sensitivity and specificity[23,45].

It is not easy to diagnose BA through solely non-invasive methods. Extrahepatic bile ducts can be visualized with ERCP with high sensitivity (86%–100%) and specificity (79%–94%), and with high PPV (88%–96%) and NPV (100%)[46,47], although the procedure requires an experienced endoscopist and a neonatal dudenoscope, which very few centers keep. In a large patient-series study, the success of the ERCP technique was reported to be 89.2%[46].

Among the histopathological findings of BA are duct/ductular bile plugs, ductular reaction and bile duct proliferation, portal stromal edema, marked portal fibrosis, pseudorosette formation, peribiliary neutrophilic infiltrates and interlobular bile duct injury (Figure 1). Giant cell transformation may be observed in BA, but not as intense as in neonatal hepatitis[48]. A multicenter study concluded that duct/ductal bile plugs and portal stromal edema were the strongest independent histologic predictors of obstruction[17]. The sensitivity and specificity of histological findings are over 90%, although histopathological findings similar to those seen in BA may also be observed with other neonatal cholestasis diseases [such as alpha 1 antitrypsin deficiency, progressive familial intrahepatic cholestasis (PFIC), cystic fibrosis], though not necessarily in the early period[49,50]. The absence of an extrahepatic biliary tree in intraoperative cholangiography is, therefore, the leading indicator of BA[2]. In our center, where the pathological differential diagnosis of cholestasis cannot be sufficiently performed, suspected BA cases are referred immediately to the pediatric surgery department for intraoperative cholangiography in the early period. As a result, 68% of cases undergoing intraoperative cholangiography were diagnosed with BA and underwent the Kasai procedure[22]. This procedure can also be carried out laparoscopically[51]. If BA is confirmed, the Kasai procedure can be performed in the same session or in a second session. If extrahepatic bile ducts are present, a liver biopsy is taken and the procedure is terminated.

While performing all these diagnostic procedures, we recommend each center use the procedures they are most experienced with to make the diagnosis as early as possible and to avoid any delay.

In recent years there have been studies reporting the high sensitivity and specificity (> 90%) of serum matrix metalloproteinase-7 as a biomarker for the diagnosis of BA[52,53].

Differential diagnosis

As several diseases can cause neonatal cholestasis, efforts should focus both on the identification of BA and the exclusion of other diseases.

Choledochal cysts: Infants with choledochal cysts sometimes present with cholestasis. Generally, ultrasonography is sufficient to distinguish choledochal cysts from BA, although it may be difficult to identify the cystic dilated BA form, and so other diagnostic tests can be performed.

Alagille syndrome: This is a cholestatic disease that is characterized by bile duct paucity, and that can be difficult to recognize in the neonatal period. A typical facial appearance (prominent forehead, deep-set eyes, pointed chin and straight nose), and ocular, cardiac, renal and skeletal anomalies may accompany. In Alagille, GGT can reach very high values. If a differential diagnosis is difficult, a liver biopsy can be performed before resorting to intraoperative cholangiography. Bile duct proliferation is a prominent feature in BA, while bile duct paucity is present in Alagille[54].

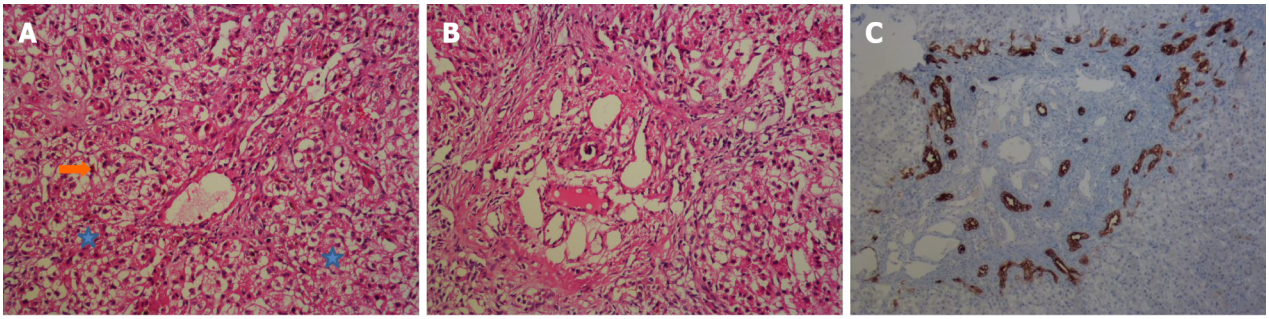

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Figure 1 Liver biopsy of a patient with biliary atresia. A: Cholestasis (arrow) and ballooning degeneration (asterisks) (hematoxylin-eosin, magnification × 100); B: Portal fibrosis (hematoxylin-eosin, magnification × 100); C: Bile duct proliferation (Cytokeratin 19, magnification × 100).

PFIC

PFIC 1-2 is the cause of cholestasis when GGT is normal, while PFIC-3 is the cause of cholestasis with high GGT. Persistent acholic stool is not an expected finding in PFIC-3[55].

Cystic fibrosis

Cystic fibrosis may cause neonatal cholestasis, and GGT may increase in cystic fibrosis. Persistent acholic stool is not an expected finding. Family history, abnormal neonatal screening test, and presence of meconium ileus or steatorrhea are strong indicators of cystic fibrosis[56].

Bile acid synthesis disorders

Bile acid biosynthesis defects are a known cause of neonatal cholestasis. Acholic stool may be observed in some cases. It is differentiated from BA when the GGT level is normal or low. Where possible, it can be confirmed through the measurement of urine bile acids, which will be normal or low[57].

Inborn errors of metabolism

Several inborn metabolism errors can lead to neonatal cholestasis that may be difficult to distinguish from BA[2]. In our center we routinely check glucose (for hypoglycemia), blood gasses, serum amino acids, urine organic acid and lactate-pyruvate levels while making differential diagnoses of cholestasis. Acyl carnitine profile, succinyl acetone and galactose-1-phosphate uridylyltransferase enzyme activity can be planned in some cases.

Endocrine disorders

As the initial differential diagnosis in our center, we routinely check fasting glucose, serum thyroid-stimulating hormone, free t4, morning fasting cortisol and adrenocorticotropic hormone for the evaluation of the hypopituitarism, hypothyroidism and adrenal insufficiency causing cholestasis[1].

Infections

All patients with cholestasis should be tested for urinary infection, regardless of whether they have acholic stool or not, for which a urine culture should be taken[58]. CMV infection is the most common of all congenital infections around the world, and is confirmed by the presence of serum CMV immunoglobulin M, or by the more sensitive blood or urinary CMV polymerase chain reaction. However, two significant problems may be encountered here. First, CMV infection and BA may coexist, and second, the patient may have CMV viremia rather than CMV infection and so we recommend intraoperative cholangiography so as not to delay diagnosis in the absence of other findings of CMV (intracranial calcification, chorioretinitis, deafness). Although there are inter-communal differences, toxoplasma, rubella, herpes and syphilis are rare, but should be investigated[59]. Although hepatitis b and c rarely cause neonatal cholestasis, they should be tested[1].

Alpha 1 antitrypsin deficiency

Alpha 1 antitrypsin deficiency with a ZZ phenotype may cause neonatal cholestasis, and acholic stool may even be observed. A normal serum alpha 1 antitrypsin level, which is an acute-phase reactant, does not exclude alpha 1 antitrypsin deficiency. If there is a strong suspicion of alpha 1 antitrypsin deficiency, such as the presence of family history, a phenotype analysis and liver biopsy may be performed[60], although intraoperative cholangiography should not be delayed by such diagnostic procedures.

Gestational alloimmune liver disease

Gestational alloimmune liver disease should also be considered in patients with cirrhosis and liver

failure in the neonatal period. High bilirubin levels are always present in gestational alloimmune liver disease, while transaminases may not be too high. Ferritin and alpha-fetoprotein are high but not specific to the disease. Hypoglycemia, marked coagulopathy, hypoalbuminemia, edema and death are important findings. Recurrent miscarriages, history of siblings with neoanatal hemocromatosis, intrauterine growth retardation, oligohydramnios and premature birth are greater indicators of gestational alloimmune liver disease than BA[61].

Treatment

In cases where the extrahepatic biliary tree cannot be visualized in intraoperative cholangiography, bile drainage is provided *via* Kasai hepatoportoenterostomy. A biliary anastomosis is performed at the liver hilum involving the creation of a Roux-en-Y bowel loop[6]. The syndromic type does not benefit from the Kasai procedure. If the Kasai portoenterostomy is successful, bilirubin will begin to decrease within a few weeks. If there is no improvement in cholestasis, early LT is inevitable. Should the Kasai procedure be unsuccessful, revisional surgery is not recommended as the chance of success is not high, leading to increased adhesions and complicating a subsequent LT. If cholestasis improves while cholestasis recurs, however, second surgery may be considered[62]. In the original Kasai portoenterostomy, fibrous biliary remnants from the hepatic hilum are resected and a jejunal anastomosis is performed. There have been several modifications to this technique over time. In the ''extended Kasai portoenterostomy'' technique, a deeper and longer incision is made into the portal hilus to the bifurcation of the portal vein. The rationale for this technique is that ducts may be present along the entire line and therefore this entire area should be included in the hepaticojejunostomy. It has been suggested that an extended Kasai portoenterostomy is superior to the traditional technique[63]. The Kasai procedure can also be performed laparoscopically, and it has been suggested that the success of laparoscopic surgery is similar to that of open surgery, offering better perioperative results such as fewer intraoperative blood transfusions and the early initiation of postoperative oral feeding. A laparoscopic Kasai procedure may reduce postoperative complications that necessitate re-laparotomy in LT, such as bowel perforation, re-bleeding or portal vein reconstruction.

Adjuvant treatments

The use of corticosteroids to increase choleresis in the postoperative period was shown not to be beneficial in the START study[64], and there may even be negative effects on growth, although some centers still use corticosteroids. Another drug used to increase choleresis is ursodeoxycholic acid–a hydrophilic bile acid. Although there have been a few studies reporting that ursodeoxycholic acid improves liver enzymes, reduces itching and improves weight gain, others state that it does not change the LT requirement[65]. We use it in doses of 15–30 mg/kg/day in our center.

Nutrition

Patients with BA can encounter malabsorption and malnutrition due to chronic liver disease, absence of gallbladder and cholestasis. The daily calorific requirements of these patients increase, and it should be ensured that patients maintain a 125–150 percent intake of the recommended dietary calorie allowance. Enteral nutrition is usually required, and should include middle-chain triglycerides (MCT) due to their ability to be absorbed directly through the portal vein. Some 30%–70% of the energy derived from fats can be obtained from MCT, although the diet should also contain long-chain fatty acids to avoid essential fatty acid deficiencies. If necessary, tube feeding (nasogastric or gastrostomy) should be provided[66]. In the presence of cholestasis, vitamins A, D, E and K should be given to prevent the development of fat-soluble vitamin deficiency, with vitamin A 5000–25000 IU/day, vitamin E 25 IU/kg day, vitamin D 1200–4000 IU/day and vitamin K 2.5 mg three times a week recommended. Vitamin levels and prothrombin time should be monitored regularly[20].

Complication

Patients who have undergone a Kasai portoenterostomy procedure are at risk of ascending cholangitis due to the resulting abnormal biliary anatomy. More than two-thirds of cases experience at least one episode of cholangitis, and each attack can shorten the time to LT. Although the effectiveness of antibiotic prophylaxis is uncertain, 4–5 mg/kg/ trimethoprim is used daily for 3–12 mo[2], after which, prophylaxis can be given in cases with frequent cholangitis attacks.

Prognosis

Survival rates without LT range from 41%–87% at 5 years, 35%–76% at 10 years and 26%–60% at 20 years[29], although this may vary depending on the success of the Kasai procedure. There are several factors affecting the success of the Kasai procedure, the most important of which is the timing of the operation. The performing of the Kasai procedure at the age of < 60 d gives the best (up to 90%) results in the maintenance of bile flow, while the outcomes after > 90 d are the worst (20%–25%)[5,45]. The second factor is whether a visible bile duct exists to be anastomized during the operation[66], and those with a visible duct in porto hepatitis have a good prognosis. The third factor is the experience of the surgical team. Serum bilirubin levels have prognostic value for the success of the Kasai procedure. The

complete improvement of jaundice within 3 mo of a Kasai hepatoportoenterostomy is considered the best prognostic marker. In a large prospective cohort study, 2 years transplant-free survival was significantly higher in the TB < 2.0 mg/dL group than in the TB ≥ 2 mg/dL group (86% *vs* 20%)[67]. If jaundice persists, survival rates drop.

LT

Overall, more than 60% of patients require LT, and with the advances in surgical techniques, new immunosuppressive therapies and advances in infection treatment, LT can be successfully performed in cases of BA. Unless there are significant complications (*e.g.*, hepatopulmonary syndrome, sepsis, *etc.*), the success of LT is higher than 95% in patients > 10 kg or > 2 years of age[68]. Accordingly, certain conditions should be met for transplantation, among which progressive liver dysfunction (cirrhosis) is the most common. Growth retardation is another indication for transplantation, with cases of moderate and severe growth retardation despite nutritional support, in particular, being considered. Another LT indication is the primary failure of the Kasai procedure, with persistent jaundice after the operation indicating early LT. The guidelines of the American Association for the Study of Liver Diseases, the American Society of Transplantation and the NASPGHAN, it is recommended that "BA patients who are post-hepatoportoenterostomy should be promptly referred for LT evaluation if the total bilirubin is greater than 6 mg/dL 3 mo after hepatoportoenterostomy; and liver transplant evaluation should be considered in BA patients with a total bilirubin of 2–6 mg/dL"[68]. In general, LT success is high in patients with BA. In a large study involving 1818 children who underwent LT for BA, the 1- and 5-year patient survivals for patients transplanted younger than 2 years and older than 2 years were, 95.2%, 93.8%, and 97.8 % and 97.1%, respectively[69].

CHOLEDOCHAL CYSTS

Choledochal cysts are rare congenital anomalies of the biliary system, and can be intrahepatic, extrahepatic or both. They are more common in females than males (3:1 to 4:1), and while the incidence is 1:100000 in live births in Western countries, this can reach as high as 1:1000 in live births in Asia. The progression of liver damage due to recurrent cholangitis and the malignant transformation of choledochal cysts is an important disease[53].

Types

There are five types of choledochal cysts (Table 2 and Figure 2), among which type Ia, Ic and IVa choledochal cysts are associated with pancreatobiliary junction anomalies[4].

Clinical features

Choledochal cysts can produce symptoms at any age, including infancy, childhood or adulthood. Less than a quarter of cases are diagnosed at under 1 year of age, while most are symptomatic under 10 years of age[53]. The most common symptom in children is jaundice, while the classic triad of abdominal pain and jaundice with a palpable mass in the right upper quadrant is uncommon in children. Abdominal pain in children is usually associated with pancreatitis, as in adults, and nausea, vomiting and fever can be observed in those with cholangitis[70].

Pathogenesis

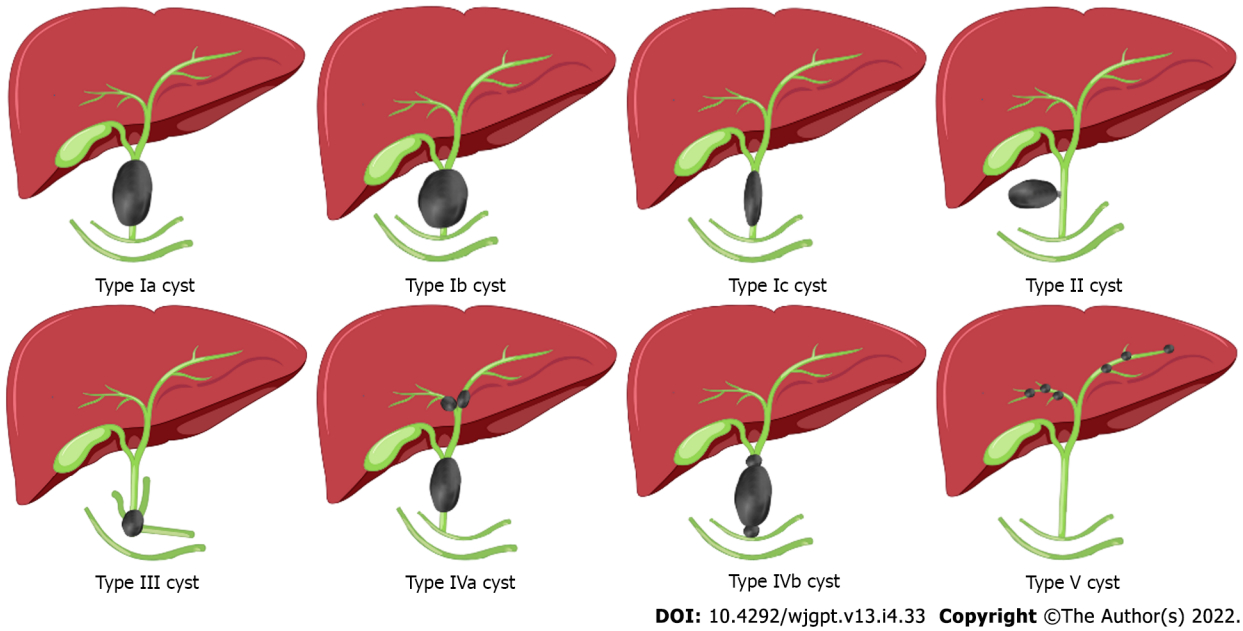
The pathogenesis of choledochal cysts is not yet as well-known as BA, although several theories have been put forward. The first relates to the reflux of pancreatic fluid into the bile duct due to an abnormality in the common bile duct and the pancreatic duct union (pancreaticobiliary maljunction or malunion) in the proximal of the Oddi sphincter, resulting in epithelial damage and subsequent weakness in the bile duct wall[71]. Normally, the common bile duct and pancreatic duct join just before entering the duodenum and open into the papillae vateria. In a pancreaticobiliary junction anomaly, however, the bile duct and pancreatic duct unite outside the duodenal wall, and enter *via* a common channel, which means that the Oddi sphincter cannot perform its anti-regurgital function. Pancreaticobiliary junction anomalies can result from a migration abnormality during the embryological period. The second theory is that an abnormal union leads to mechanical dilation, while a third suggestion relates to the presence of a congenital weakness in the duct wall that may even be segmental. Viral infection during the intrauterine period may result in an abnormality in the formation of the biliary epithelium[72]. Fourth, there may be genetic or environmental toxin exposure, with studies suggesting that common choledochal cysts are seen together with other anomalies as a result of this, including BA, duodenal atresia, anal atresia, congenital absence of the portal vein, and autosomal recessive and autosomal dominant polycystic kidney disease[73].

Histology

An acute and chronically inflamed fibrotic cyst wall is frequently observed in children. In adults,

Table 2 Classification of the choledochal cysts

Type	Description
Type I	Cystic dilatation of the common bile duct. Also cysts there may be at extrahepatic right and left hepatic ducts and at common hepatic ducts. Intrahepatic bile ducts are unaffected
Type Ia	Large saccular cystic dilatation of the common bile duct, with dilatation of the common hepatic duct and the right and left hepatic duct
Type Ib	Focal and segmental dilation of the common bile duct
Type Ic	Diffuse fusiform dilation of the common bile duct
Type II	Common bile duct diverticulum
Type III	Cysts in the intraduodenal part of the common bile duct – known as choledochocele
Type IV	Multiple extrahepatic alone, or multiple extrahepatic and intrahepatic cysts together
Type IVa	Extrahepatic and intrahepatic cysts
Type IVb	Multiple extrahepatic cysts (common hepatic duct, common bile duct and intraduodenal common bile duct)
Type V	One or more cystic dilatation of the intrahepatic bile duct. Multiple intrahepatic bile duct cysts are defined as Caroli disease



DOI: 10.4292/wjgpt.v13.i4.33

Figure 2 Classificiation of choledochal cysts[4].

metaplasia and biliary intraepithelial neoplasia, which are precursors of cholangiocarcinoma, may also be observed[53].

Diagnosis

The initial examination of a patient with jaundice or right upper quadrant pain should involve ultrasonography, on which intrahepatic and/or extrahepatic cysts will be well-defined. The subsequent diagnosis is confirmed with MRCP, which can also accurately identify any biliary or pancreatic duct anomalies and variations. ERCP (Figure 3) can be used, offering the advantage of preemptive treatment by sphincterotomy in the presence of bile duct or pancreaticodudenal junction obstructions, or in the presence of cholododocell[53]. In our center, ERCP is performed for Type-I and Type-III cysts.

Treatment

The timing of surgery for cysts is controversial. The treatment of choledochal cysts depends on the type of cyst, the age of the patient and the presence of recurrent cholangitis. Patients with choledochal cysts experience cholangitis attacks at different frequencies, and such attacks may complicate surgery due to adhesions. In addition, liver fibrosis of varying degrees may be observed in patients with choledochal cysts. Choledochal cysts have malignancy potential, with the risk being higher in older ages (0.4% in

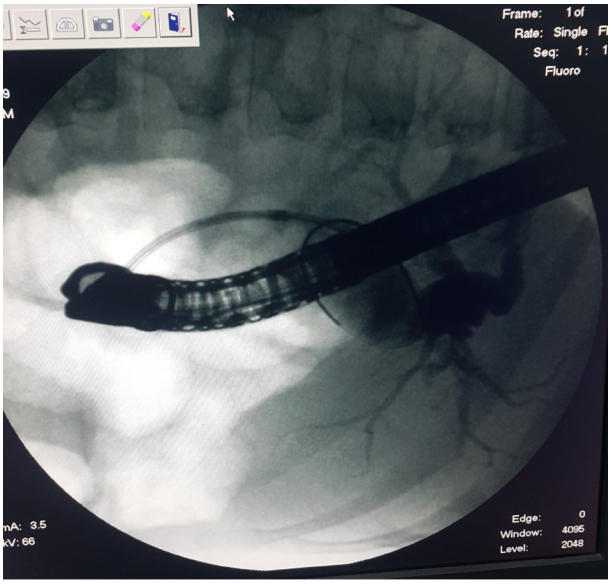


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Figure 3 An endoscopic retrograde cholangiopancreatography image of type IVa choledochal cyst.

those under the age of 18, and between 5% and 50% in adults). Elderly adults are at the greatest risk, and Type I and Type IV cysts have the highest risk of malignancy[74]. Although the risk is lower in other cysts, such risks still exist, and given all the above reasons, it would be prudent to treat them without delay after diagnosis. In cases diagnosed in the neonatal period, surgical treatments can be performed successfully when the patient is a few months old, while the success of surgical treatment in older children is similar to that of adults.

The standard approach in Type-I and Type-IV cysts is complete cyst excision and Roux-en-Y choledochojejunostomy. Intrahepatic cysts in type IVa choledochal cysts should be excised due to the risk of cholangitis and the malignancy potential, and a hepatic segmentomy may be required. For Type-IVa cysts, a hepatico jejunostomy is performed, while for Type-II cysts, cyst excision is sufficient[72]. If type III cysts are symptomatic, they are treated with endoscopic sphincterotomy, and although the risk of malignant transformation is low, surgical treatment may be required in asymptomatic or symptomatic cases. A mucosal biopsy should be taken from the cyst wall during ERCP to evaluate whether the cyst mucosa has a duodenal or biliary epithelium. Endoscopic or surgical excisions may be required in the presence of biliary epithelium, as the risk of malignancy from the biliary epithelium is higher than that of the duodenal epithelium[75]. If Type-V cysts cause frequent cholangitis and the cysts are segmental, a resection or hepatectomy can be performed. LT may be required in symptomatic cysts with diffuse distribution[72].

In cysts extending distally, the pancreaticobiliary junction is preserved during surgical treatment, while the cystic mucosa in this part should be excised due to the risk of malignancy in remnant tissues [76].

Biliary tract surgery is a complex procedure. The common treatment option for choledochal cysts is the traditional open surgery technique, but with the development of laparoscopic techniques in recent years, choledochal cysts have come to be treated laparoscopically in children. It has been suggested that laparoscopic cyst excision and Roux-en-Y hepaticojejunostomy in children provide better intraoperative and postoperative results than open surgery[76].

Monitoring

There is no widely accepted follow-up procedure for patients who have undergone surgery, although we recommend that patients be followed up for anastomotic stricture and malignancy. We periodically check liver enzymes, ultrasonography and carbohydrate antigen 19-9, and as such patients may still have cholangitis, appropriate antibiotics should be administered.

CONCLUSION

In conclusion, BA and choledochal cysts are diseases that cause obstructive cholestasis. While the diagnosis of BA can be rather complicated, it is important to diagnose as early as possible and to perform a Kasai hepatoportoenterostomy before the age of 2 mo for a good prognosis. All patients with persistent acholic stool and elevated GGT should be evaluated in terms of BA. Normal ultrasonography

will not rule out BA, and such patients are candidates for intraoperative cholangiography. Choledochal cysts can present symptoms at any age, and since recurrent cholangitis attacks will lead to chronic liver disease, and due to their malignant potential, treatment and long- term follow-up are important.

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Observational Study

Primary hyperparathyroidism presenting as acute pancreatitis: An institutional experience with review of the literature

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Abstract

BACKGROUND

Acute pancreatitis (AP) presenting as an initial manifestation of primary hyperparathyroidism (PHPT) is uncommon, and its timely diagnosis is crucial in preventing recurrent attacks of pancreatitis.

AIM

To determine the clinical, biochemical, and radiological profile of PHPT patients presenting as AP.

METHODS

This is a retrospective observational study, 51 consecutive patients admitted with the diagnosis of PHPT during January 2010 and October 2021 at a tertiary care hospital in Puducherry, India was included. The diagnosis of AP was established in the presence of at least two of the three following features: abdominal pain, levels of serum amylase or lipase greater than three times the normal, and characteristic features at abdominal imaging.

RESULTS

Out of the 51 consecutive patients with PHPT, twelve (23.52%) had pancreatitis [5 (9.80%) AP, seven (13.72%) chronic pancreatitis (CP)]. PHPT with AP (PHPT-AP) was more common among males with the presentation at a younger age (35.20 ±

16.11 *vs* 49.23 ± 14.80 years, P = 0.05) and lower plasma intact parathyroid hormone (iPTH) levels [125 (80.55-178.65) *vs* 519.80 (149-1649.55, P = 0.01)] compared to PHPT without pancreatitis (PHPT-NP). The mean serum calcium levels were similar in both PHPT-AP and PHPT-NP groups [(11.66 ± 1.15 mg/dL) *vs* (12.46 ± 1.71 mg/dL), P = 0.32]. PHPT-AP also presented with more gastrointestinal symptoms like abdominal pain, nausea, and vomiting with lesser skeletal and renal manifestations as compared to patients with PHPT-NP.

CONCLUSION

AP can be the only presenting feature of PHPT. Normal or higher serum calcium levels during AP should always draw attention towards endocrine causes like PHPT.

Key Words: Acute pancreatitis; Chronic pancreatitis; Parathyroid hormone; Primary hyperparathyroidism; Skeletal manifestations

Core Tip: Acute pancreatitis (AP) is a rare complication of primary hyperparathyroidism (PHPT) and can be its only presenting symptom. In this study, we retrospectively analyzed our single-center data of 51 PHPT patients between 2010 and 2021. The study showed that 9.8% of PHPT patients presented with AP. Patients with PHPT with AP patients presented at a younger age with a male preponderance and a lower frequency of skeletal and renal involvement as compared to patients with PHPT without pancreatitis. Early diagnosis and surgery for PHPT in AP will prevent recurrent attacks of AP and other PHPT-related complications.

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INTRODUCTION

Primary hyperparathyroidism (PHPT) is an endocrine disease characterized by excessive secretion of parathyroid hormone (PTH) from one or more parathyroid glands[1]. PHPT has become an asymptomatic disease in most Western countries. However, in developing countries such as India, it continues to be a symptomatic disease with skeletal, renal, cardiovascular, neuropsychiatric, and gastrointestinal manifestations[2-4].

Traditionally, 80% of acute pancreatitis (AP) cases are related to alcohol abuse and biliary stone disease, and < 10% have metabolic causes such as diabetic ketoacidosis, hypertriglyceridemia, and hypercalcemia with or without PHPT as an etiology[5]. PHPT has been linked with the development of both AP and chronic pancreatitis (CP). The first case report of AP in PHPT was published by Smith and Cook in 1940[6]. Later, in 1980, a study by Bess *et al*[7] from the Mayo Clinic involving 1153 patients with histopathologically confirmed PHPT showed that only 17 (1.5%) had coexisting or prior pancreatitis. This frequency was comparable to the reported incidence of pancreatitis among patients admitted to a hospital without PHPT. However, the link between the two diseases cannot be excluded based on data from hospitals with a large number of symptomatic PHPT patients[8-11]. Shepherd reported this association in Australia, where seven (5.1%) of 137 PHPT patients had pancreatic disease[12]. Western studies have shown a pancreatitis prevalence in PHPT patients that ranges from 5.1 to 8.1 percent, with predominantly AP cases[8,9,12]. However, studies from India have reported a higher prevalence of AP in PHPT patients, ranging from 12.9 to 16 percent, with a roughly equal number of CP and AP patients [11,13]. Despite its rarity, the fact that parathyroidectomy has been shown to prevent the recurrence of pancreatitis attacks suggests a causal link between the two diseases[14-16].

Serum calcium plays a crucial role in the pathogenesis of pancreatitis. Three mechanisms have been suggested for the development of AP in patients with PHPT. The earliest abnormalities of AP arise within the acinar cells. Calcium is a vital intracellular second messenger in acinar cells that initiates enzyme release through phosphorylation cascades. Elevated extracellular calcium levels due to PHPT may augment intracellular calcium signaling[17], and activate calcium-dependent proteins, such as calcineurin, as well as pancreatic proteases (especially trypsin)[18,19], or activate NF-κB,[20]leading to initiation of the pancreatic inflammatory cascade. In addition, hypercalcemia can lead to the formation of pancreatic calculi, ductal obstruction, and subsequent attacks of AP or CP[21]. Felderbauer *et al*[22]

showed that PHPT patients with AP had a higher prevalence of mutations in serine protease inhibitor kazal type 1 (SPINK-1), cystic fibrosis transmembrane conductance regulator (CFTR), and chymotrypsin C genes. Hence, hypercalcemia per se, as well as genetic factors, may be implicated in the pathogenesis of pancreatitis in PHPT. Hence, we conducted this retrospective study to determine the prevalence of AP in PHPT patients and to distinguish PHPT-AP patients from PHPT-NP patients based on their clinical, biochemical, and radiological profiles.

MATERIALS AND METHODS

This retrospective study included 51 patients admitted with a diagnosis of PHPT between January 2010 and October 2021. Data from these patients were obtained from the PHPT registry of the Department of Endocrinology, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India. The study was approved by the Institutional Ethics Committee (JIP/IEC/2021/329). PHPT was diagnosed based on elevated levels of plasma intact parathyroid hormone (iPTH) in the presence of hypercalcemia or normocalcemia. All patients had sporadic PHPT. Patients with a diagnosis of multiple endocrine neoplasia, a history of alcoholism and smoking, evidence of hypertriglyceridemia, and the presence of gallstone disease on abdominal imaging were excluded. The medical records of all the patients were studied for clinical, biochemical, and radiological parameters. The clinical symptoms were categorized as skeletal, renal, gastrointestinal, and neuropsychiatric symptoms. Data on biochemical parameters [serum calcium, serum phosphorous, serum magnesium, serum albumin, serum alkaline phosphatase (ALP), serum 25-OH vitamin D, and plasma iPTH] and radiological investigations were obtained from case records as well as from the Hospital Information System (HIS) and the Picture Archiving and Communication System (PACS).

AP was diagnosed by the presence of two of the following three features: (1) Abdominal pain consistent with AP; (2) Serum lipase (or amylase) elevated more than 3-fold the upper normal range; and (3) Characteristic features of AP, such as edema or pancreatic necrosis and/or collection[23]. The diagnosis of CP was made based on clinical and radiological investigations. A thorough diagnostic evaluation was performed in patients with chronic abdominal pain (> 6 mo duration), and the diagnosis of CP was established if there was evidence of pancreatic calcification on abdominal X-ray and/or ultrasonography and/or abdominal computed tomography[24]. Parathyroid tumor localization was performed using ultrasound of the neck or technetium-99m *sestamibi parathyroid single-photon emission* computed tomography (SPECT)/contrast-enhanced *computerized tomography***.**

Serum calcium [reference range (RR), 8.8-10.6 mg/dL], inorganic phosphorous (RR, 2.5-5 mg/dL), magnesium (RR, 1.9-2.5 mg/dL), albumin (RR, 3.5-5.2 g/dL), serum alkaline phosphatase (ALP) (RR, 30-120 IU/L), serum creatinine (RR, 0.5-0.9 mg/dL), serum lipase (RR, 0-67 IU/L), and serum amylase (RR, 22-80 IU/L) were measured using an autoanalyzer (Beckman-Coulter AU5800 clinical chemistry analyzer). Serum 25-OH vitamin D (RR, 20-100 ng/mL) and plasma iPTH (RR, 18.4-80.1 pg/mL) were quantified using the ADVIA Centaur XP VitD assay (Rev. C, 2012-08, Siemens) kit and ADVIA Centaur XP PTH assay (Rev. B, 2017-07, Siemens) kits, respectively. Vitamin D deficiency was defined as a serum 25-OH vitamin D level of < 12 ng/mL.

STATISTICAL ANALYSIS

Statistical analysis was carried out using MedCal Statistical software version 20.015. Categorical variables are described in terms of frequency and percentage. Continuous data are expressed as the mean ± SD or median with interquartile range (IQR). The student's *t* test was used for normally distributed data, while the Mann-Whitney *U* test was used for comparing nonparametric variables. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 51 PHPT patients were included in the study. The patients' ages ranged from 38.25 to 60 years, and the mean age of presentation was 47.80 ± 14.51 years, with a female-to-male ratio of 1.55:1, as shown in (Table 1). The major clinical presentation of PHPT was bone pain (54.90%), followed by fatigue (49.01%), abdominal pain (43.13%), nephrolithiasis (33.33%), and nephrocalcinosis (21.56%). The mean serum calcium level was 12.41 ± 1.58 mg/dL, and the median plasma iPTH level was 328.10 (143-1111) pg/mL.

Twelve out of 51 (23.52%) PHPT patients had pancreatitis. Five (9.8%) patients had AP, and seven (13.72%) had CP. All of them had abdominal pain (100%) as the major presentation, followed by nausea with vomiting (91.67%) and anorexia (83.33%). The mean serum calcium level of PHPT-AP/CP patients was 12.26 ± 1.05 mg/dL, and the mean plasma iPTH was 283.48 pg/mL.

Table 1 Demography, clinical and biochemical profile of all primary hyperparathyroidism patients

Parameters	*n* = 51
Age (yr)	47.80 ± 14.51
Female gender	31 (60.78%)
Sex (female: male)	1.55:1 (female 31, male 20)
Bone pain	28 (54.90%)
Fracture	04 (7.84%)
Pain abdomen	22 (43.13%)
Nausea and vomiting	16 (31.37%)
Weight loss	12 (23.52%)
Fatigue and weakness	25 (49.01%)
Anorexia	16 (31.37%)
Psychiatric features	06 (11.76%)
Nephrolithiasis	17 (33.33%)
Nephrocalcinosis	11 (21.56%)
Cholelithiasis	04 (7.84%)
Serum creatinine (mg/dL)	0.80 (0.63-1.14)
Serum corrected calcium(mg/dL)	12.41 ± 1.58
Serum phosphorous (mg/dL)	2.7 (2.2-3.17)
Serum magnesium (mg/dL)	1.80 (1.7-2)
Serum albumin (g/dL)	3.90 (3.5-4.2)
Serum alkaline phosphatase (IU/L)	196 (127.5-502)
Serum 25-OH vitamin D (ng/mL)	18.09 ± 9.93
Plasma iPTH (pg/mL)	328.10 (143-1111)

PHPT: Primary hyperparathyroidism; iPTH: Intact parathyroid hormone.

PHPT-AP patients were younger than PHPT patients without pancreatitis (PHPT-NP) (35.20 ± 16.11 *vs* 49.23 ±14.80 years, $P = 0.05$), and all of them were male, as shown in (Table 2). The PHPT-AP patients also presented with more gastrointestinal symptoms, such as abdominal pain (100%), nausea, and vomiting (100%), whereas skeletal disease (bone pain 56.41% and fracture 10.26%) and renal manifestations (nephrocalcinosis 23.07% and nephrolithiasis 35.89%) were more frequently seen in PHPT-NP. The mean calcium levels in patients with PHPT-AP were above the normal range (8.8-10.6 mg/dL). Serum ALP and plasma iPTH were significantly higher in PHPT-NP patients than in PHPT-AP patients (242 *vs* 112 IU/L, $P = 0.03$ and 519.80 *vs* 125 IU/L, $P = 0.01$, respectively) (Figure 1). The biochemical and imaging characteristics of PHPT-AP are shown in (Table 3) wherever available.

In our study, ultrasonography of the neck was performed in 34 patients, technetium-99m *sestamibi parathyroid* SPECT was performed in 48 patients, and computed tomography of the neck was performed in 18 patients for localizing parathyroid lesions, with sensitivities of 79.06%, 95.83%, and 100%, respectively.

DISCUSSION

The causal relationship between PHPT and pancreatitis has been debated for decades. There have been at least 12 retrospective studies or case series[25,26] on pancreatitis associated with PHPT since 1980, originating from the United States, India, France, Australia, Spain, and Germany, as shown in (Table 4).

Our experience with five PHPT-AP patients and the findings of an additional 111 such patients in the literature establish an etiological relationship between PHPT and AP. In our study, 23.52% of PHPT patients had pancreatitis; of these, 9.80% presented with AP at the time of diagnosis. However, studies from the Western population have shown a prevalence of AP as 0.86%-5.1% in patients with PHPT (Table 4). Several factors, including severity, delays in diagnosis, and asymptomatic *vs* symptomatic

Table 2 Comparison between primary hyperparathyroidism without pancreatitis and primary hyperparathyroidism with acute pancreatitis

Parameters	PHPT-NP, *n* = 39	PHPT-AP, *n* = 05	*P* value
Age (yr)	49.23 ± 14.80	35.20 ± 16.11	0.05
Female gender	27 (69.23%)	0	
Bone pain	22 (56.41%)	1 (20%)	0.17
Fracture	04 (10.26%)	0	
Pain abdomen	10 (25.64%)	5 (100%)	< 0.01
Nausea and vomiting	05 (12.82%)	5 (100%)	< 0.01
Weight loss	06 (15.38%)	1 (20%)	1
Fatigue and weakness	18 (46.15%)	2 (40%)	1
Anorexia	06(15.38%)	4 (80%)	< 0.01
Psychiatric features	03 (7.69%)	0	
Nephrolithiasis	14 (35.89%)	0	
Nephrocalcinosis	09 (23.07%)	0	
Cholelithiasis	02 (5.12%)	1 (20%)	0.31
Serum creatinine(mg/dL)	0.80 (0.60-1.19)	0.74 (0.66-0.89)	0.66
Serum corrected calcium(mg/dL)	12.46 ± 1.71	11.66 ± 1.15	0.32
Serum phosphorous (mg/dL)	2.7 (2.2-3.17)	2.7 (2.02-2.90)	0.62
Serum magnesium (mg/dL)	1.82 ± 0.33	1.76 ± 0.34	0.72
Serum albumin (g/dL)	3.90 (3.5-4.1)	4.2 (3.7-4.75)	0.18
Serum ALP (IU/L)	242 (148-764.5)	112 (106.25-147)	0.03
Serum 25-OH vitamin D(ng/mL)	15.48 (10.24-21.37)	25.91 (13.88-31.72)	0.33
Plasma iPTH (pg/mL)	519.80(149-1649.55)	125 (80.55-178.65)	0.01

PHPTAP: Primary hyperparathyroidism with acute pancreatitis; PHPT-NP: Primary hyperparathyroidism without pancreatitis; ALP: Alkaline phosphatase; iPTH: Intact parathyroid hormone.

Table 3 Biochemical and imaging findings of patients with primary hyperparathyroidism with acute pancreatitis

No	Age	Sex	S Amylase (IU/mL)	S lipase (IU/mL)	Imaging	Modified CT severity index
1	46	M	160	770	Acute pancreatitis on CECT	4
2	27	M	1487	NA	Acute interstitial pancreatitis on MRCP	NA
3	20	M	NA	NA	Acute pancreatitis on CECT	6
4	25	M	514	260	Acute necrotizing pancreatitis on CECT	6
5	58	M	1276	1365	Acute necrotizing pancreatitis on CECT	8

PHPT-AP: Primary hyperparathyroidism with acute pancreatitis; iPTH: Intact parathyroid hormone; MRCP: Magnetic resonance cholangiopancreatography; CECT: Contrast enhanced computed tomography; NA: Details not available.

presentation of PHPT, are possible explanations for the higher prevalence of pancreatitis in patients with PHPT in studies from India, including ours. Among the two Indian studies that have reported a higher prevalence of AP, Jacob *et al*[13] reported the occurrence of AP in 6 of 101 (5.94%) patients with PHPT, while Arya *et al*[11] reported it in 18 of 218 (8.25%) such patients. Nevertheless, pancreatitis seems to be at least ten times more common in PHPT patients than in the general population[27].

Table 4 Rates of pancreatitis among patients with primary hyperparathyroidism in different studies

Ref.	Country	Number of PHPT Patients	PHPT with pancreatitis *n* (%)	Type of pancreatitis
Bess *et al*[7]	USA	1153	17 (1.5)	10 AP (0.86%), 7 CP
Sitges-Serra *et al*[8]	Spain	86	7 (8.1)	3 AP (3.4%), 1 RP, 3 CP
Koppelberg *et al*[9]	Germany	234	13 (5.6)	9 AP (3.8%), 4 CP
Shepherd *et al*[12]	Australia	137	7 (5.1)	All AP (5.1%)
Carnaille *et al*[10]	France	1224	40 (3.3)	18 AP (1.47), 8 RP, 14 CP
Agarwal *et al*[32]	India	87	6 (6.9)	5 RP, 1 CP
Jacob *et al*[13]	India	101	13 (12.9)	6 AP (5.94%), 6 RP, 1 CP
Bhadada *et al*[29]	India	59	9 (15.3)	All CP
Khoo *et al*[33]	USA	684	10 (1.5)	All AP (1.5%)
Felderbauer *et al*[22]	Germany	1259	57 (4.52)	16 AP (1.27%), 15 CP, 26 NA
Arya *et al*[11]	India	218	35 (16)	18 AP (8.25%), 17 CP
Misgar *et al*[5]	India	242	15 (6.19)	14 AP (5.78%), 1 CP
Total		**5484**	**229 (4.17)**	**111 (2.02) AP**

AP: Acute pancreatitis; CP: Chronic pancreatitis; NA: Details Not available; PHPT: Primary hyperparathyroidism; RP: Recurrent pancreatitis.

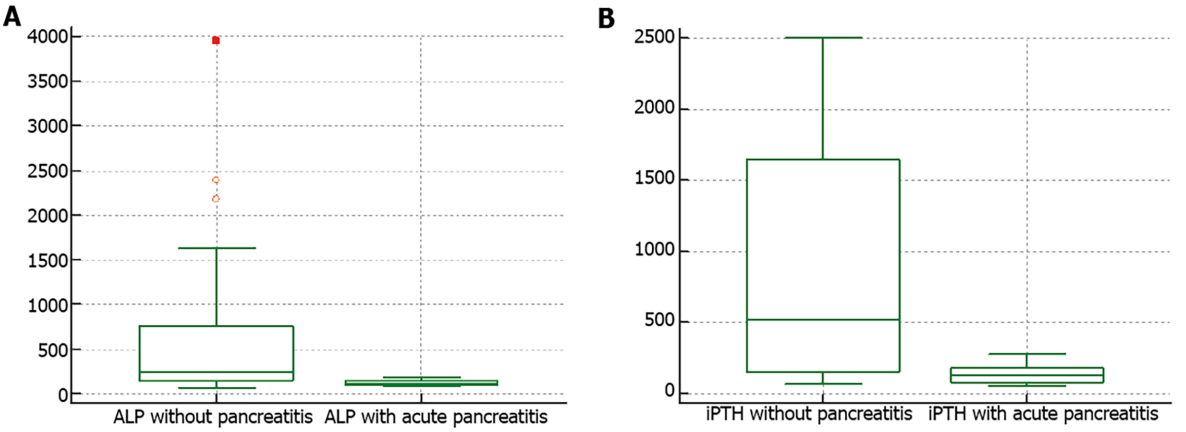

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Figure 1 Serum alkaline phosphatase and plasma intact parathyroid hormone were significantly higher in primary hyperparathyroidism without pancreatitis patients than in primary hyperparathyroidism with acute pancreatitis patients. A: Median alkaline phosphatase in primary hyperparathyroidism without pancreatitis (PHPT-NP) *vs* primary hyperparathyroidism with acute pancreatitis (PHPT-AP); B: Median intact parathyroid hormone in PHPT-NP *vs* PHPT-AP. ALP: Alkaline phosphatase; iPTH: Intact parathyroid hormone.

PHPT-AP presented at a younger age with a male preponderance, in contrast to the female preponderance (27 out of 39) seen in PHPT-NP. In both studies by Carnaille *et al*[10] from France and the study by Jacob *et al*[13] from India, a younger age of presentation with a male preponderance of AP was reported, which is in agreement with our observation. Abdominal pain was the most common (100%) clinical presentation of PHPT-AP in our study, and the same finding was reported by others[13,28,29]. Skeletal manifestations such as bone pain and fracture were respectively seen in only 20% and none of the PHPT-AP patients, which is lower than the corresponding prevalence among patients with PHPT-NP (56.4% and 10.6%, respectively). This observation is similar to those of Arya *et al*[11] and Yadav *et al*[30]. The exact pathogenesis of this younger age of presentation, male preponderance, and presence of fewer skeletal/renal manifestations has not been established. A possible explanation could be the earlier detection of disease due to AP at a relatively mild stage with a lesser degree of elevation in iPTH levels. Additionally, genetic risk factors for the development of AP could have contributed to the younger age of presentation. One patient in the PHPT-AP group had a history of gallstones and underwent treatment for the same condition elsewhere before coming to our institute with AP. In the background of hypercalcemia and other PHPT-related complications, such as renal stones, and the absence of evidence

of cholelithiasis on subsequent imaging with CT of the abdomen, the possibility of AP due to hypercalcemia was considered in this patient.

Several studies[10,13] have reported elevated serum calcium levels among PHPT patients with pancreatitis compared to patients with PHPT-NP. The results suggest that the serum calcium level above a threshold predisposes PHPT patients to pancreatitis. However, in our study, PHPT patients with AP had serum calcium levels similar to those in PHPT patients without pancreatitis. At the time of presentation, normocalcemia was seen in 1 (20%) patient and could be attributed to saponification of calcium in the pancreatic tissue. The diagnosis of PHPT was suspected in this patient due to the absence of other risk factors for AP, and the patient was subsequently found to have increased plasma iPTH levels. Thus, a normal calcium level at the time of presentation in patients with an acute episode of pancreatitis does not exclude the possibility of PHPT. The current study highlights the importance of measuring intact PTH levels and rechecking calcium levels in patients with an unexplained etiology of AP. Because pancreatitis primarily occurs in severely hypercalcemic patients, it is rarely associated with PHPT in developed countries where PHPT is diagnosed at a much earlier and milder stage. Serum ALP was significantly higher in patients with PHPT-NP than in PHPT-AP patients, most likely due to more severe bone disease.

In patients with PHPT who undergo parathyroidectomy, the course of pancreatitis is unclear due to a lack of long-term studies. Most published reports had a follow-up of only approximately two years. Despite this short period, there was a 42%-100% reduction in pancreatitis recurrence rates[31]. In our study, all patients with PHPT and pancreatitis underwent parathyroidectomy. After successful parathyroidectomy, four out of five patients with PHPT-AP did not report a recurrence of pancreatitis over a median follow-up of 8 mo (range, 8-50 mo). Histopathology revealed parathyroid adenoma in 3 cases and parathyroid carcinoma in 1 case. However, the report was inconclusive in one patient. Additionally, this patient had recurrent episodes of pancreatitis, and further evaluation could not be performed, as the patient was lost to follow-up due to the COVID pandemic. Our findings, like others, emphasize the importance of parathyroid surgery in these patients. It has been suggested that parathyroid surgery should precede any pancreatic surgery because of its beneficial effect on the course of the latter.

The limitations of this study are that we were not able to perform a gene mutation analysis of SPINK-1 and CFTR; hence, the exact prevalence of genetic risk and idiopathic pancreatitis could not be established. Additionally, we could not determine the cause of the lower frequency of renal manifestations in patients with PHPT-AP compared to patients with PHPT-NP, as data on urinary calcium profiles were not available for all patients given the retrospective nature of this study.

CONCLUSION

The current study demonstrated a causal relationship between PHPT and AP. Compared to patients with PHPT-NP, patients with PHPT-AP were younger, had a male preponderance, and had a lower frequency of skeletal and renal involvement. Our findings emphasize the importance of thoroughly investigating for PHPT in any patient with pancreatitis and high-normal or elevated serum calcium levels, especially in the absence of other common causes of pancreatitis. Pancreatitis should be an anticipated complication of PHPT and may be the sole presenting complaint of PHPT. Early diagnosis and resection of parathyroid lesions will prevent recurrent attacks of AP and other PHPT-related complications.

ARTICLE HIGHLIGHTS

Research background

Primary hyperparathyroidism (PHPT) is an endocrine disease characterized by excessive secretion of parathyroid hormone (PTH) from one or more parathyroid glands. PHPT has been linked with the development of both acute and chronic pancreatitis.

Research motivation

Early diagnosis and surgery for PHPT will prevent the recurrence of acute pancreatitis (AP).

Research objectives

To determine the prevalence of AP in PHPT patients and to distinguish PHPT with acute pancreatitis (PHPT-AP) from PHPT without pancreatitis (PHPT-NP) patients based on their clinical and biochemical and radiological profiles.

Research methods

This is a retrospective observational study done on 51 consecutive patients admitted with the diagnosis of PHPT between January 2010 to October 2021 at a tertiary care hospital in Puducherry, India.

Research results

In our study, the prevalence of AP in PHPT was found to be 9.80%. PHPT with AP was more common among males with the presentation at a younger age with lower plasma intact parathyroid hormone levels compared to PHPT-NP.

Research conclusions

The current study demonstrates a causal relationship between the PHPT and AP. Evaluation for PHPT should be considered in any patient with pancreatitis with high normal or elevated serum calcium levels, especially in the absence of other common causes of pancreatitis.

Research perspectives

Pancreatitis should be an anticipated complication of PHPT and may be the sole presenting complaint of PHPT. Early diagnosis and surgery for PHPT in AP will prevent recurrent attacks of AP and other PHPT-related complications.

FOOTNOTES

Author contributions: Rashmi KG, Palui R and Roy A acquisition of the data and the drafting of the work; Sahoo J, Kamalanathan S and Naik D conceptualized the work, supervised the writing, gave intellectual inputs, and critically revised the manuscript; Mohan P and Pottakkat B designed the work, gave intellectual inputs and critically revised the manuscript; Kar SS interpreted the data and gave intellectual inputs; all of them approved the final version of the manuscript to be published.

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ORIGINAL ARTICLE

Observational Study

Overweight and abdominal fat are associated with normal bone mineral density in patients with ulcerative colitis

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Abstract

BACKGROUND

Low bone mineral density (BMD) is common in patients with inflammatory bowel disease. However, nutritional risk factors for low BMD in the ulcerative colitis (UC) population are still poorly understood.

AIM

To investigate the association of anthropometric indicators and body composition with BMD in patients with UC.

METHODS

This is a cross-sectional study on adult UC patients of both genders who were followed on an outpatient basis. A control group consisting of healthy volunteers, family members, and close people was also included. The nutritional indicators evaluated were body mass index (BMI), total body mass (TBM), waist circumference (WC), body fat in kg (BFkg), body fat in percentage (BF%), trunk BF (TBF), and also lean mass. Body composition and BMD assessments were performed by dual-energy X-ray absorptiometry.

RESULTS

The sociodemographic characteristics of patients with UC (n = 68) were similar to those of healthy volunteers (n = 66) (P > 0.05). Most patients (97.0%) were in remission of the disease, 58.8% were eutrophic, 33.8% were overweight, 39.0% had high WC, and 67.6% had excess BF%. However, mean BMI, WC, BFkg, and TBF of UC patients were lower when compared to those of the control group (P < 0.05). Reduced BMD was present in 41.2% of patients with UC (38.2% with osteopenia and 2.9% with osteoporosis) and 3.0% in the control group (P < 0.001). UC patients with low BMD had lower BMI, TBM, and BFkg values than those with normal BMD (P < 0.05). Male patients were more likely to have low BMD (prevalence ratio [PR] = 1.86; 95% confidence interval [CI]: 1.07-3.26). Those with excess weight (PR = 0.43; 95%CI: 0.19-0.97) and high WC (PR = 0.44; 95%CI: 0.21-0.94) were less likely to have low BMD.

CONCLUSION

Patients with UC in remission have a high prevalence of metabolic bone diseases. Body fat appears to protect against the development of low BMD in these patients.

Key Words: Ulcerative colitis; Bone mineral density; Body composition; Fat body; Abdominal fat

Core Tip: There is a high prevalence of osteopenia/osteoporosis in adult outpatients with ulcerative colitis in remission. Patients with ulcerative colitis had a 22.4 times greater chance of developing reduced bone mineral density than healthy individuals. Lower values of body mass index and body fat indicators were identified in patients with ulcerative colitis with low bone mineral density. Low bone mineral density was associated with males and those without excess weight and with normal waist circumference.

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INTRODUCTION

Low bone mineral density (BMD) is often seen in patients with inflammatory bowel disease (IBD)[1,2]. Patients with Crohn's disease and ulcerative colitis (UC), the main types of IBD, are at increased risk of fracture compared to healthy controls, with an osteoporotic fracture risk around 32%[3-6]. In patients with UC, the prevalence of osteoporosis varies between 2% to 9%[7].

The cause of osteoporosis in patients with IBD is multifactorial. Most studies involving patients with UC demonstrate that the main risk factors for this disease are related to genetics, chronic inflammatory status, treatment with steroids, and low weight[8-10].

Nutritional status appears to influence the BMD of patients with IBD. The inflammatory process and complications of the disease in the active phase can lead to compromised nutritional status, with reduced body mass and muscle mass reserves and micronutrient deficiency, and consequently to low BMD and increased risk of osteoporotic fractures[11,12]. Although the increased prevalence of overweight/obesity is evident in patients with UC, studies explaining the relationship between abdominal fat and disease complications in this group of patients are limited[13].

Studies that demonstrate the relationship between nutritional risk factors and low BMD are more frequent among patients with CD considering the extension and severity of the disease, which can compromise the main sites of nutrient absorption. Thus, there is little evidence that brings the relationship of nutritional risk factors with the development of reduced BMD in patients with UC. The aim of the present study was to investigate the association of indicators of total body mass and body composition with BMD in patients with UC.

MATERIALS AND METHODS

Study design and patients

This is a cross-sectional study involving adult outpatients with UC from two reference centers. Consecutive patients with a diagnosis of UC confirmed by clinical, endoscopic, radiological, and

histological criteria were included[14]. The control group consisted of healthy volunteers, family members, and close people with the same sociodemographic characteristics and lifestyle compared to the UC group. Volunteers recruited were matched for gender and age, with no history of bowel surgery or taking medications known to affect bone turnover.

Elderly people, pregnant women, patients with diseases that cause changes in bone metabolism (chronic renal failure, chronic obstructive pulmonary disease, thyroid disease, liver disease, and systemic lupus erythematosus), malignant diseases, diabetes mellitus, or celiac disease, menopausal or post-menopausal patients, and those in use of estrogen therapy were not included in the study.

Clinical data

The clinical criteria for patients with UC were activity index and disease duration, past history of intestinal resection, accumulated dose of glucocorticoids in the last year, use of glucocorticoids for 3 mo or more, extent of disease according to Montreal classification[15], and serum calcium, albumin, and C-reactive protein (CRP) levels, in addition to smoking, regular physical activity[16], and use of calcium and vitamin D supplements.

Disease activity was assessed by the Lichtiger index[17], considering activity when a score ≥ 10 points. Calcium (mmol/L) and serum albumin (g/dL) and CRP (mg/L) were collected on the same day as the BMD evaluation and performed in the same laboratory. Calcium and albumin were measured using the dry chemical method and CRP was measured by the turbidimetry method.

Anthropometric assessment and body composition

Anthropometric measurements were performed by a trained and standardized team. Height (in centimeters) and body weight (in kg) were measured in duplicate, with subjects wearing light clothing and without shoes, using a scale (Filizola, São Paulo, Brazil), 150 kg capacity and 100 g interval, with an attached stadiometer with a 0.5 cm scale. The body mass index (BMI) was obtained using the formula weight/height^2 and classified according to the World Health Organization[18]. For statistical analysis, two groups were considered, those with excess weight (BMI ≥ 25.0 kg/m^2) and those without (BMI < 25.0 kg/m^2).

Waist circumference (WC) was measured with the individual in an upright position, with feet together and without shoes. The measurement was taken with an inelastic measuring tape, which circled the individual at the midpoint between the iliac crest and the last rib[18]. High WC was considered when ≥ 80 cm for women and ≥ 90 cm for men[19].

The evaluation of body composition was performed by dual-energy X-ray absorptiometry (DXA) of the total body using a Prodigy Lunar Bone Densitometer (GE Medical Systems, United States). The equipment calibration followed the manufacturer's recommendations and both the calibration and analysis were performed by a single technician with experience in this type of assessment. The values of total body fat in percentage (BF%), total body fat in kilograms (BFkg), trunk body fat in kg (TBF), and lean mass in kilograms (LBM) were obtained. The percentage of body fat (BF%) was considered high when ≥ 25% for men and ≥ 32% for women[18].

Bone mineral density assessment

BMD was determined by DXA in the whole body, lumbar spine (L1-L4), and femoral neck. Results of DMO are expressed in g/cm^2 and also presented as T-score or Z-score. The BMD classification was based on the T-score for men 50 years of age and older and patients with UC and the Z-score for those younger than 50 years of age for men and premenopausal women. For patients with UC, the T-score was used regardless of age, considering the possibility of secondary loss of bone mass determined by the underlying disease or by the therapies used. According to the T-score, the BMD was normal up to 1 standard deviation (SD), with osteopenia values below -1 and above -2.5 SD and with osteoporosis ≤ -2.5 SD. For the Z-score, BMD ≤ -2.0 SD was considered below the estimated for the age group (BMD reduced for age). In the osteopenia/osteoporosis classification, the bone sites of the femoral neck or lumbar spine were used[20].

Statistical analysis

Results are expressed as proportions for categorical variables, the mean and SD for continuous variables with a normal distribution, and median and interquartile range for variables without a normal distribution. Mann-Whitney test was used to compare continuous variables and the chi-square test or Fisher's exact test to compare categorical variables. Poisson regression analysis with robust variance was used to obtain estimates of the prevalence ratio and the respective 95% confidence interval (CI). For all tests, a *P*-value < 0.05 was considered statistically significant. The Statistical Package for Social Science program (SPSS, Chicago, IL, United States, version 21.0) was used for data tabulation and analysis.

Ethical considerations

Informed consent was obtained from all participants and the Ethics Committee of the University Hospital Professor Edgar Santos approved the study protocol (nº117/2011).

Table 1 Demographic, clinical, nutritional, and bone density characteristics of patients with ulcerative colitis

Variable	UC (*n* = 68)	Control (*n* = 66)	*P* value
Age (yr), median (IR)	39.0 (31.0-44.8)	36.5 (29.0-43.0)	0.484
Sex (female), *n* (%)	42 (61.8)	39 (59.1)	0.867
Smoking (yes), *n* (%)	2 (2.9)	4 (6.1)	0.437
Regular physical activity (yes), *n* (%)	16 (23.5)	15 (22.7)	1.000
Duration of illness (yes), median (IR)	5.0 (2.0-8.0)		
Disease remission (yes), *n* (%)	66 (97.1)		
Intestinal resection history (yes), *n* (%)	2 (2.9)		
Extent of disease, *n* (%)			
Proctitis	13 (19.1)		
Left colitis	25 (36.8)		
Extensive colitis	30 (44.1)		
Use of glucocorticoids (yes), *n* (%)	12 (17.6)		
Use ≥ 3 mo (yes), *n* (%)	8 (66.7)		
Accumulated dose of glucocorticoids (g), median (IR)	1.7 (1.2-2.5)		
Calcium supplement (yes), *n* (%)	3 (4.4)	0 (0)	0.245
Vit D supplement (yes), *n* (%)	5 (7.4)	0 (0)	0.058
Serum calcium (mmol/L), median (IR)	2.3 (2.2-2.4)	2.4 (2.3-2.4)	0.065
Serum albumin (g/dL), median (IR)	4.3 (4.1-4.5)	4.4 (4.1-4.6)	0.801
C-RP mg/dL, median (IR)	1.4 (0.6-5.2)	5.0 (1.0-6.2)	0.004
BMI (kg/m^2), median (IR)	23.7 (20.6-26.5)	26.3 (22.8-29.0)	0.16
BMI classification, *n* (%)			0.020
Thinness	5 (7.4)	1 (1.5)	
Eutrophy	40 (58.8)	26 (39.4)	
Overweight	16 (23.5)	28 (42.4)	
Obesity	7 (10.3)	11 (16.7)	
WC (cm), median (IR)	80.5 (72.0-89.1)	84.6 (79.7-93.7)	0.156
LBM (kg), median (IR)	40.1 (34.5-49.4)	41.5 (35.3-52.2)	0.604
BF (kg), median (IR)	17.8 (11.5-22.6)	23.2 (17.8-28.4)	0.001
BF (%), median (IR)	32.9 (23.7-37.6)	34.8 (28.1-42.3)	0.168
TBF (kg), median (IR)	8.6 (6.3-12.5)	12.8 (7.8-16.5)	0.354
BMD (g/cm^2), median (IR)			
Femoral neck	0.99 (0.90-1.07)	1.06 (0.96-1.15)	0.120
Lumbar spine	1.16 (1.08-1.26)	1.21 (1.13-1.31)	0.120
Total body	1.17 (1.11-1.24)	1.22 (1.19-1.29	0.000

UC: Ulcerative colitis; SD: Standard deviation; IR: Interquartile range; BMI: Body mass index; WC: Waist circumference; LBM: Lean body mass; BF: Body fat; TBF: Trunk body fat; BMD: Bone density; C-RP: C-reactive protein.

RESULTS

Clinical and nutritional characteristics

In this study, 68 patients with UC and 66 people in the control group were included. In both groups, the majority were female and demographics, lifestyle, and use of nutritional supplements were similar (P > 0.05) (Table 1).

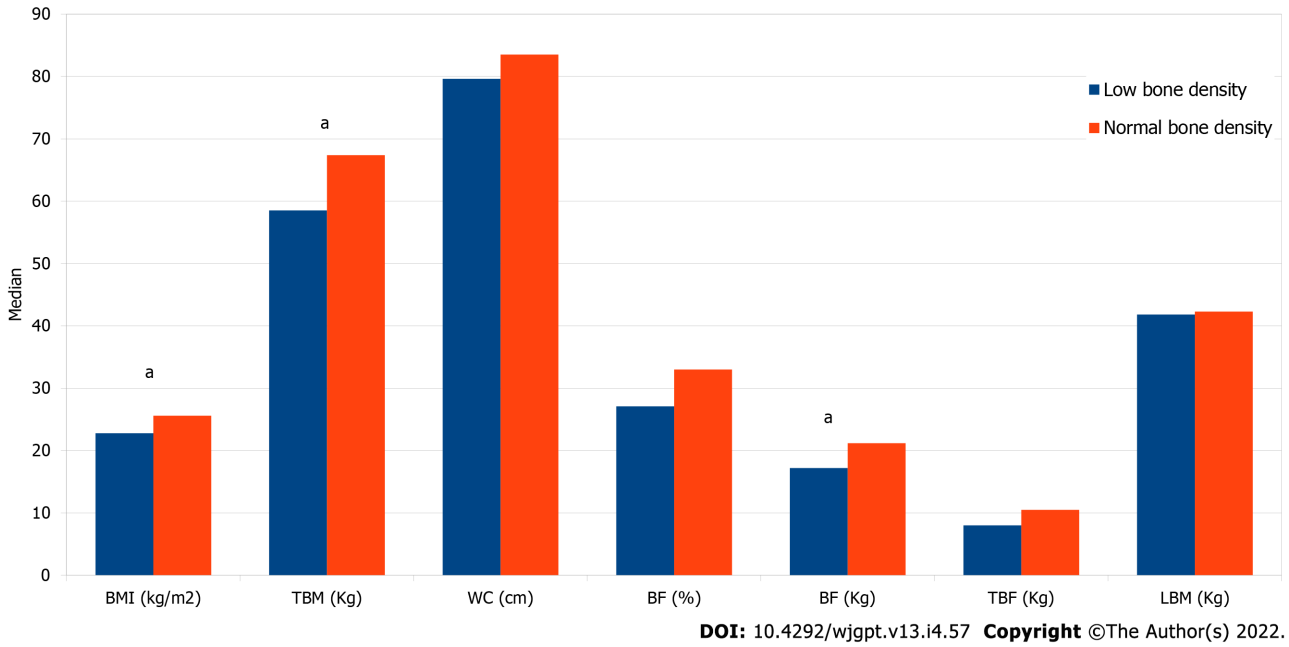

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Figure 1 Anthropometry and body composition according to bone mineral density in patients with ulcerative colitis. [a]*P* < 0.05 (Mann-Whitney test). BMI: Body mass index; TBM: Total body mass; WC: Waist circumference; BF: Body fat; TBF: Trunk body fat; LBM: Lean body mass.

Most patients (97.0%) were in remission of the disease, only 2.9% had a previous history of intestinal resection, and extensive colitis was present in 44.1%. The use of steroids in the last year occurred in 17.6% of the patients, and of these, 66.7% used it for 3 mo or more (Table 1).

Regarding the anthropometric nutritional status, it was observed that the majority of UC patients had normal weight (58.8%); however, the frequency of overweight was high (33.8%), with six (8.8%) having grade I obesity and one (1.5%) having grade II. Women had higher BF% (37.3% *vs* 19.7%; *P* = 0.00), BFkg (22.5kg *vs* 12.7 kg; *P* = 0.00), and TBF (10.8kg *vs* 7.3 kg; *P* = 0.00) than men. BFkg and TBF of UC patients were statistically lower compared to those of the control group (*P* < 0.05) (Table 1).

BMD characteristics

Low BMD was present in 41.2% (*n* = 28) of patients with UC (38.2% with osteopenia and 2.9% with osteoporosis) and in 3.0% (*n* = 2) in the control group (*P* < 0.001). It was observed that UC patients had a 22.4 times greater chance of developing reduced BMD than healthy individuals (odds ratio = 22.4; 95%CI: 5.06 – 99.19). The majority (71.4%; 20/28) of UC patients with low BMD were younger than 45 years of age. The BMD of total body in UC patients was statistically lower compared to that of the control group (*P* < 0.05) (Table 1).

UC patients who had low BMD were mostly male, without regular physical activity, and had left colitis compared to those with normal BMD (*P* < 0.05) (Table 2). Serum calcium had a lower concentration in those with low BMD, although with a clinically irrelevant difference (Table 2). Low BMD occurred equally at both sites, the spine and femur.

Individuals in the control group who had low BMD (3.0%; 2/66) had osteopenia located in the lumbar spine, and all were female and without regular physical activity.

Anthropometric indicators and body composition vs BMD

Male patients with UC were more likely to have low BMD (PR = 1.86; 95%CI: 1.07-3.26), and those with excess weight (prevalence ratio [PR] = 0.29; 95%CI: 0.13-0.66) and high WC (PR = 0.36; 95%CI = 0.17-0.75) were less likely to have low BMD (Table 3). Patients with UC with low BMD had a lower BMI value than those with normal BMD (22.8 [20.5-24.4] *vs* 25.6 [21.9-28.4] kg/m^2; *P* = 0.02), TBM (58.5 [52.7-65.7] *vs* 67.4 [59.1-76.8] kg; *P* = 0.02), and BFkg (17.2 [9.9-21.3] *vs* 21.2 [15.4-28.4] kg; *P* = 0.01) (Figure 1).

No significant differences were found in anthropometric nutritional characteristics or body composition between those with UC with low and normal BMD when stratified by sex.

DISCUSSION

Our data demonstrate that in a sample of patients with UC, predominantly in remission, with reduced frequency of glucocorticoid use and excess body fat, low BMD had a high prevalence, in patients under 45 years of age, being that excess weight and abdominal fat are associated with normal BMD.

Table 2 Demographic and clinical characteristics according to normal and low bone mineral density of patients with ulcerative colitis

Variable	Normal BMD (*n* = 40)	Low BMD (*n* = 28)	*P* value
Age (yr), median (IR)	37.5 (30.0-43.0)	40.0 (32.5-46.0)	0.193
Age group, *n* (%)			
< 45 yr	31 (77.5)	20 (71.4)	0.57
≥ 45 yr	9 (22.5)	8 (28.6)	
Sex, *n* (%)			
Male	11 (27.5)	15 (53.6)	0.03
Female	29 (72.5)	13 (46.4)	
Regular physical activity, *n* (%)			
No	27 (67.5)	25 (89.3)	0.04
Yes	13 (32.5)	3 (10.7)	
Duration of illness (yr), median (IR)	5.0 (2.0-9.0)	4.5 (1.2-6.7)	0.98
Extent of disease, *n* (%)			
Proctitis	12 (30.0)	1 (3.6)	0.01
Left colitis	11 (27.5)	14 (50.0)	
Extensive colitis	17 (42.5)	13 (46.4)	
Use of glucocorticoids, *n* (%)			
No	33 (84.6)	22 (78.6)	0.75
Yes	6 (15.4)	6 (21.4)	
Use of glucocorticoids ≥ 3 mo, *n* (%)			
No	3 (50.0)	1 (16.7)	0.54
Yes	3 (50.0)	5 (83.3)	
Accumulated dose of glucocorticoids (g), median (IR)	1.8 (1.3-2.3)	1.5 (1.1-3.5)	0.55
Serum calcium (mmol/L), median (IR)	2.3 (2.3-2.4)	2.2 (2.2-2.3)	0.03
Serum albumin (g/dL), median (IR)	4.4 (4.1-4.6)	4.3 (4.0-4.5)	0.57
PCR mg/dL, median (IR)	3.1 (0.9-6.1)	1.6 (1.6-6.3)	0.56

SD: Standard deviation; IR: Interquartile range; BMD: Bone mineral density; C-RP: C-reactive protein.

It is recommended that patients with IBD be screened based on established guidelines for the general population (pre-existing fragility fracture, women aged 65 years and older and men aged 70 years and older, and those with risk factors that increase probability of detecting low bone mass)[21]. However, this is a matter of concern considering that in this sample the majority of patients with UC with reduced BMD were younger than 45 years of age, with reduced frequency of glucocorticoid use and in remission.

Bone mass loss is a frequent complication in patients with UC[22-24] and with a higher prevalence when compared to that in healthy controls[25]. Greater bone fragility increases the risk of fractures, and consequently morbidity and reduced quality of life for patients. The mechanisms reported in the literature associated with bone loss in UC patients are mainly related to the UC itself, the use of steroids, hospitalization[25-27], and low BMI values[28-31].

The role of obesity in patients with IBD is still uncertain, although initially it is believed that the greater inflammatory potential of adipose tissue could have a negative impact on the evolution of the disease in these patients[32,33]. The effect of body weight on bone mass can be attributed to the mechanical compression of weight on the skeleton, and in response, it increases bone mass to accommodate greater load[34]. In UC patients, obesity appears to be associated with a lower risk of low BMD[35], with a 5 kg/m^2 increase in BMI decreasing by 57% the chance of having low BMD in 327 patients with UC and ileo-anal anastomosis with pouch illegitimate[29].

The effects of body fat on BMD in patients with IBD have been discussed[36], considering the increase in the prevalence of overweight individuals diagnosed with UC[37,38]. Although there is no clear consensus in the literature, body fat seems to have a positive effect on bone mass, as a result of the anabolic effect of mechanical tension of the fat mass on bone, in addition to the action of hormones

Table 3 Prevalence and prevalence ratio of low bone mineral density according to demographic, clinical, and nutritional characteristics of patients with ulcerative colitis

Variable	Prevalence of low BMD, *n* (%)		PR (95%CI)	*P* value
Sex				
Female	15	57.7	1.00	
Male	13	31.0	1.86 (1.07 – 3.26)	0.029
Age group				
< 45 yr	20	39.2	1.00	
≥ 45 yr	8	47.1	1.38 (0.46 – 4.16)	0.583
Regular physical activity				
Yes	3	18.8	1.00	
No	25	48.1	2.56 (0.89 – 7.39)	0.081
Steroid use				
No	23	38.3	1.00	
Yes	5	62.5	1.63 (0.87 – 3.05)	0.126
Steroid use				
< 3 mo	1	25.0	1.00	
≥ 3 mo	5	62.5	2.50 (0.42 – 14.8)	0.313
BMI classification				
Not overweight	23	51.1	1.00	
Overweight	5	21.7	0.43 (0.19 – 0.97)	0.043
WC classification				
Normal	21	52.5	1.00	
Elevated	6	23.1	0.44 (0.21 – 0.94)	0.034
BF classification (%)				
Normal	10	45.5	1.00	
Elevated	18	39.1	0.86 (0.48 – 1.54)	0.614

PR: Prevalence ratio; CI: Confidence interval; BMI: Body mass index; WC: Waist circumference; BF: Body fat; BMD: Bone density; C-RP: C-reactive protein.

released by adipocytes, which influence the activities of bone cells, both osteoblasts and osteoclasts[34].

The influence of gender on the BMD of patients with IBD is discordant[1,4]. In our study, male patients were more likely to have reduced BMD, which we suppose at the expense of lower body fat compared to females.

No studies were found evaluating the association between WC/abdominal fat and BMD in patients with IBD. It is known that the relationship between abdominal fat and BMD is quite complex and the results of studies in the general population are conflicting[39,40]. The two adipose tissues present in the abdominal region (subcutaneous and visceral) are highly metabolic, with the production of adipokines, estrogens, and metabolic factors derived from bones, with feedback mechanisms that affect bone remodeling and body composition[40].

Our study has some limitations. For example, serum levels of alkaline phosphatase, parathyroid hormone, and vitamin D were not measured in this study. On the other hand, it has the advantage of assessing body mass by DXA. More robust, prospective studies with larger samples and techniques for more accurate quantification of adipose tissues are needed to better explain the relationship between total and abdominal body fat and BMD.

CONCLUSION

In conclusion, we observed that male UC patients in remission have a high prevalence of metabolic bone diseases, and nutritional parameters related to body fat seem to protect against the development of low

BMD. Understanding the protective effect that each nutritional component exerts on the bone mass of patients with IBD is important to assist in the development of strategies that can provide the control of metabolic bone diseases in these patients.

ARTICLE HIGHLIGHTS

Research background

Inflammatory bowel disease is associated with complications such as low bone mineral density and increased risk of fracture compared to healthy controls. In patients with ulcerative colitis, the prevalence of osteoporosis varies between 2% to 9% and the main risk factors are related to genetics, chronic inflammatory status, treatment with steroids, and low weight.

Research motivation

There is little evidence that brings the relationship of nutritional risk factors with the development of reduced bone mineral density (BMD) in patients with ulcerative colitis, despite the studies demonstrating the relationship between nutritional risk factors and low BMD are more frequent in patients with Crohn's disease, considering the extension and severity of factors the disease, which can compromise the main sites of nutrient absorption

Research objectives

To investigate the association of indicators of total body mass and body composition with BMD in patients with ulcerative colitis (UC).

Research methods

This is a cross-sectional study on adult UC patients of both genders who were followed on an outpatient basis. A control group consisting of healthy volunteers, family members, and close people was also included. The nutritional indicators evaluated were body mass index (BMI), total body mass (TBM), waist circumference (WC), body fat in kg (BFkg), BF in percentage (BF%), trunk body fat (TBF), and also lean mass. Body composition and BMD assessments were performed by dual-energy X-ray absorptiometry.

Research results

Most UC patients (97.0%) were in remission of the disease, 58.8% were eutrophic, 33.8% were overweight, 39.0% had high WC, and 67.6% had excess BF%. However, mean BMI, WC, BFkg, and TBF of UC patients were lower when compared to those of the control group ($P < 0.05$). Reduced BMD was present in 41.2% of patients with UC (38.2% with osteopenia and 2.9% with osteoporosis) and 3.0% in the control group ($P < 0.001$). UC patients with low BMD had lower BMI, TBM, and BFkg values than those with normal BMD ($P < 0.05$). Male patients were more likely to have low BMD (prevalence ratio [PR] = 1.86; 95% confidence interval [CI]: 1.07–3.26). Those with excess weight (PR = 0.43; 95%CI: 0.19-0.97) and high WC (PR = 0.44; 95%CI = 0.21-0.94) were less likely to have low BMD.

Research conclusions

Patients with UC in remission have a high prevalence of metabolic bone diseases and body fat appears to protect against the development of low BMD in these patients

Research perspectives

The future perspective is to evaluate other nutritional characteristics such as food consumption.

FOOTNOTES

Author contributions: Lopes MB, Rocha R, Coqueiro FG, and Santana GO designed the research; Lopes MB, Coqueiro FG, and Lima CA performed the research; Lopes MB, Rocha R, and de Oliveira CC analyzed the data; Lopes MB, Lyra AC, Rocha R, and Santana GO wrote the paper.

Institutional review board statement: The Ethics Committee of the University Hospital Professor Edgar Santos approved the study protocol (nº117/2011).

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: All authors declare that they have no conflict of interest to disclose.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at raquelrocha2@yahoo.com.br. Participants gave informed consent for data sharing. No additional data are available.

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