GALLBLADDER CONTRACTILITY IN CHILDREN WITH CHRONIC ABDOMINAL PAIN

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Dissertation submitted to

The Tamil Nadu Dr. M.G.R Medical university, Chennai

In partial fulfillment of the requirements for the degree of

Doctor of Medicine in Paediatrics

Under the guidance of

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MAY 2018

CERTIFICATE

This is to certify that the thesis entitled **"GALLBLADDER CONTRACTILITY IN CHILDREN WITH CHRONIC ABDOMINAL PAIN" Dr.C.RAAGHUL**, done under the guidance of **DR. K. NEELAKANDAN** Professor and Head of the Department of Paediatrics PSG IMS&R, Coimbatore in fulfilment of the regulations laid down by The Tamilnadu Dr.M.G.R Medical University for the award of MD degree in Paediatrics.

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DECLARATION

I, hereby declare that this dissertation entitled **"GALLBLADDER CONTRACTILITY IN CHILDREN WITH CHRONIC ABDOMINAL PAIN"** was prepared by me under the guidance and supervision of **Dr. K.NEELAKANDAN** Professor and Head of the Department of Paediatrics, PSGIMS&R, Coimbatore.

This dissertation is submitted to The Tamilnadu Dr.M.G.R Medical University, Chennai in fulfilment of the university regulations for the award of MD degree in Paediatrics. This dissertation has not been submitted elsewhere for the award of any other Degree or Diploma.

Dr. C. RAAGHUL

CERTIFICATE-II

This is to certify that this dissertation work titled **"GALLBLADDER CONTRACTILITY IN CHILDREN WITH CHRONIC ABDOMINAL PAIN"** of the candidate **Dr.C. RAAGHUL** with registration Number **201517503** for the award of DOCTOR OF MEDICINE in the branch of PAEDIATRICS. I personally verified the urkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows **0%** of plagiarism in the dissertation.

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INTRODUCTION

Child presenting with chronic abdominal pain is one of the most commonly encountered symptom. The exact prevalence of chronic abdominal pain is not exactly known, but the literature reports that 13% of middle school children and 17% of high school children experience weekly abdominal pain and this accounts for about 2% to 4% of all pediatric office visits [(1)]. Chronic abdominal pain and recurrent abdominal pain terms are used interchangeably. The definition of "chronic" is from definition by Apley of recurrent paroxysmal abdominal pain in children between the ages of 4 and 16 years that persists for greater than 3 months duration and affects normal activity [(2)]. At least as many children experience chronic pain but maintain normal activity and rarely come to the attention of the physician [(3,5)]. The Pediatric Rome group has subcategorized the chronic abdominal pain based on clinical presentation:

(1) Isolated paroxysmal abdominal pain,

(2) Abdominal pain associated with symptoms of dyspepsia,

(3) Abdominal pain associated with altered bowel pattern, and

(4) Abdominal migraine [(6).]

Chronic abdominal pain in children is either organic or inorganic. An organic cause was found in 70 (82.4%) patients and non-organic cause identified (NORAP) in 15 (17.6%) cases. Giardiasis was the commonest organic cause in 57 (67.0%) cases, either alone or with other parasitic infestations including ascariasis, trichuriasis and enterobiasis[(7)]. Cohort studies from India and

Pakistan suggest that RAP is most likely to have an organic cause (up to 82% of cases), with giardiasis being the most common underlying condition [7, 8]. However, another Indian cohort and a Sri Lankan cohort showed that non-organic RAP is more prevalent (74% and 76%, respectively) [9, 10]. In Malaysia, both urban and rural population-based cohorts had a similar prevalence of RAP at 9.6% and 11%, respectively [11, 12].

OBJECTIVE

PRIMARY OBJECTIVE:

To know whether gallbladder dysmotility constitutes in children with chronic abdominal pain

SECONDARY OBJECTIVE:

To find out any associating factors for children with chronic abdominal pain

MATERIALS AND METHODS

Setting:

Place of Study:

The study was done in the department of Pediatrics, PSG Institute of Medical Sciences and Research, Coimbatore. Cases were recruited from Pediatric out patient department, PSG Hospitals, Coimbatore. PSG Hospitals is a nine hundred bedded multispecialty ISO and NABH accredited teaching hospital that offers comprehensive tertiary level health care for patients with various ailments and from many nearby districts of western part of Tamilnadu.

Study Design:

The study is a case-control type, where children who fulfilled the clinical criteria for chronic abdominal pain were compared with age and sex matched controls. The cases were children between 5 to 15 years of age, who were brought to the Pediatric OPD with abdominal pain and fulfilled the inclusion criteria. After enrollment of the cases, healthy age and gender-matched controls were subjected into the study.

Time Frame:

The study was conducted for one year i.e. from 1stJanuary 2016 to 31st August 2017.

SAMPLE SIZE:

Thirty cases with chronic abdominal pain and an equal number of healthy controls were included in the study.

INCLUSION CRITERIA:

- Children of both gender aged between 5 to 15 years of age with chronic abdominal pain according to ROME III criteria.
- Healthy children, with no clinical evidence of any chronic illness or on medications were recruited as controls.

EXCLUSION CRITERIA:

- Non consent
- Children with past abdominal surgical history or known chronic abdominal pathology
- Children who had obvious causes for chronic abdominal pain following ultrasonographic examination of the gallbladder.
- Children who could not tolerate or cannot complete the fatty meal.

METHODOLOGY:

Children from 5 to 15 years of age attending Pediatrics out patient department for chronic abdominal pain were requested to respond to a questionnaire based on the ROME III criteria. Child fulfilling ROME III criteria for chronic abdominal pain were included in the study after obtaining an informed consent from parents and children, if they could assent for the

study. The cases were subjected to ultrasonographic examination of the gallbladder after a fasting of at least 6 hours. Following the baseline ultrasound study, the subjects were instructed to eat a fatty meal. The fatty meal is a special diet prepared by our hospital dietician according to basis of their fat quantity required to produce gallbladder contraction. The standard meal contained fat ranging from 30 to 70 g and quantity of fat was decided according to child's age. Following the fatty meal the subjects were subjected to a second ultrasonographic examination of the gallbladder to assess for gall bladder contractility.

During ultrasonographic examination of the gallbladder, the greatest length (L), greatest transverse width (W), and greatest anteroposterior diameter (A) of the gallbladder was measured in the fasting state and postprandial period of 30min. Dodd's Formula was used to measure the gall bladder volume.

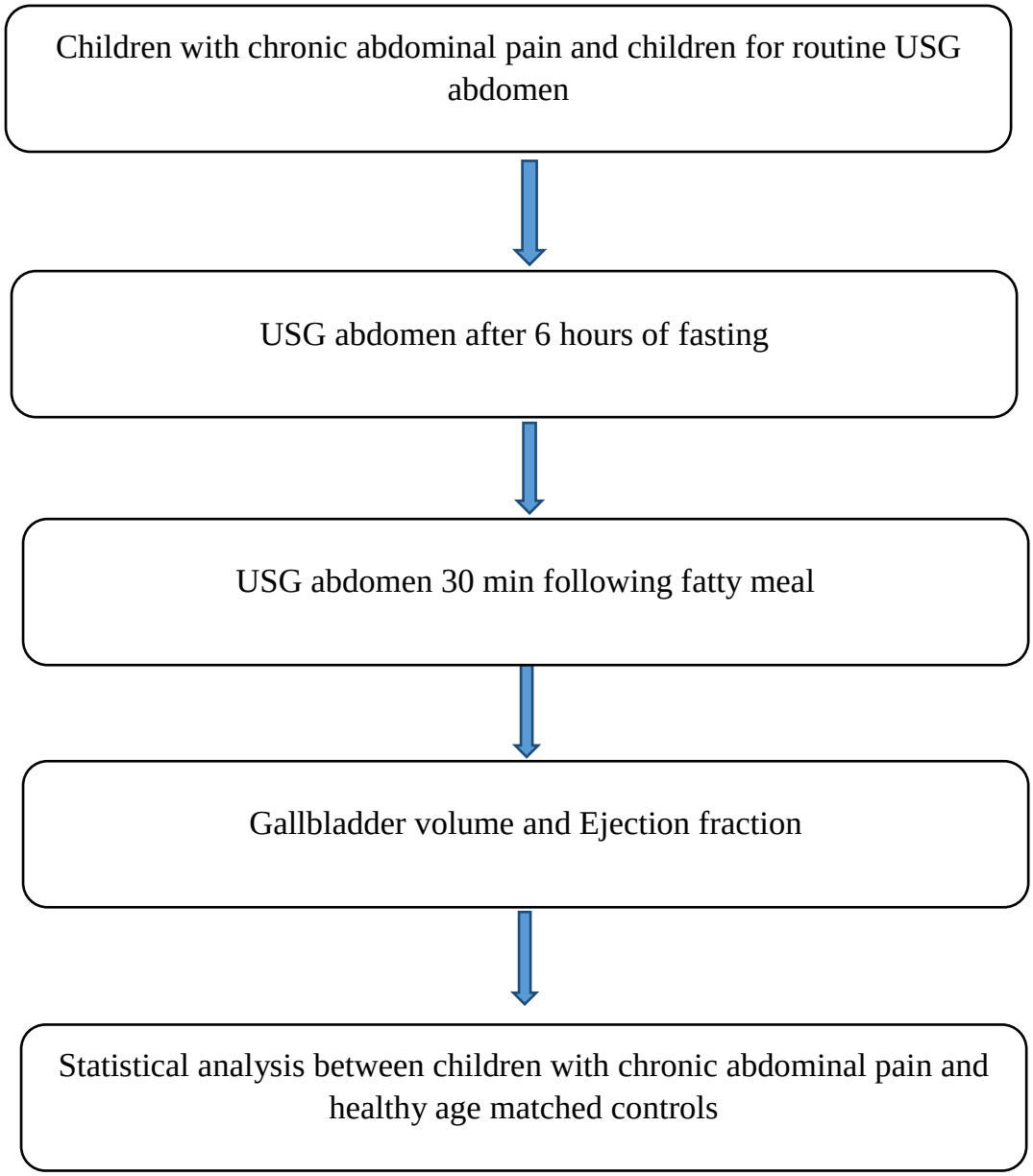
$$\textbf{Volume (V) } (\textbf{cm}^3) = 0.52 \times L \times W \times A$$

The gallbladder ejection fraction (EF) for each examination was obtained from two-volume data using the following equation. Where V_0 = gallbladder volume before the test meal, Vn = gallbladder volume after the test meal.

$$\textbf{EF (\%)} = ((Vo-Vn) / Vo) \times 100\%$$

Children with ejection fraction of less than 40% were considered to have gallbladder dysmotility [182]

FLOW CHART


Children with chronic abdominal pain and children for routine USG abdomen
USG abdomen after 6 hours of fasting
USG abdomen 30 min following fatty meal
Gallbladder volume and Ejection fraction
Statistical analysis between children with chronic abdominal pain and healthy age matched controls

Statistical Analysis:

The statistical analysis was done using SPSS software (statistical package for the social science version-19).

1. The Independent studentst test was applied to compare the means of quantitative data.

   Values were expressed as Mean ± SD. The p values were interpreted as shown below

   a. $p > 0.05$ was considered not significant.
   b. $p < 0.05$ was considered statistically significant.

2. The ejection fraction of the cases was correlated with their BMI for any possible association using Pearson's correlation analysis

REVIEW OF LITERATURE

Gallbladder – The gallbladder is a thin-walled sac, placed between both hepatic lobes. It is divided in to three parts anatomically. It is the fundus, corpus, and infundibulum [13].Anatomically the human gallbladder and gallbladder of most mammalian species dogs, cats, guinea pigs, and mice are fairly similar. The gallbladder ends with cystic duct. Cystic duct has a diameter of 7 mm with amucosa containing spiral valves (valves of Heister). The cystic duct then drains into the common bile duct and there is no sphincteric structure. The course of common bile duct is through the head of thepancreas ending in the sphincter of Oddi.

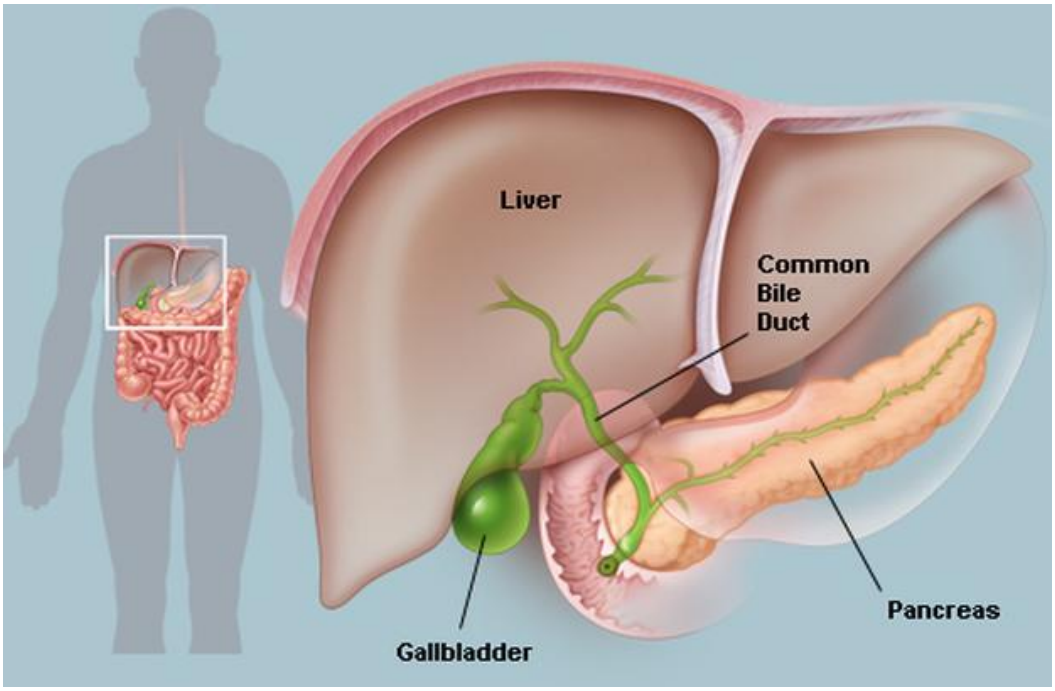


Figure 1: Structure of gallbladder

Now sphincter of Oddi and common bile duct penetrates theduodenal wall to form the ampulla of Vater. Cystic duct or the common bile duct has no peristaltic motility.

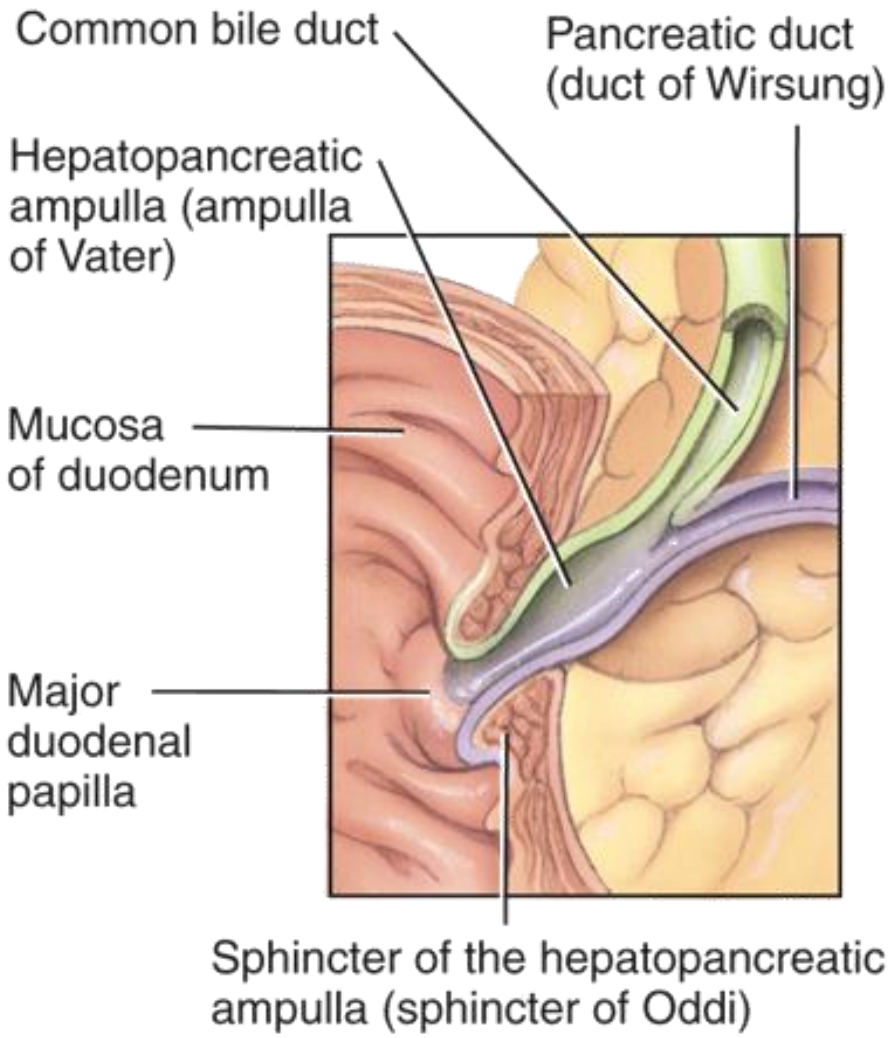


Figure 2: Sphincter of Oddi

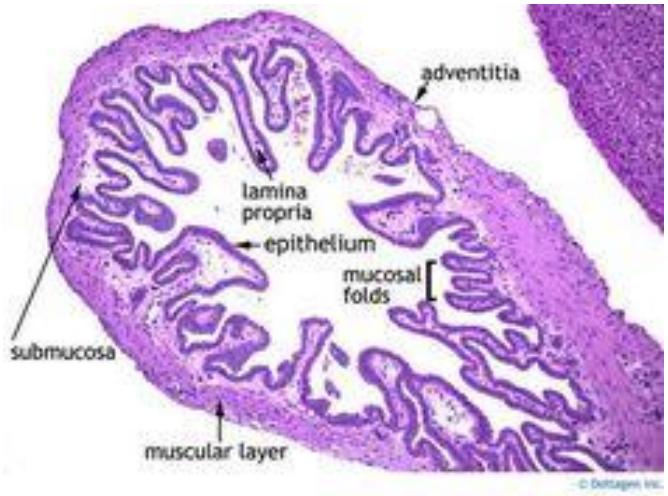


Figure 3: Gallbladder histology

Gallbladder Histology – it consists of mucosa with a single layer of epithelial cells, a lamina propria, a single layer of muscle that resembles the muscularis mucosa of the gastrointestinal tract, and a serosal layer [14].

Concentration of hydrophobic bile salts is done by epithelial layer by absorbing water and electrolytes. Small quantities of bile salts and chloride are transported by passive diffusion by mucosal layer [15, 16]. Hydrophobic bile salts are aggressive against stomach, esophagus etc. but the epithelial cells tolerates it by its cytoprotective with help of prostaglandin E2 (PGE2). Epithelial cells are covered by mucin, which is secreted by prostaglandin and this prevents damage by inactivating bile salt induced free radicals. Vagus and splanchnic nerves innervate the muscular layer and this synapses with intramural neurons. In the fasting and digestive phase of biliary tract, it is integrated with by neurohormonal mechanism of the digestive tract [14]. The bile is continuously secreted by liver in to intrahepatic and from there it flows in to extra hepatic ducts. Sphincter of Oddi (SO) helps the gallbladder to fill with bile, which is

then stored and concentrated in the fasting state. And during all three phases of digestive periods the concentrated bile is emptied. Only about 10% of the hepatic bile drain in to the duodenum during the interdigestive period that is during intervals between the phasic contractions of the sphincter of Oddi (diastolic periods). This occurs when sphincter of Oddi basal pressure is exceeded by the ductal pressure[17]. It is the remaining 90% bile that is redirected towards the cystic duct and gets stored in the gallbladder. By passive and active mechanisms the gallbladder distends with entry of bile. Active relaxation or accommodation of the gallbladder is mediated by adrenergic and noncholinergic nonadrenergic nerves it is gradually induced by the incoming bile. The vagus and splanchnic nerves and the hormone cholecystokinin (CCK) are the main neurohormonal mechanisms regulating the motility of the gallbladder [18–20]. The efferent and afferent fibers are from vagus nerve [21]. The efferent fibers form as preganglionic neurons and synapse to intramural postganglionic cholinergic neurons. The intramural postganglionic neurons are present within the wall of the gallbladder. Gallbladder contraction is stimulated by efferent fibers of vagus nerve,hexamethonium and atropine are muscarinic receptor antagonist that acts by ganglionic blocker. Gallbladder relaxes by splanchnic nerve stimulation and propranolol blocks this relaxation [22]. Atropine treated cat gallbladder muscle strips demonstrated the inhibitory innervation [23]. The strips blocked by propranolol were stimulated by electrical field, there was relaxation the strips in response to electrical field stimulation but was unaffected by partial antagonists of the vasoactive intestinal peptide

(VIP) suggesting that the stimulus was acting on sympathetic postganglionic neurons releasing epinephrine as the neurotransmitter that act primarily on beta-adrenergic receptors. However, different results were obtained when the atropine-treated cat gallbladder was relaxed by stimulating the vagus nerve. Under these experimental conditions the relaxation was resistant to propranolol but was abolished by pretreatment with an antiserum against VIP suggesting that this peptide is the neurotransmitter responsible for it [24]. It is conceivable that the VIP antiserum is a more effective antagonist against VIP than the partial VIP antagonists that were used in muscle strips. These discrepancies between in vitro and in vivo studies cannot be fully explained at this time although it is possible that both neurotransmitters are involved in the gallbladder relaxation. Further studies are needed to reconcile these different observations that were demonstrated using different experimental conditions. During the fasting period the gallbladder maintains a moderate tonic contraction that is superimposed with nonpropulsive and propulsive contractions [25, 26]. These tonic and rhythmic contractions were demonstrated in dogs in vivo. The nonpropulsive contractions are probably designed to keep the bile insoluble constituents in solution preventing their precipitation, particularly precipitation of cholesterol that can lead to gallstone formation. These contractions are even observed in muscle strips from normal human gallbladders [26]. The propulsive contractions empty fractions of gallbladder bile contributing to the small percentage of bile that enters the duodenum during this interdigestive period. These contractions also occur in the fasting

period during the migrating motor complex that is known to stimulate the gallbladder motility. The increased number of gallbladder contractions coincides with the phase 3 of the antral migrating motor complex and with the phase 2 of the duodenum [27]. Thesecontractions are responsible for the additional albeit small discharge of gallbladder bile in the duodenum that takes place during this period.In the digestive period strong gallbladder contractions and sphincter of Oddi relaxation lead to the high rates of bile discharge flowing into the common bile duct and duodenum.During this period, the gallbladder motor activity like the rest of the gastrointestinal tract is influenced by the three phases of digestive process: cephalic, antral, and duodenal [28]. The cephalic phase is initiated by stimuli that activate the central nervous system, as individuals are exposed to olfactory, visual, and the taste of food. This phase is mediated by preganglionic vagal fibers that synapse with postganglionic cholinergic neurons. It is estimated that as much as 30–40% of the gallbladder bile may be emptied during this phase. Once food reaches the stomach it triggers an antral-gallbladder reflex also mediated by vagal fibers. The gallbladder emptiesmost of its remaining contents during the intestinal phase induced by the release of CCK from the duodenum and proximal jejunum [29]. Duodenal CCK contracts the gallbladder mostly by acting directly on cholinergic neurons [18] and like with the pancreas, and it may also activate long reflexes through the vagus nerve. Meals containing proteins and fats act on duodenal CCK containing endocrine cells that stimulate vagal sensory fibers followed by activation of preganglionic and postganglionic cholinergic neurons

[30]. Either mechanism stimulates the final pathway of postganglionic cholinergic neurons, since atropine pretreatment blocks the gallbladder contraction induced by physiological concentrations of CCK- 8 [31] or by a protein-fatty meal. CCK-1 receptors are alsopresent in the gallbladder muscle, but they only can be stimulated by pharmacological concentrations of CCK, since they are not blocked by either atropine or tetrodotoxin.

Functional GB Disorder

Definition:

Gallbladder dysfunction is a motility disorder of the GB that manifests symptomatically with biliary pain as a consequence of either an initial metabolic disorder (i.e., supersaturated bile with cholesterol)[32] or a primary motility alteration of the GB in the absence, at least initially, of any abnormalities of bile composition[33]. It is likely that the latter condition, by causing bile stasis, may alter over a period of time, bile recycling and bile composition within the GB. Both conditions may eventually lead, over a period of time, to thedevelopment of organic abnormalities (example gallstones and acute cholecystitis). The symptoms of these organic and functional conditions appear to be indistinguishable from one another, and therefore their differential diagnoses require a careful diagnostic workup.

Epidemiology:

The prevalence of GB dysfunction is not known. Large population-based studies have reported that prevalence of biliary pain in ultrasonography (USG)-negativesubjects with GB in situ varies from 7.6% in men to 20.7% in women [34,35].

Clinical Presentation:

The most specific symptom attributed to functional disorders of the GB appears to be biliary pain, and therefore the crucial steps in the diagnosis are a thorough history supported by objective evidence of GB dysfunction and exclusion of structuralabnormalities. These patients will need to be evaluated with longer follow-ups for at least 1 year after cholecystectomy.

Criteria for this diagnosis:

1. Absence of gallstones, biliary sludge, or microlithiasis
2. An abnormal GB ejection fraction of less than 40% by using a continuous intravenous cholecystokinin octapeptide infusion over a 30-minute period
3. A positive therapeutic response with absence of the recurrent pain for longer than 12 months after cholecystectomy

Laboratory and Instrumental Investigations:

The symptoms of GB dysfunction must be differentiated from organic disease and other more common functional disorders including functional dyspepsia and IBS in which symptoms do occur daily for at least short

intervals (few days or weeks). Tests of liver biochemistries and pancreatic enzymes should be obtained in those patients with the previously mentioned symptomatic criteria. These tests are normal in the presence of GB motility dysfunction. The findings of abnormal liver or pancreatic enzyme levels or both indicate that other diagnoses should be considered.

Ultrasound:

Transabdominal ultrasonographic study of the entire upper abdomen is mandatory in patients with the previously mentioned symptoms. In the presence of GB dysfunction, the biliary tract and pancreas appear normal on USG. In particular, gallstones or sludge cannot be shown. USG usually detect stones within the GB equal to or greater than 3 to 5 mm in diameter, but it has a low sensitivity to detect smaller stones [(36)]. USG detection of stones or sludge within the common bile duct is even more difficult. Endoscopic USGis more sensitive than traditional transabdominal USG in detecting microlithiasis (tiny stones 3 mm) and sludge within the biliary tract [(37)].

Endoscopy:

In the presence of normal laboratory and ultrasonographic findings, an upper gastrointestinal endoscopy is usually indicated. The diagnosis of GB dysfunction is suspected in the absence of significant abnormalities in the esophagus, stomach, and duodenum.

Microscopic bile examination:

To exclude microlithiasis as a cause for these symptoms, a careful microscopic examination of GB bile could be performed. The detection of microlithiasis and cholesterol microcrystals is best accomplished by a careful examination of GB bile obtained directly at the time of ERCP or by aspiration from the duodenum during endoscopy after cholecystokinin (CCK) stimulation. The resultant bile should appear deep golden yellow to dark green-brown. Pale yellow bile from the common duct is not appropriate. Evenin those patients with cholesterol gallstones or sludge, this hepatic bile is often free of cholesterol microcrystals being insufficiently concentrated to nucleate. The collected bile should be immediately centrifuged and examined.

Two types of deposits may be evident

1. Cholesterol crystals and/or
2. Calcium bilirubinate granules.

Cholesterol microcrystals are birifringent and rhomboid shaped and best visualized by polarizing microscopy. The presence of cholesterol crystals provides a reasonably high diagnostic accuracy for microlithiasis [38-40]. Bilirubinate granules are red-brown and can be detected by simple light microscopy. These crystals are significant only in freshly analyzed bile.

TESTS OF GB MOTOR DYSFUNCTION

Assessment of GB emptying by cholescintigraphy:

Cholescintigraphy is performed after the administration of technetium 99m–labelled iminodiacetic acid analogs. These compounds have a high affinity for hepatic uptake, are readily excreted into the biliary tract, and concentrated in the GB. The net activity-time curvefor the GB is then derived from subsequent serial observations, after either CCK administration or the ingestion of a meal containing fat. GB emptying is usually expressed as GB ejection fraction, which is the percentage change of net GB counts after the cholecystokinetic stimulus. A low GB ejection fraction has been considered evidence of impaired GB motor function that, in the absence of lithiasis, could identify patients with primary GB dysfunction. The most widely used and validated stimulus to contract the GB has been the slow intravenous infusion of CCK analogs, especially CCK-8 over a 30-minute period [41, 42]. Fatty meals and variable bolus injections of CCK do not yield consistent results. Reduced emptying can arise from either impaired GB contraction or increased resistance of the SO because of an elevated basal tone. Furthermore, several other conditions that do not necessarily present with biliary pain can be associated with reduced GB emptying such as obesity, diabetes, and several drugs (example - calcium channel antagonists and oral contraceptives). An accurate medical history should exclude secondary causes of impaired GB motility. Two systematic reviews that did not discriminate between slow and rapid intravenous infusion of CCK have concluded that there is no sufficient

evidence to recommend the use of CCK cholescintigraphy to select patients for cholecystectomy[43, 44].

Assessment of volume changes by transabdominal real-time US:

Unlike cholescintigraphy, this method measures GB volume and obtains serial measurements during fasting or after a meal or the intravenous infusion of CCK analogs. In addition, US allows for assessment of residual volume after emptying and the rate of refilling after GB contraction.

US may be helpful when radiation should be avoided. One deficiency in the technique is the fact that it is operator dependent, and the results may not be reproducible between different centers; therefore, the diagnostic role, if any, of ultrasonographic assessment of GB emptying has not become the standard in GB dysfunction. Further prospective randomized studies are needed to better understand the predictive value of CCK cholescintigraphy or CCK USGto recommend cholecystectomy in patients with suspected GB motility dysfunction.

Pain provocation test:

A stimulation test with CCK attempting to duplicate biliary pain has been historically used as a diagnostic investigation. This test has low sensitivity and specificity in selecting patients with GB dysfunction who respond to therapy. This may relate to problems in the subjective assessment of pain and the use of bolus injections of CCK. The latter can induce pain by stimulating intestinal contractions.

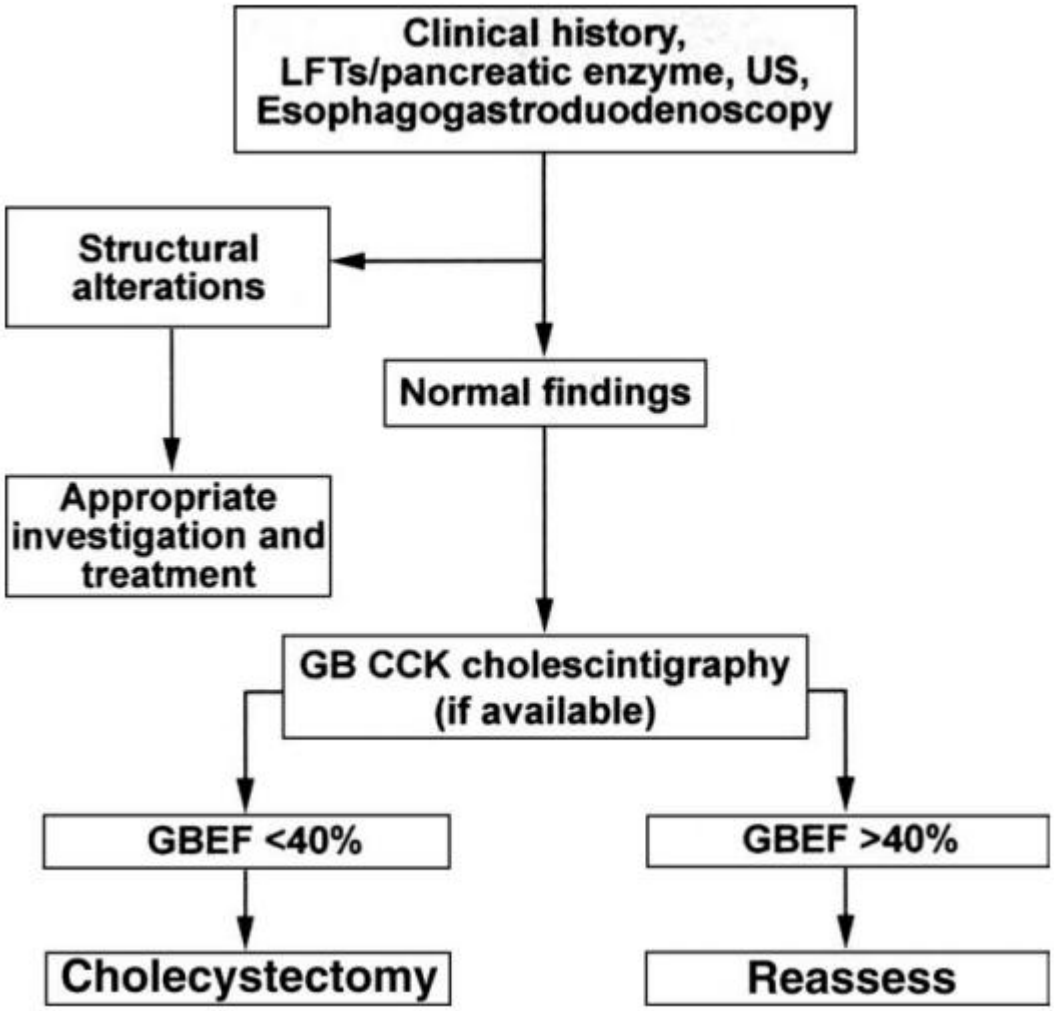


Figure 4:Algorithm of the diagnostic workup and management of functional GB disorders.

FUNCTIONAL ABDOMINAL PAIN

Introduction:

Apley and Naish described chronic abdominal pain as children presenting with intermittent episodes of abdominal pain occurring for at least 3 months without any identifiable cause and interfering with day to day activities[3]. The term 'chronic abdominal pain' is often used interchangeably with 'recurrent abdominal pain'. Abdominal pain that is continuous, persistent, or intermittent over a period of a few months is called as chronic abdominal pain. The pain varies in intensity. There may be asymptomatic periods interposed with painful periods gradually the duration of painful periods prolong, generating a condition that profoundly causes distresses in the daily life of children. The term recurrent abdominal pain represents a symptom and not a diagnosis. Many conditions can cause abdominal pain that is recurrent, but most children and adolescents presenting with this symptom have a functional disorder without any evidence of organic disease. They are considered to have functional abdominal pain.

Epidemiology:

Chronic abdominal pain is a common pediatric complaints [45], accounting for 2–4% all of pediatric hospital visits [46]. Symptoms consistent with irritable bowel syndrome (IBS),occur in 14% of all high-school students and 6% of all middle-school students [5]. IBS is much more prevalent than other medical conditions such as hypertension, asthma and diabetes that tend toreceive greater attention [47].Patients with IBS do not seek medical attention,

assessing the prevalence of IBS is often difficult. Only one in four patients with symptoms of IBS seek medical care [48].Reports from Kenya, Poland, Russia, India and Pakistan reveal that, functional abdominal pain is probably a universal problem [10, 49-51]. A Malaysian study in 1500 schoolchildren found evidence of chronic abdominal pain in 10% of children, concluding that, in spite of differences in diet, customs and culture, the overall prevalence of this entity was similar across regions[52]. A Danish study demonstrated that 15% of children aged 9–12 years had recurrent abdominal pain[53].Quality of life in individuals with IBS is substantially poorer than in general population [54].

Physiology of the gastrointestinal pain response:

Visceral pain perception passes through a complex pathway of peripheral and central nervous structures that signal, relay and modify the afferent stimulus. The enteric nervous system (ENS) is arranged into two main plexuses providing the intrinsic innervation of the gut. This forms a continuous network around the circumference of the wall of the intestine along its length. The mesenteric plexus, alsocalled as Auerbach's plexus, is located between the external longitudinal and internal circular muscle layers, and the submucosal plexus (Meissner's plexus) lies in between the circular muscle layer and the mucosa. The mesentericplexus is larger and projects fibers mainly to the smooth muscle of the gut and it controls the motility. Meanwhile, the submucosal plexus projects into the mucosa and submucosa and control the glandular secretion. The two intestinal plexuses are connected to each other by interconnections which bind the two networks into a functionally unified

nervous system. The characteristics of this mesh of sensory fibers, interneurons and motor neurons, enables this mini-brain or ‘gut brain’ to integrate the sensory information, and to organize the motor and secretory responses and influence the luminal absorption, thereby producing a functional state that is adapted to the well-being of the individual. The ENSthough it receives input from the central and autonomic nervous systems, it can function independently. The ENS performs most of its functions in the absence of central nervous system (CNS) control, locally integrating the information of intrinsic afferent fibers (for example, luminal distension and chemical stimuli) with efferent axons, resulting in motor reflexes or secretory or absorptive responses. The extrinsic nervous system functions to consist connecting the ENS with the CNS. This communication allows the CNS continuously to integrate the information from the gastrointestinal tract with incoming information from other organs and from the environment. Under physiological conditions, most of these do not reach the level of conscious perception.21 However, sensations that trigger a particularbehavior, including hunger, satiety and need to defecate, reach the conscious perception by reaching the cortex. The constant influenceof the CNS on the ENS through activation of a subset of vagal and sacral parasympathetic fibers is responsible for psychological stress and gastrointestinal response, manifested clinically by the occurrence of vomiting or diarrhea in patients experiencing a stressful event.

The ENS and the brain use multiple neurotransmitters for exchanging of inhibitory or excitatory information. They include excitatory neurotransmitters such as acetylcholine and substance P, and gut inhibitory neurotransmitters such as nitric oxide, ATP, vasoactive intestinal peptide (VIP), cholecystokinin, enkephalins, calcitonin gene-related peptide (CGRP), norepinephrine (noradrenaline), epinephrine (adrenaline) and others. Neurotransmitters such as serotonin (5-hydroxytryptamine) and histamine have more complex effects. Ninety-five per cent of the total body 5-HT lies within the gut. Of the total gut 5-HT, 90% is found in the granules of the enteroendocrine cells, and 10% in the neurons of the myenteric plexus [55, 56]. 5 HT also plays an important role in regulating GI motility and intestinal secretion[55]. 5-HT receptors appear to participate in mucosal sensory processing within the gut. Distension and stroking of mechanosensitive receptors in the enteroendocrine cells triggers the release of 5-HT [57]. There are at least seven main classes of 5-HT receptor and 22 subclasses that can be differentiated on the basis of structure and function. Four classes have been reported in the human GI tract (5-HT1, 5-HT2, 5-HT3 and 5-HT4)[58]. Serotonin action is complex, with mixed effects ranging from smooth muscle contraction, to relaxationthrough stimulation of inhibitory nitric oxidereleasing neurons. Higher levels of serotonin are present in diarrhea-predominant IBS [59]. The ENS has the ability to modulate signal transduction by enhancing or inhibiting the activation of nociceptors through alteration in smooth muscle tone and contractile activity. Visceral pain may be modulated also at the CNS level by emotional or cognitive factors, providing a rationale

for the use of centrally acting agents or cognitive behavioral treatments in functional bowel disorders. Neuroimaging studies have provided information on differences in brain processing of visceral stimuli between normal individuals and those suffering from IBS, revealing an increased activity at the level of the anterior cingulated cortex, prefrontal cortex, insular cortex and thalamus (the areas associated with emotional responses) in patients with IBS compared to asymptomatic individuals[60-62].

Pathophysiology:

Several hypotheses have been put forward to explain the cause of functional recurrent abdominal pain. We examine them in the following sections.

Visceral hyperalgesia:

The visceral hyperalgesia hypothesis proposes that greater sensitivity of visceral afferent pathways or central amplification of visceral input lead to an enhanced perception of visceral stimuli. There is evidence that the pain and discomfort of IBS might be due to hyperalgesia and allodynia of the gut. While in hyperalgesia a painful stimulus is perceived as even more painful, in allodynia a non-painful stimulus becomes painful [63]. Anoxious stimulus applied to a particular area of thegut may sensitize primary afferent fibers and nociceptors of adjacent areas, causing painful sensations with a low-intensity stimulus, resulting in primary hyperalgesia. Most IBS patients experience rectal discomfort at lower intraluminal volumes or pressures[64, 65] and have diminished tolerance to intestinal gas [66]. Trimble et al[64] found that patients

presenting with one functional bowel disorder frequently had additional symptoms referable to other parts of the digestive system, suggesting that enhanced visceral nociception may be a pan-intestinal phenomenon. For example, it has been reported that in addition to the features of rectal hyperalgesia, IBS patients have a decreased sensory threshold to balloon distension of the esophagus. Children with functional abdominal pain exhibited generalized visceralhyperalgesia, whereas IBS patients had rectal but not gastric hyperalgesia[65].Different GI symptoms were reproduced by stimulation of the predominant site of hyperalgesia, providing a physiological explanation of symptoms in children who have distinct phenotypic presentations.

Dysmotility:

In addition to a greater intestinal sensitivity, patients with functional bowel disorders may display abnormal motility. Various types of motor disturbances have been documented in IBS, apparently reflecting dysfunction at one or more levels of the brain–gut axis[67]. Although the pathophysiology of IBS is commonly attributed to dysfunction of the large intestine, evidence exists to incriminate the small bowel as well [68]. Postprandial motor dysfunction in the small bowel appears to be more prevalent among IBS patients who exhibit underlying visceral hypersensitivity in the fasting state. Abdominal cramping has been associated with the passage of high-amplitude contractions through the ileocecalregion[69]. Bloating has been explained by an abnormal transit and pooling of gas in conjunction with guthypersensitivity[66]. Manometric studies have demonstrated postprandial antral hypomotility in

children and adults with functional dyspepsia[70]. However, not all studies have demonstrated differences between patients and control subjects[71, 72]. Motility changes in IBS are neither specific nor predictable and do not serve as a diagnostic marker or as an aid to the selection of treatment[73]. It has been suggested than, rather than having a persistent motility abnormality, patients with functional bowel disorders exhibitan abnormal motor response to a variety of physiological stimuli[74].

Brain–gut interaction:

The shortcomings of isolated experimental or observational models in explaining the complex nature of functional bowel disorders have led research to focus on the alterations in the communications between the CNS and the GI tract, hence the term 'brain–gut' interaction[47, 75]. There are multiple examples of brain–gut interaction, the most common being the subjects who, under emotionally stressful situations, develop diarrhea, nausea or vomiting. Anger and aggression increase colonic motility, while hopelessness results in decreased motility[76]. The brain–gut model links alterations in peripheral sensory afferent communication from the gut (e.g. visceral hyperalgesia) toCNS processing of the sensory stimuli and its efferent signaling to the gut. In IBS patients multiple studies have shown that both gut and brain show an exaggerated responsiveness to different stimuli. Patients with IBS have significantly greater electroencephalogram (EEG) abnormalities than controls[77]. Dynamic brain imaging technologies such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have

recently been applied to the study of the gut–brain axis in order to identify the areas of the brain activated by visceral sensations. Studies with these techniques have suggested an abnormal cerebral processing of visceral stimuli in patients with functional bowel disorders [60, 61].

Inflammation:

There is evidence that IBS can occur following a gastrointestinal infection resulting in transient inflammation. Gwee et al reported that 20–25% of patients admitted to the hospital for bacterial gastroenteritis developed symptoms consistent with IBS in the first 3 months [78]. Rectal biopsies prospectively obtained during and after acute gastroenteritis from patients who developed postinfectious IBS and a control group, showed that the former group exhibited significantly greater expression of interleukin (IL)-1Beta mRNA [79]. A recent study examining full-thickness biopsies from the jejunum of patients with severe IBS revealed inflammation and neuronal degeneration in the mesenteric plexus, suggesting a possible pathogenic role of inflammation [80].Animal studies also seem to indicate that inflammation may produce persistent neuromuscular gut dysfunction[81]. Mildmucosal inflammation may perturb neuromuscular function also at remote non-inflamed sites. The gut dysfunction may persist even after reduction of the mucosal inflammation. Substances that mediate these changes are not fully understood, but there is growing recognition of the role of serotonin as a sensitizing agent.

Immunity:

The mucosal immune system mediates the clinical impact of stress and other psychological factors on the gut. Vagal afferents can be activated by products of mast cell degranulation, resulting in sensitization of silent nociceptors. Mast cell mediators may be released in response to luminal macromolecules, a phenomenon that could explain brain–immune system interactions within the gut. A descending input by the vagus nerve may also reciprocally affect mast cell degranulation, resulting in local effects on secretomotor activity.

Stressors:

Stressful events have long been believed to be important in the development of symptoms in functional bowel disorders[(82)]. Physiological reactions to stressors should be considered as attempts by the body to adapt – a natural coping mechanism, in which, if stressors are not too extreme or long standing, the subject is usually successful in reaching a homeostatic state. However, at times the body loses the capacity to adapt and deleterious behavioral responses may arise. Chronic exposure to threat is associated with alterations in theautonomic outflow, resulting in activation of thehypothalamic–hypopituitary–adrenal axis with alteration in pain modulation. Corticotropinreleasing hormone seems to be the hormonal mediator of the stress response. Intracerebroventricularinjection of corticotropin releasing factor, which mimics the responses to stress in animals,

exacerbates nociceptive responses associated with increased release of histamine[83].

In humans, possibly as a primitive response to danger, stress induces delayed gastric emptying, slower small bowel activity and accelerated colonic transit[84-87].These alterations may presumably cause diarrhea, constipation or abdominal distension depending on the predominant abnormality.

Genetics:

A recent study showed a significant association between subjects with abdominal pain or bowel disturbances and first-degree relatives with IBS and dyspepsia[88]. Twin studies have shown a 17% concordance for IBS in monozygotic patients with only 8% concordance in dizygotic twins. Although these data suggest a specific role for heredity in the development of IBS, the same study showed ahigher correlation of IBS with parental symptoms, suggesting that social learning from the patient's environment has an equal or greater influence [89].

Biopsychosocial model:

The biopsychosocial model[90] provides a framework to integrate the biological and psychosocial processes, in an attempt to understand the underlying pathophysiological mechanisms determining disease susceptibility, and to explain the clinical variability and outcome among individuals. The biopsychosocial model, proposed as an alternative to the traditional biomedical model, conceptualizes the general state of health as resulting from the

integration of medical and psychosocial factors. To understand this model, one should differentiate between disease, which is the abnormality of the structure and/or function of organs and tissues (physical component), and illness, defined as the patient's perception of health and bodily dysfunction (psychological component). In Engel's model [(90)], illness and disease result from interactions at the cellular, tissue, interpersonal and environmental levels resulting in a clinical outcome. The biopsychosocial model assumes that genetic influences on disease susceptibility and behavior result in a biological and psychosocial predisposition that will influence later psychosocial experiences, physiological functioning, or susceptibility to a pathological condition. This particular background is affected by physical and environmental exposures such as infection, food intolerance and social exposures including friends, family and community to influence the patient's attitude towards illness [(91)]. Stress acting on a vulnerable GI tract leads to an imbalance in the system, resulting in an alteration of the brain–gut axis. Multiplicity of stressors reinforces and up-regulates the response. It is well recognized that some IBSpatients report initiation or exacerbation of symptoms at times of stress, trauma and major loss[(92)]. Traumatic early life events such as child abuse may predispose to functional bowel disorders [(93)]. There have been reports of a greater prevalence of sexually and physically abusive experiences in individuals with IBS than in patients with organic gastrointestinal disorders and non-patient populations [(94)]. The interaction of the previously described subsystems with psychosocial modifiers (concurrent psychiatric diagnosis, life stress, social support, coping

mechanisms) affects the behavior of the individual, the biological nature of the condition and, ultimately, the clinical outcome. New or uncontrollable threatening situations may result in emotional and physiological arousal. Psychosocial factors may affect the end result (clinical presentation and outcome) acting on gut physiology, modulating symptoms experience, and influencing health behavior and therapeutic interventions (Figure 5).The relative contribution of the medical and psychosocial factors varies among patients. This model should be considered when planning therapy, as failure to link the disease and illness components will reduce the likelihood of an effective treatment

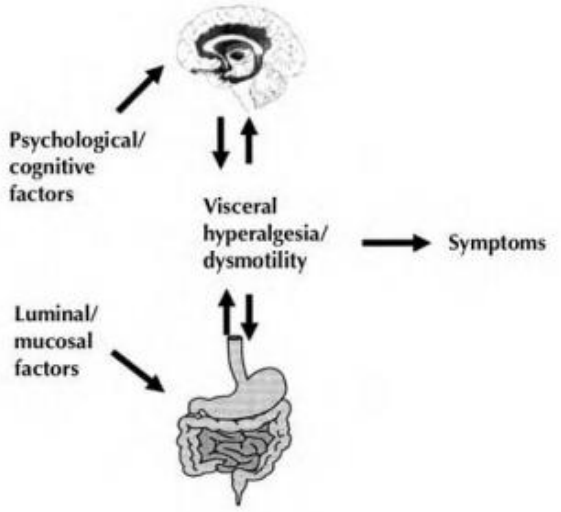


Figure 5: Proposed pathophysiological model for functional bowel disorders.

Functional bowel disorders presenting with abdominal pain by ROME III:

1. Functional dyspepsia
2. Irritable bowel syndrome
3. Abdominal migraine
4. Functional abdominal pain
5. Childhood Functional Abdominal Pain Syndrome

Differential diagnosis:

A number of clinical features (‘red flags’) are commonly considered as orienting towards an organic etiology, although definitive proof for their predictive value is scant. The presence of an isolated symptom (such as isolated abdominal pain) is usually thought to be consistent with a functional disorder, while multiple symptoms (such as abdominal pain with weight loss, or vomiting, or diarrhea) are more likely to be due to an organic condition. There are almost endless causes of chronic organic abdominal pain in children.

Organic causes of chronic abdominal pain:

Gastrointestinal

Esophagitis, gastritis, duodenitis, peptic ulcer, eosinophilic gastroenteritis, malrotation, cysts (duplication or mesenteric), celiac disease, parasites, hernias, tumors, foreign body, intussusception, inflammatory bowel disease

Hepatobiliary

Chronic hepatitis, cholelithiasis, cholecystitis, choledochal cyst, sphincter of Oddi dysfunction

Pancreatic
Pancreatitis, pseudocyst
Respiratory
Infection, tumor or inflammation vicinity of diaphragm
Genital
Hematocolpos, endometriosis, mittelschmertz tumor
Urinary
Ureteropelvic junction obstruction, recurrent pyelonephritis, recurrent cystitis
hydronephrosis, nephrolithiasis
Metabolic
Porphyria, diabetes, lead poisoning
Hematological
Angioedema, collagen vascular disease, sickle cell disease
Musculoskeletal
Trauma, inflammation, infection, tumor
Psychiatric
Conversion reaction

Peptic disease:

Pain related to peptic ulcer disease is usually epigastric and non-radiating, but may also be generalized or periumbilical. It occasionally awakens the patient from sleep. It may occur at any time of the day and frequently

children experience exacerbation rather than relief with meals. A review of 160 children concluded that epigastric pain, food-related pain, vomiting, bleeding and family history were important factors in the diagnosis of peptic ulcer in childhood [95]. However, the clinical presentation of ulcer mayhave symptoms that overlap with some functional bowel disorders such as functional dyspepsia. A favorable response to antacids or H2 blockers may orient towards a peptic disease, but there is evidence that anti-secretory therapy may also be effective in dyspepsia. Therefore, as symptoms and therapeutic response may be indistinguishable, the definitive diagnosis of peptic disease requires esophagogastroduodenoscopy [96]. While it is accepted that H. pylori infection causes both gastritis and duodenal ulcer disease, its etiologic role in functional dyspepsia is still controversial. Dyspepsia associated with epigastric pain was frequently found in preschool and school children infected by H. pylori[96, 97].These findings are contradicted by other reports. A German study concluded that H. pylori infection in children was mostly asymptomatic and not associated with specific gastrointestinal symptoms [98]. A review of 2715 children with H. pylori infection found abdominal pain in 5–17% of cases. However, abdominal pain was also found in 5–29% ofpatients without H. pylori infection [99]. Universal testing or treatment of H. pylori infection in children with either recurrent pain referable to the epigastrium or recurrent periumbilical abdominal pain is currently not recommended.

Pancreatitis:

Pain resulting from pancreatic inflammation is usually epigastric, radiating to the sides or back, with pain episodes frequently triggered or aggravated by meals. Nausea and vomiting are often present. Severe abdominal tenderness in the epigastric area and decreased bowel sounds are characteristic. Chronic pancreatitis is an inflammatory disease characterized by recurrentepisodes of abdominal pain that in certain individuals may result in progressive structural changes and permanent impairment of exocrine and endocrine functions [(100)].

Carbohydrate intolerance:

In children with chronic abdominal pain, increased flatulence and bloating, the diagnosis of carbohydrate intolerance should be considered. The breath hydrogen test following a lactose or fructose load will confirm the diagnosis. Exclusion of these offending agents may improve the symptoms. On the other hand, lactose intolerance has a very high prevalence in the general population and symptoms after a lactose load develop in only a few of the self-reported milk-intolerant subjects [(101)]. In a large sample of American patients, lactose malabsorption was found in 21–25% of IBS patients [(102)], a prevalence considered comparable to that in the general American population. Lebenthal et al [(102)] found a similar prevalence of lactase deficiency in children with recurrent abdominal pain and in children of a control group of similar ethnic background. Moreover, lactose free elimination diet resolved symptoms in a similar percentage of patients in the lactose absorbers and in the lactose

malabsorbers. As a result of the high independent prevalence of both conditions in the general population, the presence of chronic abdominal pain and lactose intolerance in one patient may be merely coincidental. Thus, the recommendation of an exclusion diet should be made with reasonable expectations, as it may be helpful in the resolution of symptoms in only a limited number of patients.

Inflammatory bowel disease:

Occult IBD was found in 1% of adult patients[103]and in 3–4% of pediatric patients[104] evaluated for IBS. Some patients may complain for months or years of vague abdominal pain and intermittent diarrhea before being diagnosed as having IBD. The presentation of the abdominal pain is variable, depending on the site of bowel involvement. Terminal ileum and cecal disease in the setting of Crohn's disease is often associated with right lower quadrant discomfort and tenderness. Diagnosis is frequently delayed, with an average lag in diagnosis of approximately 7 months [105]. A decrease in growth preceded the onset of any symptoms by at least 1 year in 24 of 50 patients with Crohn's disease [106].

Chronic constipation:

IBS with constipation predominance and chronic constipation present many descriptive similarities [107]. However, constipation in combination with abdominal pain has a wide differential diagnosis and constipation should not be judged as causing abdominal pain without consideration of alternative

diagnoses. In chronic constipation physical examination may reveal a fecal mass in the left lower quadrant and suprapubic region. Examination of the perineum should include assessment of the lower back, sacrum and site of the anus. Anal examination may reveal the presence of a fissure or a sentinel skin tag indicative of a fissure. Rectal examination may reveal the presence of a dilated rectum containing a hard fecalmass. A flat plate radiograph may help in the diagnosis in cases where obesityprecludes an appropriate abdominal examination.

Gallstones:

Cholelithiasis is considered uncommon in infancy, childhood and adolescence, with a prevalence ranging from 0.2 to 0.5% [(108)]. In older children, obesity, ileal disease and a family history of childhood gallstones have been associated with cholelithiasis[(109)]. Children with gallstones may have colicky or unspecific pain or remain asymptomatic. The pain is mostly located in the right upper quadrant or in the epigastrium, and may radiate to the back or right shoulder. Nausea and vomiting are present in more than 50% of cases. Fatty food intolerance is not commonly reported in children. Other biliary tree pathologies such as choledochalcyst may present with abdominal pain. Presentation is age dependent, with jaundice prevailing in children and abdominal pain in adults [(110)].

Parasitic infections:

Positive fecal ova and parasite tests were found in only 2% of adult patients with IBS[(103)].Giardia lamblia, Dientamoebafragilis, Cryptosporidium

and Blastocystishominismay be found in patients presenting with abdominal pain, often accompanied by anorexia, abdominal distension and diarrhea. Blastocystishominisis most likely to be non-pathogenic in the immunocompetent human host [111].

Small-bowel bacterial overgrowth:

Symptoms of IBS may overlap with those of small-intestinal bacterial overgrowth (SBBO). Pimentel et al [112], in a prospective study, showed that 78% of IBS patients had SBBO diagnosed by a lactulose hydrogen breathe test, and that the eradication of the overgrowth improved diarrhea and abdominal pain. A study of IBS patients with SBBO demonstrated significant motility abnormalities [113], leading the authors to conclude that dysmotilitywas the pathogenic mechanism linking SBBO to IBS. Another controlled study looking at the effects of antibiotics on IBS patients with alterations of the duodenal and colonic flora has also shown a significant improvement of symptoms in the group of patients receiving antibiotics [114].

Celiac disease:

Patients with celiac disease may present with symptoms mimicking other conditions [115]. A recent study has shown that celiac disease patients were initially diagnosed as having IBS in 37% of cases [116]. In this study, only 32% of adults with celiac disease were underweight, and only 50% reported frequent diarrhea and weight loss. Anemia was present in 67% of the cases. Patients frequently presented with abdominal pain and bloating or gas which are

common clinical manifestations of functional bowel disorder. The Dutch College of General Practitioners states that celiac disease should be added to the differential diagnosis of IBS [117]. A Canadian study revealed that, prior to being diagnosed as celiac disease, 37% of respondents consulted four or more family doctors [118]. An Israeli study in 270 consecutive patientswhounderwent endoscopy for abdominal pain demonstratedceliacdisease in one out of 23 of the patients [119].

Genitourinary disorders:

Pyelonephritis and obstructive conditions such as ureteral or pelviureteric junction obstruction may present with recurrent cramping abdominal pain, despite normal physical examination and urinalysis [120].Hematuria can be present in the setting of urinary tract infections, abuse, trauma, Henoch– Schönleinpurpura, or renal stones. Dysuria associated with abdominal pain can represent a sign of pyelonephritis, abuse, trauma, or a sexually transmitted disease[121]. In adolescent girls, a history of mid lower abdominal pain was found to have low sensitivity but high specificity for gynecological diseases [122].Gynecological pathology such as ovarian cysts, congenital uterine abnormalities and endometriosis should also be considered in the differential diagnosis of abdominal pain. Hematocolpos[123] due to imperforate hymen may present with periodic lower abdominal pain and urinary retention. Endometriosis may begin 3–4 years after menarche. Clinically it may manifest as cyclic abdominal pain, nausea, vomiting, constipation or diarrhea [124].

Congenital anomalies:

Malrotation presents usually early in life, with 85% of all cases of midgut volvulus occurring in the first year. In neonates, symptoms are usually dramatic with sudden onset of bilious vomiting and a visibly seriously ill patient. Older infantsmay present with episodes of colicky abdominalpain. In one series, 20% of cases of malrotation in patients over 1 year of age presented with chronic abdominal pain [(125)]. These patients often have vague, long-standing abdominal complaints with or without emesis. The pain is often postprandial and may be accompanied by bilious emesis and diarrhea or evidence of malabsorption or proteinlosingenteropathy associated with bacterial overgrowth. Duplications of the alimentary tract are uncommon congenital abnormalities. The clinical presentations may be vague and diverse, depending on the location of the duplication [(126)]. Presenting signs and symptoms include abdominal mass, vomiting, decreased oral intake, gastrointestinal bleeding, periumbilical tenderness and abdominal distension.

Musculoskeletal pain:

Pain related to trauma is usually well localized and sharp in nature, and may be exacerbated by movement. Patients usually are able to recall a history of trauma or strain, but occasionally that history cannot be elicited. The diagnosis of costochondritis should be considered in adolescent patients complaining of chest or upper abdominal pain. Costochondritispain originates in the anterior chest wall, from where it may radiate into the chest, back, or

abdomen. Pain is reproducible by palpating the affected costal cartilage[127].

Diagnostic testing:

In patients with no alarm symptoms, the Rome criteria have a positive predictive value of approximately 98%, with additional diagnostic tests providing a yield of 2% or less [128]. When needed, the exclusion of an organic condition can be accomplished by utilizing inexpensive, non-invasive and easily available diagnostic tests such as complete blood cell count, erythrocyte sedimentation rate, chemistry panel, liver and thyroid function studies, urine analysis and stool examination for blood, ova and parasites. Need for other diagnostic tests should be based on history and physical examination findings. The physician should avoid the lure of having to 'rule out' an organic disease at all cost. Performing multiple tests may provide results that often are unrelated to the presenting symptom or have no clinical relevance (such as a mildly elevated sedimentation rate). Repeating tests to confirm the serendipitous findings may further increase anxiety and undermine the clinical diagnosis of functional bowel disorder. One could use time as the physician's ally, assuring the patient that no test is necessary at this point but if further symptoms present or the current symptom worsens the physician will not hesitate to proceed with further work-up.

Blood and stool studies:

Hamm et al [103] studied 1452 patients with an established diagnosis of IBS and found that screening tests showed a low incidence of thyroid dysfunction, ova and parasite infestation, or colonic pathology. The authors

concluded that limited detection rates, added costs and the inconvenienceof these tests made the routine use of endoscopy,radiography, thyroid function tests, fecal ova and parasite determination and the lactulose hydrogen breath test questionable in the diagnostic evaluation of established IBS patients. In accordance with these results, Tolliver et al [(129)] performed fecal ova and parasite determinations in 196 patients with a possible diagnosis of IBS, and found no evidence of infection in any of them. In the same study, complete blood cell count, sedimentation rate, serum chemistries, thyroid profile and urinalysis were normal or yielded no useful clinical information.

A study designed to investigate the prevalence of elevated antiendomysial antibody titers in children with recurrent abdominal pain compared with healthy children found no association between abdominal pain and celiac disease [(130)]. The study showed that 1% of patients in each group had positive celiac disease antibodies. An adult investigation studied serum antibody testing for celiac disease in patients with IBS symptoms and a control group, followed by upper endoscopy in positive cases. The study revealed that 4.6% of patients in the group with possible IBS had positive antibodies in comparison with 0.67% in the control group, suggesting that testing for celiac disease may be one of the few cost-effective evaluations in patients with IBS [(131)].

Endoscopic studies:

A study investigating the presence of gastroesophageal reflux in children with recurrent abdominal pain concluded that pathological gastroesophageal reflux is a frequent finding in such children [(132)]. Treatment of gastroesophageal reflux in this group of patients resulted inresolution or improvement of abdominal pain in71% of cases.Another study evaluating findings on endoscopic examinations in 62 Indonesian children with recurrent abdominal pain revealed pathological abnormalities including esophagitis, erosions and duodenitis in 50% of the patients[(133)]. In the absence of peptic ulcers, it is unclear how much these pathological findings contribute to the patients' symptoms. Endoscopy and biopsy performed in children evaluated for dyspepsia demonstrated that most children did not have significant mucosal disease. Inflammation without evidence of peptic ulceration was found in 38% of the patients with H. pylori being identified in only five cases (134). Follow-up at 6 months to 2 years revealed that most subjects improved, regardless of the cause of dyspepsia.

Ultrasound:

The diagnostic yield of a sonographic examination of the abdomen in children presenting with functional bowel disorders seems to be extremely low. Yip et al, in a retrospective evaluation of 644 ultrasound studies performed in children with the diagnosis of recurrent abdominal pain found abnormalities in only ten children, concluding that only children who have abdominal pain with atypical clinical features should receive sonographic screening [(135)]. In another

study, the evaluation of 57 patients with chronic abdominal pain by abdominal and/or pelvic sonography revealed only one case of ovarian cyst that later resolved spontaneously[136]. Stordal et al [137] studied 44 children with recurrent abdominal pain without finding any abnormalities on ultrasound that could be related to the symptoms.

Intraesophageal pH monitoring:

The diagnostic yield of esophageal pH monitoring in children presenting with chronic abdominal pain is controversial. A study of 44 children presenting with recurrent abdominal paindemonstrated gastroesophageal reflux in 25% of cases [137].No studies have compared outcomes between children who had pH monitoring studies and those who did not. The inconvenience associated with this test and itscost preclude its use at least in the initial evaluation of chronic abdominal pain.

Lactose hydrogen breathe test:

This test is often used to diagnose lactose intolerance in patients with functional bowel disorders, but the cause–effect relationship between lactose intolerance and symptoms has been questioned [102]. Lactose intolerance is discussed in more detail in a previous section of this chapter.

Treatment:

There is no uniformly successful treatment or cure for functional bowel disorders. Once the diagnosis has been made, it is essential to emphasize the benign aspects of the history, physical examination and laboratory tests in order

effectively to reassure the patient and the family of their significance. Initial treatment of functional pain is based on reassurance and establishing an effective physician–patient–family relationship. Alleviatingsymptoms is one of the main goals of caring forpatients with functional bowel disorders, but a rational management of these disorders is often challenging, owing to the lack of objective diagnostic criteria and unclear pathogenesis. As a consequence, there are no specific, universally effective therapies [(138)].

Reassurance:

It is of great importance to assure the family and the patient that the physician believes that the symptoms are 'real' and that an organic or progressive disease is not present. An extensive explanation of the nature of the disorder should be given, discussing the problem as a common diagnosis and not just an exclusion of an organic disease. A comprehensive but easily understandable description of the nature of this group of disorders should be attempted. Comparisons with other common and benign entities such as headaches or muscle cramps may help. The family and the patient should be encouraged to ask questions and share their concerns, which should be addressed in depth to avoid fears and misconceptions. The main goal of the therapy is to re-establish a normal daily life for the patient and the family. The family should be discouraged from reinforcing the symptoms by allowing the child to miss school and leisure activities. Patients with perceived low self-worth and academic competence may find the relief of responsibility asa benefit of the pain experience [(139)] meanwhile, patients with adequate

perception of their self-worth may find it discouraging. Fordyce and others have suggested that positive attention from others may serve as a secondary gain, transforming the painful experience into a rewarded activity that in turn couldreinforce symptoms, leading to further disability [140, 141]. However, negative attention to pain in children with low self-esteem has been associated with increased pain behavior, possibly by creating affective distress that may further contribute to somatic symptoms[139]. Thus, the parents' attitude towards the pain experience should be balanced, showing support and understanding, but being aware that excessive attention to the painful experience and missing activities may allow some patients (especially those with low self-worth) to develop a sick role, perpetuating the symptoms. Behavior alternative to assuming the sick role should be encouraged and rewarded. Patients should be encouraged to discuss perceived triggering factors. Psychosocial stressors at home or school should be addressed. At school, strict toilet times or issues relating to social embarrassment to attend the restrooms should be discussed. It is often useful to communicate with the school nurse or teacher inorder to address these issues. Owing to the high index of symptomatic success with reassurance, medications are not necessary for every patient with functional abdominal pain. Drug therapy should be recommended only for patients with symptoms interfering with satisfactory quality of life.

Diet:

A detailed dietary history may identify factors that patients may feel as aggravating or provoking the symptoms. Food intolerance was perceived as a problem by 20% in an unselected UK population who responded to a questionnaire, but with controlled challenge the prevalence was slightly higher than 1%[142]. Food-induced symptoms are common reports among IBS patients, with 20–65% attributing their symptoms to adverse food reactions [143, 144]. In a study of 200 IBS patients[143], the effect of an exclusion diet was evaluated, with a symptomatic improvement in almost 50% of patients, indicating that a significant proportion of IBS patients could benefit from therapeutic dietary manipulation. However, such intervention is still controversial because the observed response rate replicates the average placebo response rate in IBS trials [73]. Within IBS patients the subgroup of patients with diarrhea-predominant symptoms seems to benefit the most by a trial of exclusion diet. Among those with abdominal pain with or without diarrhea, lactose, or excessive fructose or sorbitol intake may induce symptoms. The avoidance of gas- forming foods such as legumes, complex carbohydrates, lactose and fructose may provide symptomatic relief in some patients. High-fiber diets have long been used in adult IBS patients but the data in children are still preliminary and accomplishing a substantial increase in fiber consumption may be difficult [145, 146]. As fibers decrease the whole-gut transit time, fiber-enriched diets may be more useful in the subgroup of patients with constipation [147, 148]. Fiber may also decrease intraluminal pressures, reducing walltension and pain

[149]. In committed familieswishing to increase dietary fibers, the change should be attempted gradually, as the excess of undigested carbohydrates in the colon results in fermentation with consequent increase of gas, aggravating IBS symptoms[150].

Laxatives:

Patients with severe constipation may find relief by combining fiber with a laxative. It is our preference to use polyethylene glycol or a senna derivative, but other laxatives may be used according to the practitioner's preference. Lactulose should be avoided, as the increase of gas production derived from its use may trigger pain.

Anticholinergic and antidiarrheal medications:

Some patients with diarrhea seem to benefit from an antidiarrheal preparation such as loperamide or diphenoxylate. Studies in adults6 and anecdotal experience seem to demonstrate that some patients find relief by using anticholinergics such as hyoscyamine[151],dicyclomine or others that may modify intestinal tone and motility. These agents are best used on a sporadic basis, whenever the symptoms are present much like analgesics are used for headaches. When giving medications for pain, the high placebo response rate should be considered, as several preparations may work in the short term, only to relapse after a variable period of time [152].

Tricyclic antidepressants:

An additional option for treating chronic abdominal pain is the use of tricyclic antidepressants (TCA). TCA are used at smaller doses (0.2–0.4 mg/kg per day, 5–50mg/day) than needed for treatment of clinical depression. The analgesic effects of TCA and other antidepressants are independent of their effects on depression, and this information should be shared with the family and the patient. The beneficial effect of the TCA starts 3–7 days after the beginning of the treatment, while it takes 2–3 weeks for the onset of the antidepressant effects[153]. Relief of chronic pain with the use of antidepressants has been documented in the absence of any measurable antidepressantresponse, both in depressed patients [154] and in patients without clinical depression. In addition to its action on noradrenergic and serotoninergic receptors, the TCA have antimuscarinic and antihistaminic effects. Thus, these agents are especially effective in diarrhea-predominant patients [155] and those with disturbed sleep, when slowing intestinal transit and the side-effects of sleepiness may be of therapeutic value. The medication is best administered at bedtime. Other side-effects such as undesirable weight gain and the possibility of cardiac arrhythmias, although rare at such low doses, demand caution when prescribing these drugs. Electrocardiogram (EKG) monitoring can be performed at the practitioner's discretion. Amitriptyline, although probably more effective, has greater sedative and anticholinergic effects than imipramine [156]. It is recommended that the medication be started at low doses, increasing the dose progressively as

needed to achieve a full dose in weeks [157]. Other antidepressant drugs, such as selective serotonin reuptake inhibitors (SSRIs) are also being used in the relief of chronic pain [158].

Selective serotonin re-uptake inhibitors:

SSRIs, such as paroxetine, fluoxetine, or sertraline, also seem to have therapeutic value in relieving symptoms in adult patients with functional bowel disorders[151]. SSRIs have become the most frequently prescribed antidepressant medications, owing to their favorable side-effect profile [159]. Despite the growing popularity of SSRIs, there are few controlled studies of their efficacy in managing chronic pain syndromes. The effects of TCAsand SSRIs in the GI tract are different, with the TCAs slowing intestinal transit and SSRIs increasing motility in the small intestine [72, 160]. Thus, a patient in whom the main symptom is constipation may benefit most from an initial trial of an SSRI, whereas a patient with increased bowel frequency may benefit from an antidepressant with anticholinergic properties. Recent reviews concluded that, although SSRIs may be effective, in most circumstances TCAs should remain the first-line antidepressant agents for chronic pain [154].

Serotonin receptor antagonists:

There has been much recent interest in clinical gastrointestinal pharmacology focused on 5-HT3 and 5-HT4 receptors. Such receptors have beenshown to be involved in diverse sensory and motor regulatory processes in the GI tract. The 5-HT3 receptor has a role in modulating colonic motility and

visceral pain, increasing the threshold for sensation and discomfort, slowing colonic transit and improving stool consistency [161]. A number of selective 5-HT3 antagonists have been developed including ondansetron, granisetron, tropisetronrenzapride andzacopride. Ondansetron was the first 5-HT3 to be evaluated for its effects on the gut. It demonstrated some benefits in diarrhea-predominant IBS, but no improvement in abdominal pain. Similarly, no reduction in pain was seen with granisetron. This modest efficacy led to the search for a 5-HT3 with greater potency. Alosetron, a newer 5-HT3 receptor antagonist, has greater potency than ondansetron, and good bioavailability [162]. Treatment with alosetron has led to significant relief of abdominal pain and discomfort in women with diarrhea-predominant IBS. Though generally safe, its use has been associated with severe constipation and ischemic colitis. It is currently available in the USA as part of a limited access program. 5-HT4 agonists such as tegaserod and prucalopride, have been developed for patients with IBS and constipation. Tegaserod has demonstrated efficacy in the short-term relief of abdominal pain and discomfort in adult women with constipationpredominant IBS[163] and is commercially available for this indication. Adverse events, particularly loose stools, are compatible with an exaggerated pharmacological response to tegaserod and are most common during the first 2 days of therapy.

Alternative and complementary therapy:

Despite the interventions described above, some patients will continue to experience symptoms, suggesting that current treatments that target the

predominant symptom are only partially effective, presumably because they do not resolve the underlying cause of functional bowel disorder [73]. The large number of patients in whom these therapies fail has prompted an interest in alternative therapies such as diet supplements, probiotics and ancient therapeutic modalities such as Chinese medicine. Peppermint oil (Menthapiperita), which is commonly found in many over-the-counter preparations for IBS, has long been recognized as a spasmolytic agent that relaxes GI smooth muscle, relieving pain. Placebo-controlled studies have shown an overall improvement in IBS patients who used peppermint oil [164, 165]. A double-blind clinical trial in Chinese medicine demonstrated that herbal therapy was effective in the management of symptoms related to IBS [166]. Natural and 228 Functional abdominal pain and other functional bowel disorders herbal medications are not without adverse effects and patients should not take these products without medical supervision. A variety of other herbal preparations have been studied with different methodologies, resulting in mixed results. More well-designed, controlled trials must be performed to identify other complementary therapies, with validation of the safety and efficacy of their use [95]. Another alternative therapeutic strategy for patients with significant pain is to use hypnotherapy or psychotherapy[167-169]. Hypnotherapy has been shown to be effective in the treatment notonly of gastrointestinal symptoms but also ofurological, sexual and psychological symptoms that are often associated features of IBS in adults [170]. Effective psychological treatments include cognitive–behavioral interventions, dynamic

or interpersonal psychotherapy and stress management. In a review of published psychological trials, Talley et al found methodological problems in all the studies, concluding that the efficacy of psychological treatment for IBS could not yet be established [171].Despite the fact that alterations of enteric flora may play a role in IBS, convincing evidence for a pathogenic role of bacterial overgrowth or for a beneficial effect of probiotic therapy is still scant. A review of the therapeutic role of probiotics concluded that further studies are needed to identify particular subgroups of patients with IBS who could benefit from their use [172]. More recently, however, a very encouraging randomized, doubleblind and placebo-controlled study in adults with diarrhea-predominant IBS showed efficacy for the probiotic preparation 'VSL3' [173]. These findings will of course have to be reproduced in children. In chronic cases of refractory pain, referral to specialized treatment centers for an interdisciplinary pain management approach may be the most efficient method of treating disability. Natural history Functional abdominal pain is not always a benign condition with a satisfactory outcome. Long-term psychiatric disorders have been identified in patients suffering from functional abdominal pain in childhood[174]. Children with abdominal pain do not necessarily continue to experience physical symptoms in adulthood but may have an increased risk of adult psychiatric disorders [175].

Future trends:

The key to revealing the mechanisms and improving therapy of functional bowel disorders lies in the collaborative efforts among basic scientists, clinical

investigators, physicians and behaviorists. Progress in better understanding of the sensory mediators and the causes of visceral afferent dysfunction should lead to treatments that reduce the visceral perception or reflex motor responses that lead to symptoms. We should continue to pursue investigations looking for biological markers of this group of disorders. Education of patients and physicians on the nature and therapy of this group of conditions, in conjunction with early identification of psychosocial variables and development of better therapies, are fundamental strategies in order to reduce patient suffering and the elevated costs to society associated with functional bowel disorders

RESULTS

Children who attended the PediatricsOPD for abdominal pain were given a questionnaire developed from Rome III Diagnostic Questionnaire for the Pediatric Functional GI Disorders. Parents filled up the questionnaire and children who fulfilled the ROME III criteria for chronic abdominal pain (i.e. abdominal pain more than 2 months) were explained about the study. Saps et al and Tilburg et alprovide for validation of ROME III questionnaire [184, 185]. After obtaining informed consent children were then included in the study. Total of 66 children were included in this study, of them cases were 31 and controls were 35. Ultrasound gallbladder measurements were done for the study population with 6 hours of fasting and 30 minutes following standard meal containing 30 gram of fat. Children were age and gender matched.

I. Base line characteristics of cases and controls

There were total of 66 children included in this study. The mean age of cases and controls were 10.14 ± 2.71 years and 11.54 ± 1.94 years respectively **(Table 1)**. The mean age of boys and girls in the cases group were 10.4 ± 2.73 years (ranging from 6.5 to 15 years) and 10.1 ± 2.71 years (ranging from 5 to 15 years) respectively. The mean age of boys and girls in the controls group are 11.6 ± 1.92 years (ranging from 5 to 15 years) and 12.2 ± 1.61 years (ranging from 7 to 14 years). The mean height of the cases group was 132.9 ± 15.9 (ranging from 100 to 165cms) and that of controls was 145.14 ± 11.6 (ranging from 110 to 159cms). The mean weight of cases and controls were 27.3 ± 10.5 and 33.8 ± 6.6 respectively. The mean body mass index (BMI) was 14.9 ± 2.8

kg/m^2 (range of 11.3 to 26.3 kg/m^2) in case group and 15.9 ± 1.8 kg/m^2 (range from 11.9 to 19.5 kg/m^2) in the control group **(Fig 6)**. Out of 31 cases there were 11 boys (35.5%) and 20 (64.5%) girls respectively. And in 35 controls there were 23 (65.7%) boys and 12 (34.3%) girls respectively. So a total of 34 boys and 32 girls were included in this study.

II. Symptoms associated in children with chronic abdominal pain

The following symptoms were reported by 31 children in the case group: abdominal pain (n=31), upper abdominal pain (n=11), lower or periumbilical abdominal pain (n=20), relieving of abdominal pain following defecation (n=7), change in pain with frequency of passing stool (n=1), change in pain with form of stool (n=2), 2 or more episodes in last year lasting more than 1 hour or longer and restricting daily activities (n=5), symptom free period between pain (n=30), any associated symptoms like no appetite, nausea, vomiting, pale skin, headache, eyes sensitive to light, headache, difficulty in sleeping, pain in arms, legs, or back, fainting or dizziness (n=10) and misses activities once in a while (n=10) **(Table 2)**. In the case group 77.4% continued to have abdominal pain even after defecation.In cases almost 26 (83.9%) did not have any restriction of activities due to abdominal pain. in cases 96.8% of them had symptom free period between abdominal pain episodes.

III. Comparison of pre-prandial and post-prandial gallbladder volumes in cases and controls

The mean pre-prandial gallbladder volumes of cases and controls were 8.35 ± 3.97 (cm^3) and 7.46 ± 3.04 (cm^3) respectively **(Fig 7)**. Though the pre-prandial GB volume was visibly greater than the control group, yet there was no statistical significance (*p* value – 0.232) **(Table 3)**. The mean post-prandial volumes of cases and controls were 3.52 ± 1.73 (cm^3) and 2.83 ± 1.04 (cm^3) respectively **(Fig 8)**. Though the post-prandial GB volume was visibly greater than the control group, yet there was no statistical significance (*p* value – 0.390) **(Table 4)**. The baseline gallbladder volume changes in cases and controls, comparing their pre-prandial and post-prandial were 42% and 37%

IV. Gallbladder ejection fraction in cases and controls

Ejection fraction is measured with the obtained GB pre-prandial and post-prandial GB volume. The mean ejection fraction of cases and controls were 51.72 ± 17.76% and 57.37 ± 23.26% respectively **(Fig 9)**. But there was no statistical significance in ejection fraction of cases and controls (*p* value – 0.158) (**Table 5)**

V. Pain distribution and ejection fraction relation in cases

To identify the association, if exists, between upper abdominal pain and GB dysmotility, the ejection fraction of GB in children with upper abdominal pain was compared with ejection fraction of GB in children with lower abdominal pain. Ejection fraction was compared with the site of abdominal

pain between upper abdominal pain and periumbilical/lower abdominal pain. This was done because in location to GB in right upper quadrant, so cases with upper abdominal are high likely to have less ejection fraction in cases group. The mean ejection fractions of cases with upper abdominal pain and periumbilical or lower abdominal pain were 41.7 ± 17.1% and 57.2 ± 15.9% respectively **(Fig 10)**. This is statistically significant (*p* value – 0.000), it shows that children with upper abdominal pain had lesser GB contractility than in children with lower or periumbilical abdominal pain **(Table 6)**.

VI. Correlation with BMI and GB contractility

In order to identify any possible association between increasing BMI and GB contractility among cases and controls, a subgrouping of cases were done into 2 groups namely, BMI<15 and BMI ≥ 15. The mean ejection fraction of cases with BMI< 15 and ≥ 15 were 54.28 ± 17.99 % and 48.19 ± 17.53 % **(Fig 11)**, it is statisticallysignificant (*p* value is 0.000) **(Table 7)**. In cases children with BMI<15 had better ejection fraction than those with BMI ≥ 15. In Pearson's correlation method showed a weak negative correlation between BMI and gall bladder contractility in cases. The mean ejection fraction of controls with BMI< 15 and ≥ 15 were 39.18 ± 28.16 % and 63.68 ± 17.94 % **(Fig 12)**, it is statistically significant (*p* value is 0.003) **(Table 8)**. In the control group the mean ejection fraction was more in children with BMI ≥ 15.

VII. Correlation of cases and controls with gallbladder ejection fraction < 40% and BMI

In the case group there were 8 children with gallbladder dysmotility (i.e. gallbladder ejection fraction less than 40%). Among the 8, 4 children had BMI < 15 and 4 children had BMI ≥ 15. And there were totally 9 children with gallbladder dysmotility in the control group. In them 5 children had BMI <15 and 4 of them had BMI≥ 15. In both cases and controls the children with gallbladder dysmotility (i.e. ejection fraction less than 40%) were compared with BMI of the study population by chi-square method and Pearson's correlation **(Fig 13 and 14)**. On applying Chi-Square test, this observation was not statistically significant (*p* value – 0.103) **(Table 9 and 10)**

Table 1: Baseline characteristics of study population

	Cases	**Controls**
N	31	35
Age ±SD (in years)	10.14 ± 2.71	11.54 ± 1.94
Height ±SD (cm)	132.9 ± 15.9	145.14 ± 11.6
Weight ±SD (kg)	27.3 ± 10.5	33.8 ± 6.6
BMI ±SD (kg/m^2)	14.9 ± 2.8	15.9 ± 1.8

Figure 6: Baseline characteristics of study population

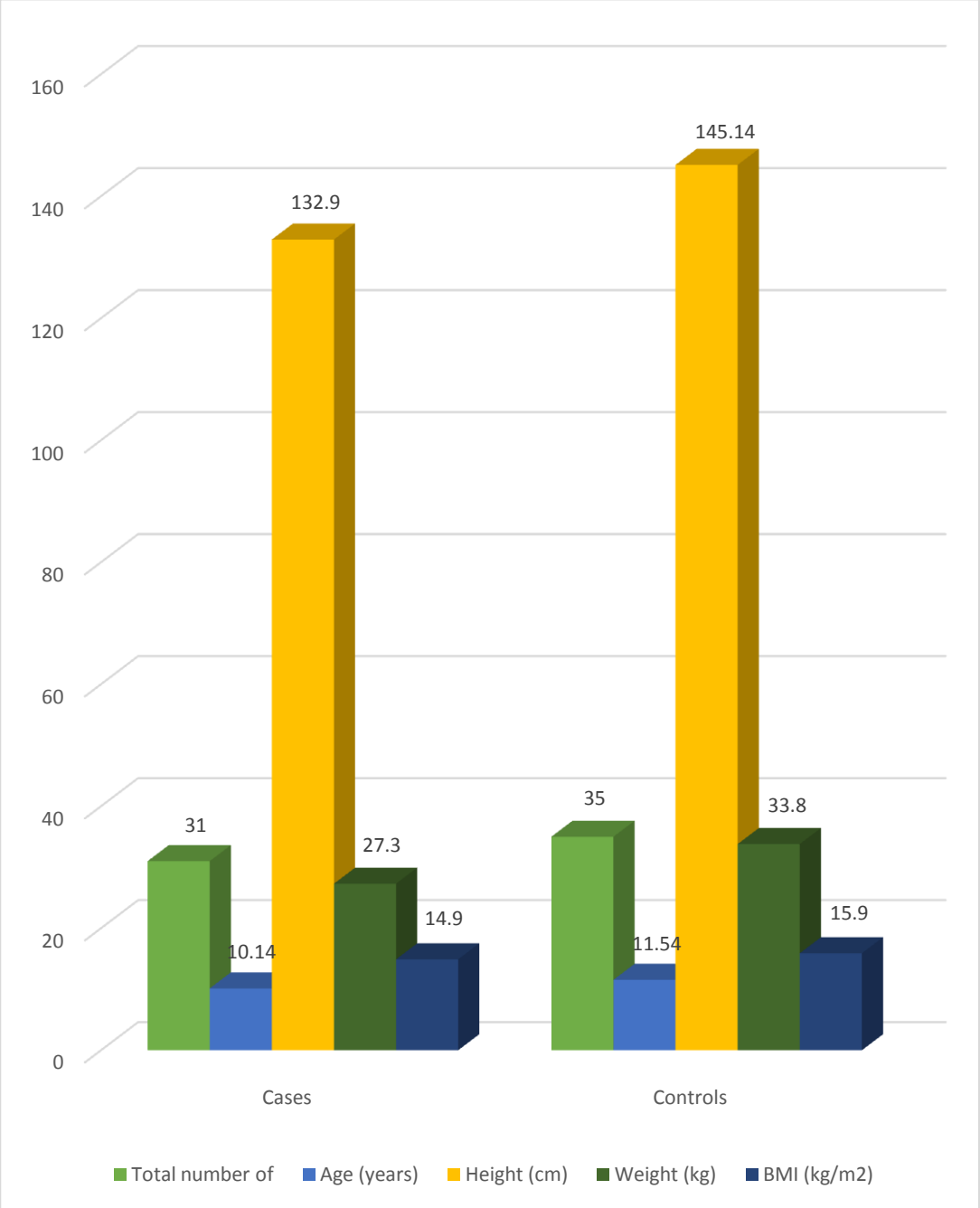


Table 2: Cases presenting with various symptoms

Symptoms	Number of children in cases group
Upper abdominal pain	11
Lower or periumbilical abdominal pain	20
Decrease in abdominal pain after defecation	7
Change in pain with frequency of passing stool	1
Change in pain with form of stool	2
2 or more episodes in last year lasting more than 1 hour or longer and restricting daily activities	5
Symptom free period between pain	30
Associated symptoms like no appetite, nausea, vomiting, pale skin, headache, eyes sensitive to light, headache difficulty in sleeping, pain in arms, legs, or back, fainting or dizziness	10
Misses activities once in a while	10

Table 3: Pre-prandial gallbladder volume in cases and controls

	Mean
Pre-prandial gallbladder volume in cases (cm^3)	8.35 ± 3.97
Pre-prandial gallbladder volume in controls (cm^3)	7.46 ± 3.04
***P* value (t test method)**	0.232

Figure 7: Pre-prandial gallbladder volume in cases and controls

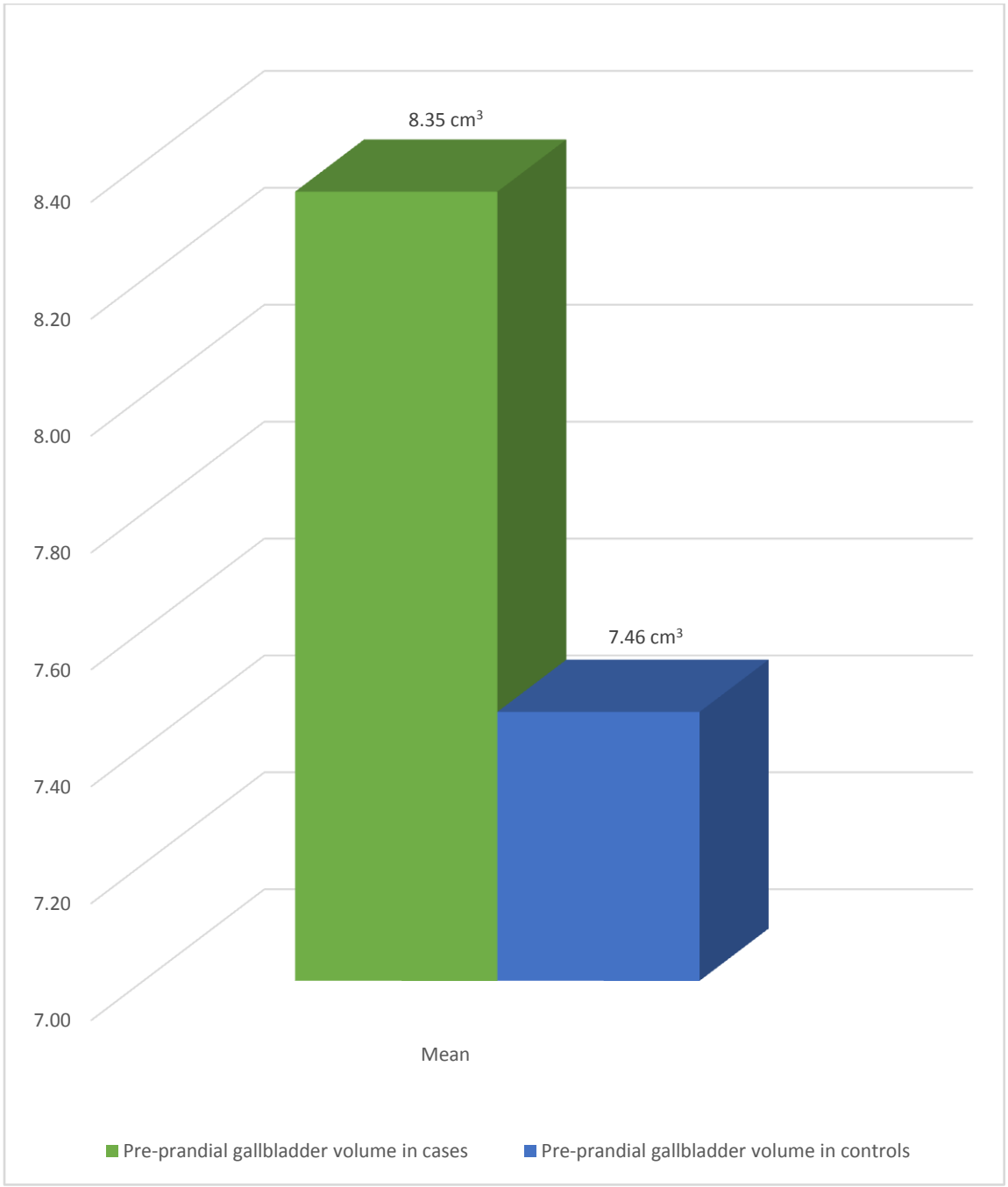


Table 4: Post-prandial gallbladder volume in cases and controls

	Mean
Post-prandial GB volume in cases (cm^3)	3.52 ± 1.73
Post-prandial GB volume in controls (cm^3)	2.83 ± 1.40
***P* value (t test method)**	0.390

Figure 8: Postprandial gallbladder volume in cases and controls

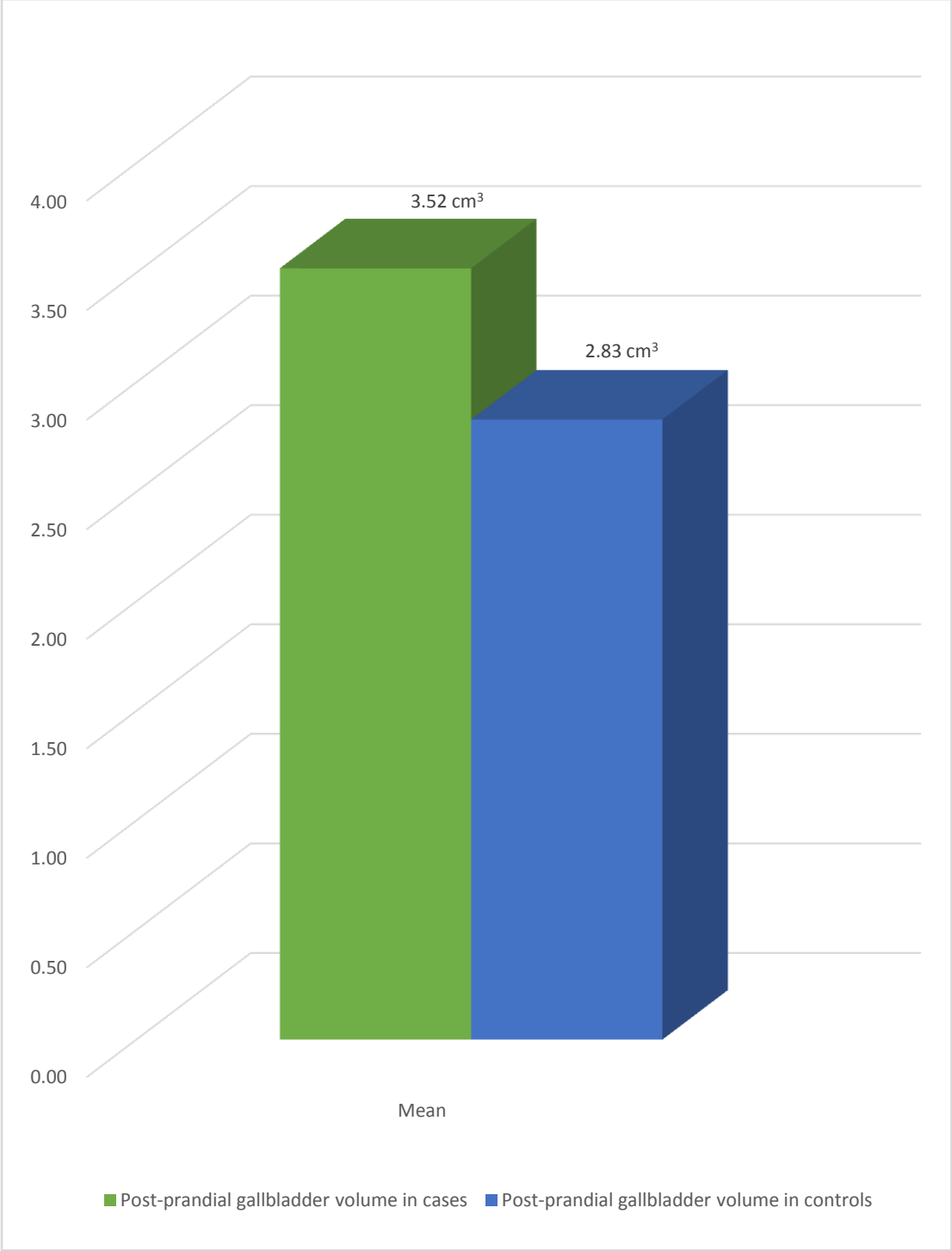


Table 5: Gallbladder ejection fraction in cases and controls

	Mean
Gallbladder ejection fraction in cases (%)	51.72 ± 17.76
Gallbladder ejection fraction in controls (%)	57.37 ± 23.26
***P* value (t test method)**	0.158

Figure 9: Gallbladder ejection fraction in cases and controls

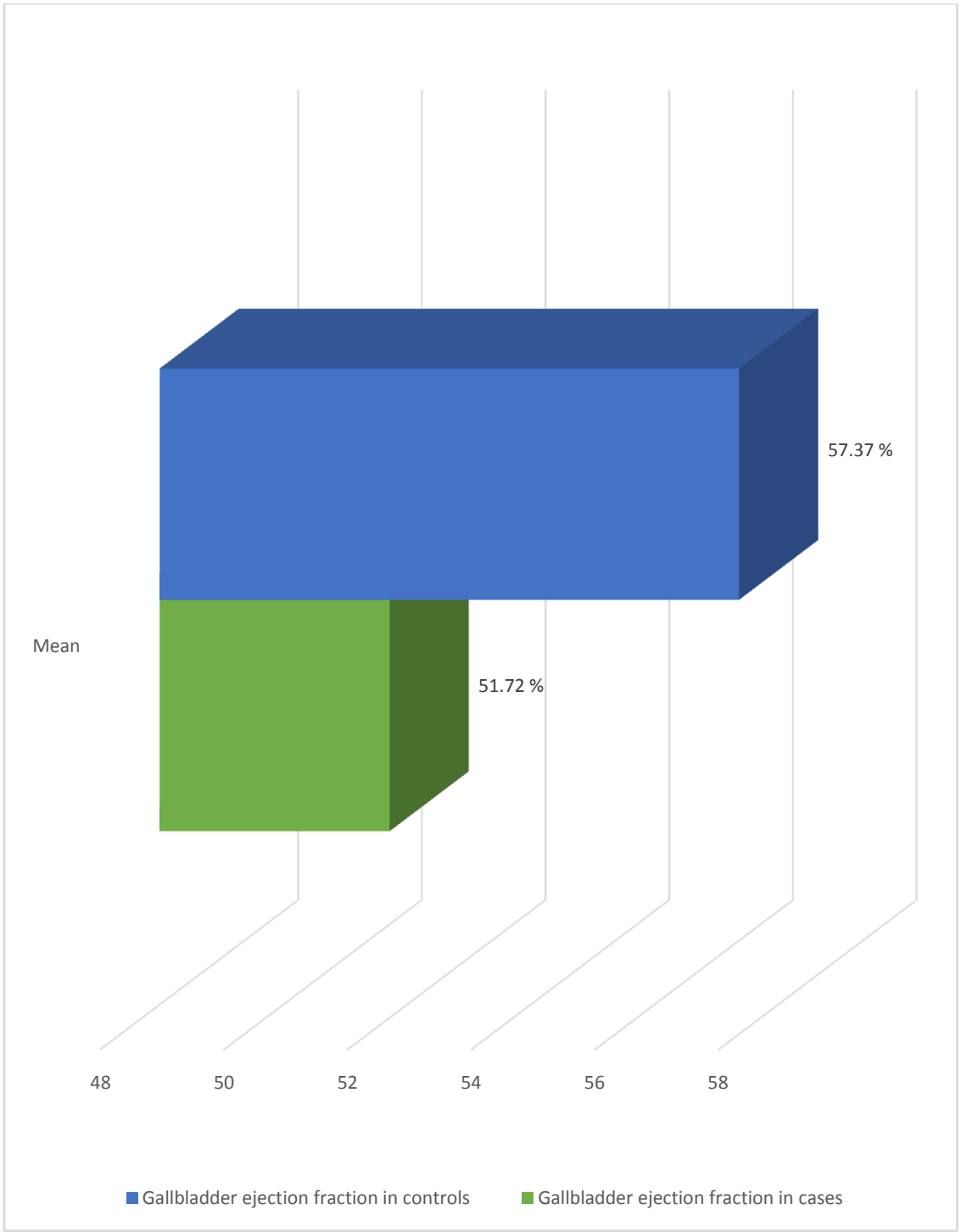


Table 6: Ejection fraction in cases with upper abdominal pain and lower or periumbilical abdominal pain.

	Mean ejection fraction
Upper abdominal pain	41.7 ± 17.1%
Lower or periumbilical abdominal pain	57.2 ± 15.9%
***P* value (t test method)**	0.000

Figure 10: Ejection fraction in cases with upper abdominal pain and lower or periumbilical abdominal pain.

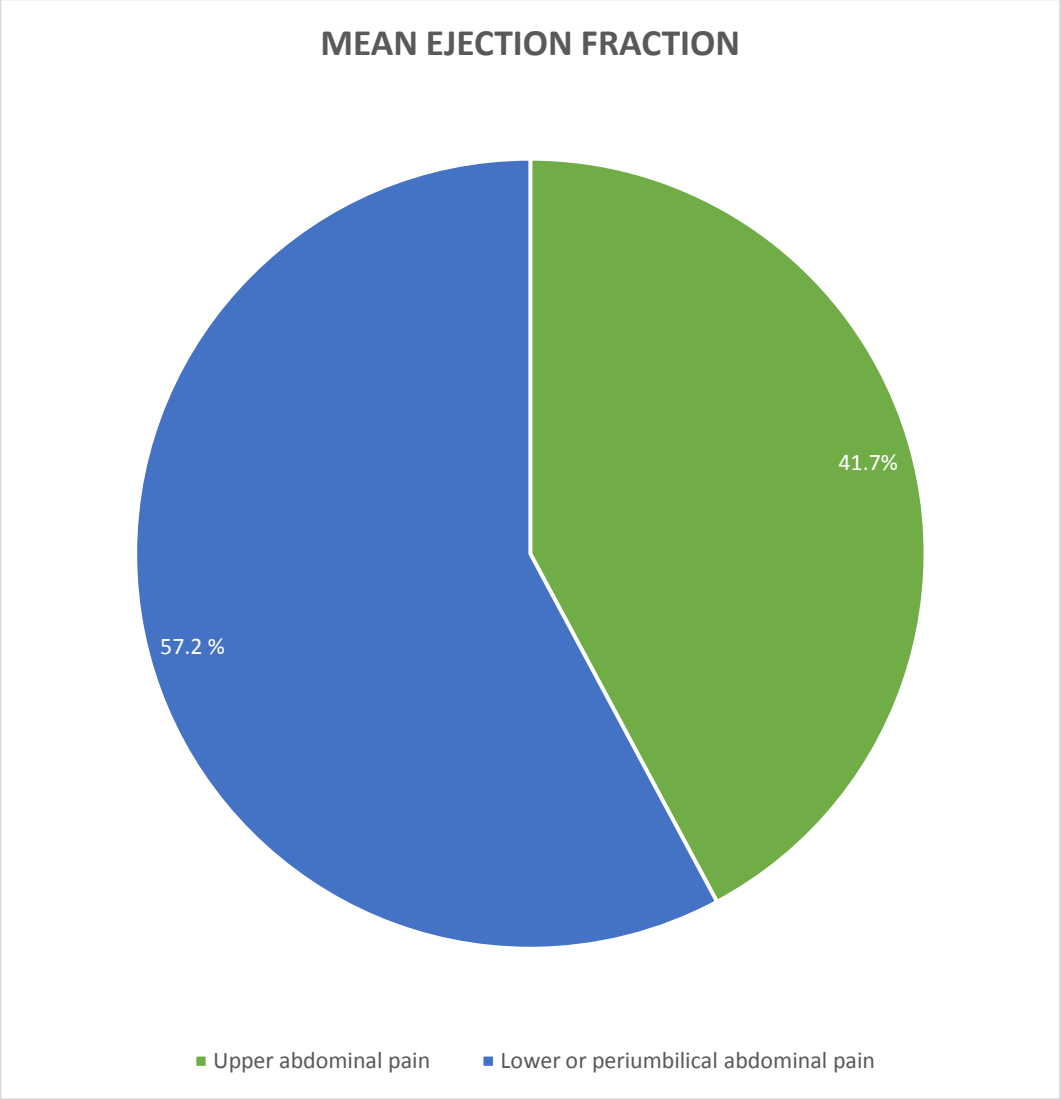


Table 7: Correlation between BMI and ejection fraction in cases

	Mean ejection fraction in Cases
BMI < 15	54.28 ± 17.99 %
BMI ≥ 15	48.19 ± 17.53 %
***P* value (t test method)**	0.000

Figure 11: Correlation between BMI and ejection fraction in cases

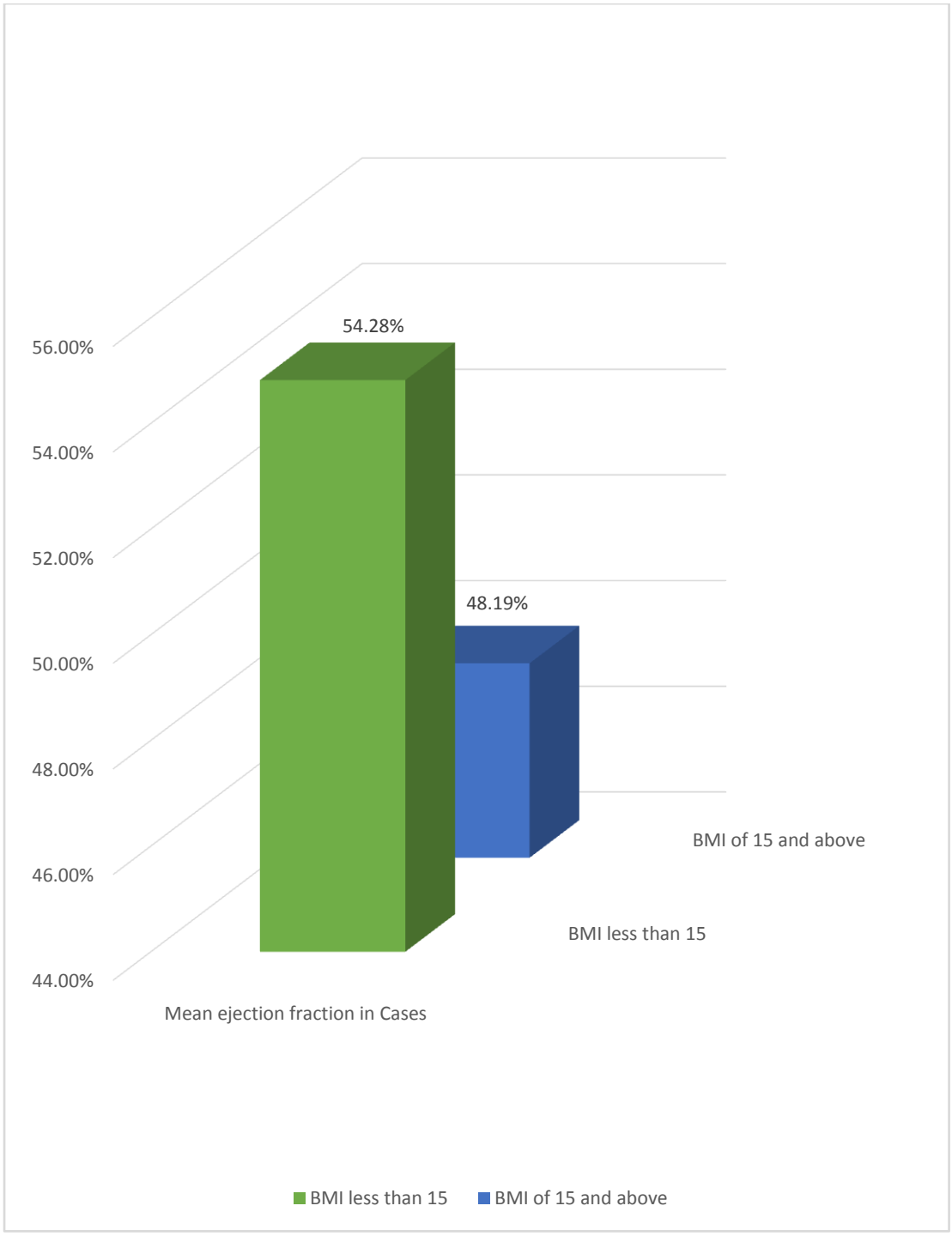


Table 8:Correlation between BMI and ejection fraction in controls

	Mean ejection fraction in controls
BMI < 15	39.18 ± 28.16 %
BMI ≥ 15	63.68 ± 17.94 %
***P* value (t test method)**	0.003

Figure 12: Correlation between BMI and ejection fraction in controls

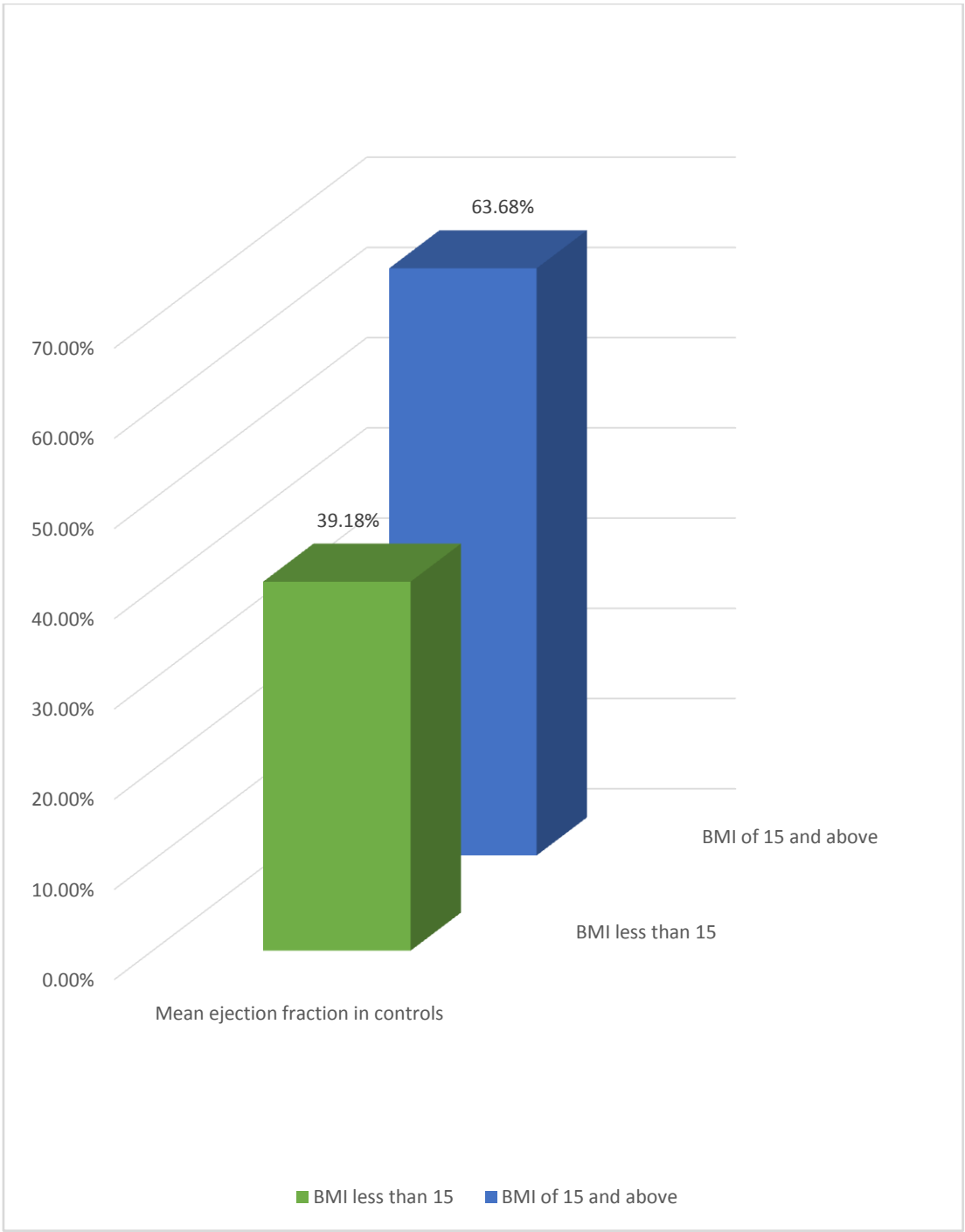


Table 9:Correlation between ejection fraction and BMI in cases

BMI < 15	**Ejection fraction </= 40%**	**Ejection fraction >40%**	**Total**
BMI < 15	4	13	17
BMI ≥ 15	4	10	14
Total	8	23	31
***P* value (chi-square method)**	1.0000		

Figure 13: Correlation between ejection fraction and BMI in cases

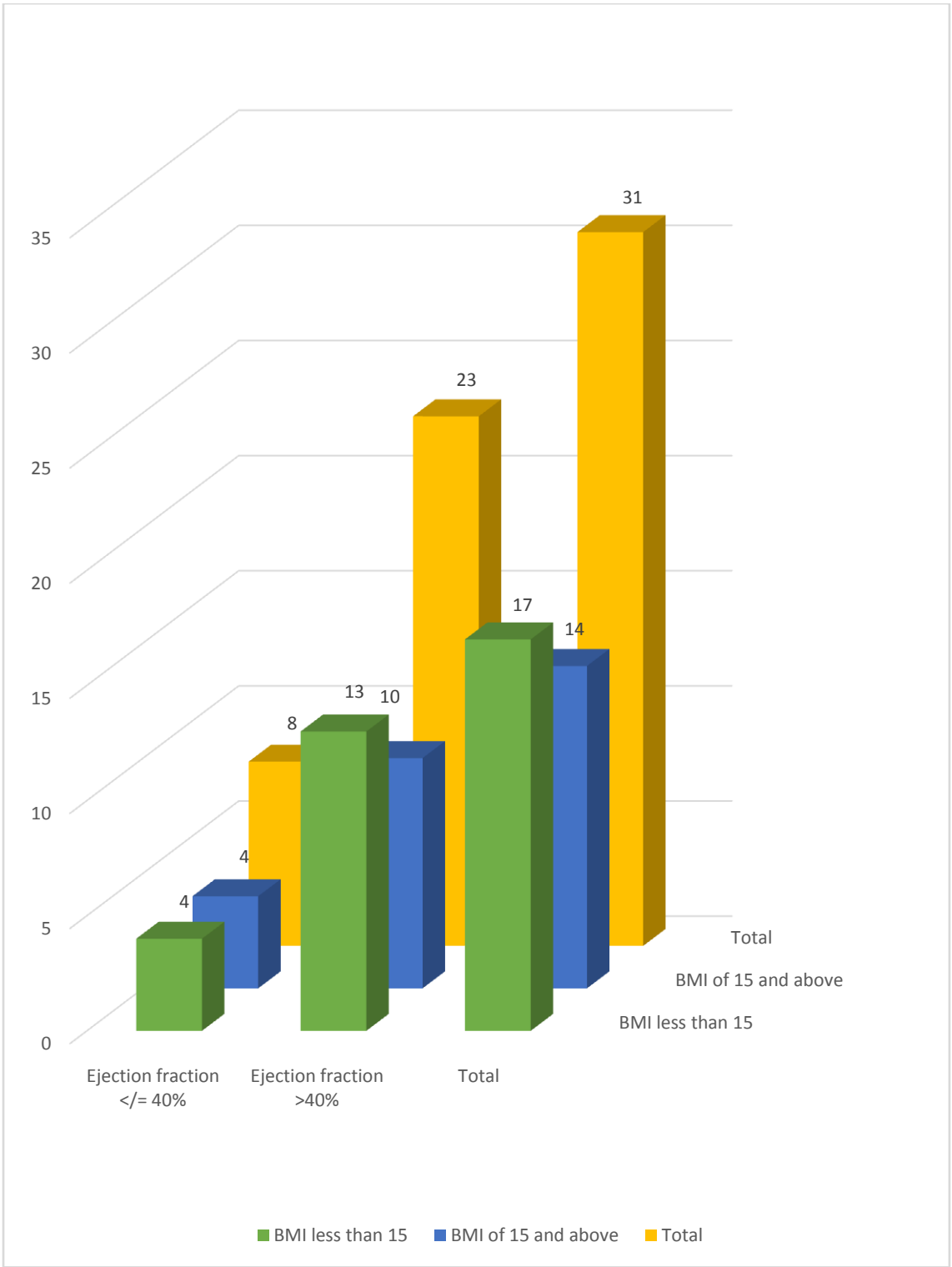
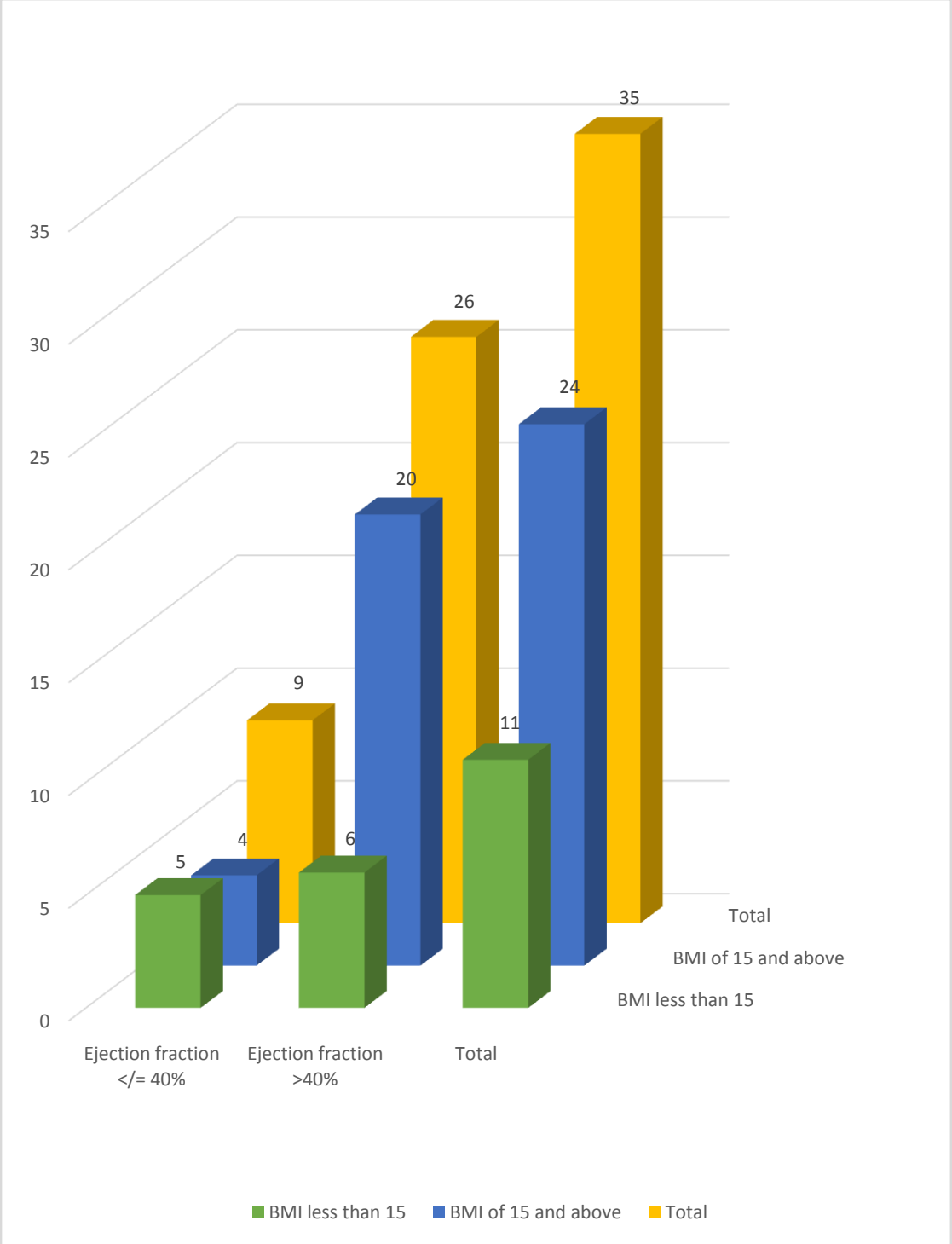


Table 10:Correlation between ejection fraction and BMI in controls

	Ejection fraction </= 40%	**Ejection fraction >40%**	**Total**
BMI < 15	5	6	11
BMI ≥ 15	4	20	24
Total	9	26	35
***P* value (chi-square method)**	0.103		

Figure 14: Correlation between ejection fraction and BMI in controls



DISCUSSION

Chronic abdominal pain is one of the commonest gastrointestinal symptoms in children presenting to outpatient department [(1)].Campbell et al study on children with chronic abdominal pain undergoing laparoscopic cholecystectomy for biliary dyskinesia diagnosed by quantitative cholescintigraphy with CCK stimulation showed86% of children had chronic abdominal pain [(187)].In the present study 32.2% of the children missed their day today activities due to chronic abdominal pain.

Though the exact prevalence of CAP in our country is not exactly known, studies from the western world have documented 13% among middle school children and 17% in high school children experiencing weekly abdominal pain. Over all about 2 to 4% of all pediatric outpatient visits are due to CAP in children. Extensive evaluation for CAP in children does not show any obvious organic reason for abdominal pain. Recent evidences show causal association between gallbladder dysmotility and CAP.

In the recent times USG has been used for evaluating gallbladder ejection fraction, because of its convenience in using and no radiation advantages. Mehra et al [(183)] has prospectively studied association between gallbladder dysmotility in children with chronic functional constipation, using USG. Hence in our present study USG was used to evaluate the gallbladder.

In our study a total of 31 subjects presented with CAP, among which 25.8 % of children had an ejection fraction < 40% following a fatty meal

suggesting gallbladder dysmotility. But a majority (74.2%) of children though had CAP by definition, had an ejection fraction > 40% suggesting that some unknown cause for abdominal painunrelated to gallbladder dysmotility. Interestingly a similar percent of healthy controls (Age and Sex matched) also had gallbladder dysmotility and was symptom free. Suggesting that gallbladder dysmotility may not be symptomatic in all children.

The mean pre and post-prandial gallbladder volume of cases was 8.35 ± 3.97 (cm^3)2.83 ± 1.40 (cm^3). The volume of gallbladder among cases was significantly higher than the healthy controls who had a mean pre and post-prandial gallbladder volume of 3.52 ± 1.73 (cm^3)7.46 ± 3.04 (cm^3) respectively. A high mean pre-prandial gallbladder volume might suggested an underlying gallbladder dysmotility, though there was no significant change in the ejection fraction of gallbladder among cases and controls (51.72 ± 17.76 versus 57.37 ± 23.26*P* value 0.158).

In our study we sub grouped the cases based on the sight of abdominal pain as upper abdominal pain and lower or periumbilical abdominal pain. The mean ejection fraction among cases with upper abdominal pain was 41.7 ± 17.1% were as cases with lower or periumbilical abdominal pain had higher ejection fraction 57.2 ± 15.9% and it is statistically significant (*P*value = 0.000). In the study by Michail et al (186), who looked into clinical features of children with biliary dyskinesia and underwent laparoscopic cholecystectomy, found that 93% of children presented with right upper quadrant pain. This observation is similar to results of our study were 36.3 %

with upper abdominal painhad gallbladder dysmotility and only 15% of children with lower or periumbilical abdominal pain had gallbladder dysmotility. The mean ejection fraction among the entire population of children with upper abdominal pain was higher than the mean ejection fraction of children with lower or periumbilical abdominal pain(41.7 ± 17.1% versus 57.2 ± 15.9% *P* value = 0.000). So children with upper abdominal pain are likely to have an underlying gallbladder dysmotility.

On comparing the effect of BMI of the individual on gallbladder dysmotility we have found that children with chronic abdominal pain with BMI < 15 had better ejection fraction when compared to children with chronic abdominal pain with BMI ≥15. This difference in mean ejection fraction among cases with BMI < 15 and ≥15 was statistically significant. Suggesting that children with chronic abdominal pain with low BMI had better gallbladder contractility.

CONCLUSION

- Our study is the first of its type in evaluating causal association of gallbladder dysmotility in children with chronic abdominal pain
- The ROME III questionnaire is a reliable tool to assess and classify chronic abdominal pain in children in an office setting
- USG can be utilized in clinical practice for assessing gallbladder contractility
- In our study among 31 children with chronic abdominal pain 25.8% had gallbladder dysmotility
- The mean ejection fraction of children with chronic abdominal pain and gallbladder dysmotility was 30.2%
- 36.3% of children with upper abdominal pain had gallbladder dysmotility as compared to 15% of children with lower / periumbilical abdominal pain
- A statistically significant difference in the mean ejection fraction of children with upper abdominal pain and lower / periumbilical pain was observed (41.7 ± 17.1% versus 57.2 ± 15.9% *p* value – 0.000)
- The mean gallbladder volume among cases was higher than the healthy controls group but this difference was not statistically significant (3.52 ± 1.73 (cm^3) versus 2.83 ± 1.04 (cm^3) *p* value – 0.390)

- On applying Pearson's correlation for children with chronic abdominal pain and their BMI, there exists a negative correlation with increasing BMI (p value < 0.000)
- 25.7% of the controls also had an ejection fraction < 40% but were asymptomatic

LIMITATIONS

- Small sample size
- Bias due to inter observer variation in USG finding were few limitations of the present study
- Further studies to confirm gallbladder dysmotility by using quantitative cholescintigraphy with CCK stimulation might throw light on the reliability of USG to evaluate gallbladder dysmotility

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Department of Paediatrics
Guides: Dr N T Rajesh / Dr K Neelakandan
PSG IMS & R
Coimbatore

Ref: Project No.15/433

Date: October 20, 2017

Dear Dr Raaghul,

Institutional Human Ethics Committee, PSG IMS&R reviewed and discussed your application dated 28.12.2015 to conduct the research study entitled *"Gallbladder contractility in children with chronic abdominal pain"* during the IHEC review meeting held on 28.12.2015.

The following documents were reviewed and approved:

1. Project Submission form
2. Study protocol (Version 1 dated 28.12.2015)
3. Assent and Parental consent forms for cases (Version 1 dated 28.12.2015)
4. Assent forms for controls (Version 1 dated 30.12.2015)
5. Data collection tool (Version 1 dated 28.12.2015)
6. Permission letter from concerned Heads of Department
7. Current CVs of Principal investigator, Co-investigator
8. Budget

The following members of the Institutional Human Ethics Committee (IHEC) were present at the meeting held on 28.12.2015 at Research Conference Room, PSG IMS & R between 10.00 am and 12.30 pm:

Sl. No.	Name of the Member of IHEC	Qualification	Area of Expertise	Gender	Affiliation to the Institution Yes/No	Present at the meeting Yes/No
1	Mrs Y Ashraf	MPT	Physiotherapy	Female	Yes	Yes
2	Dr. S. Bhuvaneshwari (Member-Secretary, IHEC)	MD	Clinical Pharmacology	Female	Yes	Yes
3	Mr Gowpathy Velappan	BA., BL	Legal Advisor	Male	No	No
4	Dr A Jayavardhana	MD	Clinician (Paediatrics)	Male	Yes	Yes
5	Mr P Karuppuchamy	M Phil in PSW	Social Scientist	Male	Yes	Yes
6	Mrs G Malarvizhi	M Sc	Nursing	Female	Yes	Yes
7	Mr. R. Nandakumar	BA., BL	Legal Expert	Male	No	Yes

	(Chairperson, IHEC)					
8	Dr. Parag K Shah	DNB	Clinician (Ophthalmology)	Male	No	No
9	Dr. G. Rajendiran	DM	Clinician (Cardiology)	Male	Yes	Yes
10	Mrs P Rama	M Pharm	Non-Medical (Pharmacy)	Female	Yes	Yes
11	Dr. Seetha Panicker (Vice-chairperson, IHEC)	MD	Clinician (Obstetrics & Gynaecology)	Female	Yes	Yes
12	Dr R Senthil Kumar	MD	Clinician (Endocrinology)	Male	Yes	Yes
13	Dr. S. Shanthakumari	MD	Pathology, Ethicist	Female	Yes	Yes
14	Dr. Sudha Ramalingam (Alternate Member-Secretary, IHEC)	MD	Public Health, Epidemiology, Genetics, Ethicist	Female	Yes	Yes
15	Mrs. Swasthika Soundararaj	MBA	Lay person	Female	No	Yes
16	Dr. D. Vijaya	M Sc, Ph D	Basic Medical Sciences (Biochemistry)	Female	Yes	Yes

The study is approved in its presented form. The decision was arrived at through consensus. Neither PI nor any of proposed study team members were present during the decision making of the IHEC. The IHEC functions in accordance with the ICH-GCP/ICMR/Schedule Y guidelines. The approval is valid until one year from the date of sanction. You may make a written request for renewal / extension of the validity, along with the submission of status report as decided by the IHEC.

Following points must be noted:

1. IHEC should be informed of the date of initiation of the study
2. Status report of the study should be submitted to the IHEC every 12 months
3. PI and other investigators should co-operate fully with IHEC, who will monitor the trial from time to time
4. At the time of PI's retirement/intention to leave the institute, study responsibility should be transferred to a colleague after obtaining clearance from HOD, Status report, including accounts details should be submitted to IHEC and extramural sponsors
5. In case of any new information or any SAE, which could affect any study, must be informed to IHEC and sponsors. The PI should report SAEs occurred for IHEC approved studies within 7 days of the occurrence of the SAE. If the SAE is 'Death', the IHEC Secretariat will receive the SAE reporting form within 24 hours of the occurrence
6. In the event of any protocol amendments, IHEC must be informed and the amendments should be highlighted in clear terms as follows:
    a. The exact alteration/amendment should be specified and indicated where the amendment occurred in the original project. (Page no. Clause no. etc.)
    b. Alteration in the budgetary status should be clearly indicated and the revised budget form should be submitted
    c. If the amendments require a change in the consent form, the copy of revised Consent Form should be submitted to Ethics Committee for approval
    d. If the amendment demands a re-look at the toxicity or side effects to patients, the same should be documented

PSG Institute of Medical Sciences & Research
Institutional Human Ethics Committee
Recognized by The Strategic Initiative for Developing Capacity in Ethical Review (SIDCER)
POST BOX NO. 1674, PEELAMEDU, COIMBATORE 641 004, TAMIL NADU, INDIA
Phone : 91 422 - 2598822, 2570170, Fax : 91 422 - 2594400, Email : ihec@psgimsr.ac.in

e. If there are any amendments in the trial design, these must be incorporated in the protocol, and other study documents. These revised documents should be submitted for approval of the IHEC and only then can they be implemented
f. Any deviation-Violation/waiver in the protocol must be informed to the IHEC within the stipulated period for review

7. Final report along with summary of findings and presentations/publications if any on closure of the study should be submitted to IHEC

Thanking You,

Yours Sincerely,

SECRETARY
PSG IMS&R
COIMBATORE-641004.

Dr D Vijaya
Member - Secretary
Institutional Human Ethics Committee

SOP 03-V 3.0 / ANX09-V 2.0

Institutional Human Ethics Committee
PSG Institute of Medical Sciences and Research, Coimbatore

Assent to be in a Research Study
For children between 7-18 years old

Why are we meeting with you?

We want to tell you about something we are doing called a research study. A research study is when doctors collect a lot of information to learn more about something related to health and disease. **Dr.Raaghul.C**and some other doctors are doing a study to learn more about gallbladder contractility. After we tell you about it, we will ask if you'd like to be in this study or not.

Why are we doing this study?

We want to find out, whether gallbladder contractility has any association in children with chronic abdominal pain
So we are getting information from lots of boys and girls like you.
In the whole study, there will be about **60** children.

What will happen to you if you are in this study?

Only if you agree, two things will happen:

1. Your child will undergo ultrasound abdomen after 6 hours of fasting and 60min following a fatty meal

2. You will need to answer some questions about your child's abdominal pain

Will this study hurt?

No this study doesn't hurt

Will you get better if you are in this study?
No, this study won't make you feel better or get well. But the doctors might find out something that will help other children like you later.

Will everybody come to know about my condition? (Confidentiality)
We will not tell other people that you are in this research and we won't share information about you to anyone who does not work in the research study

Is this bad or dangerous for me? (Risks involved)
No this test is not bad or dangerous

Will you tell me the results?
No the result will not be shared

Do you have any questions?

You can ask questions any time. You can ask now. You can ask later. You can talk to me or you can talk to someone else.

Do you have to be in this study?

No, you don't. No one will be mad at you if you don't want to do this. If you don't want to be in this study, just tell us. Or if you do want to be in the study, tell us that. And, remember, you can say yes now and change your mind later. It's up to you. *This will not affect in any way your future treatment in this hospital.*

Who can I talk to or ask questions to?

List and give contact information for those people who the child can contact easily (a local person who can actually be contacted). Tell the child that they can also talk to anyone they want to about this (their own doctor, a family friend, a teacher).

If you don't want to be in this study, just tell us. If you want to be in this study, just tell us. This will not affect in any way your future treatment in this hospital.
The doctor will give you a copy of this form to keep.

SIGNATURE OF PERSON CONDUCTING ASSENT DISCUSSION

I have explained the study to _____(*print name of child here*) in language he/she can understand, and the child has agreed to be in the study.

_____ _____

Signature of Person Conducting Assent Discussion Date

_____

Name of Person Conducting Assent Discussion (*print*)

Part 2: Certificate of Assent

I have read this information (or had the information read to me) I have had my questions answered and know that I can ask questions later if I have them.

I agree to take part in the research.

OR

I do not wish to take part in the research and I have not signed the assent below._____ (initialed by child/minor)

Only if child assents:
Print name of child _____
Signature of child: _____
Date:_____
day/month/year

If illiterate:
A literate witness must sign. Participants who are illiterate should include their thumb print as well.

I have witnessed the accurate reading of the assent form to the child, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

*Name of witness (not a parent)*_____ *AND Thumb print of participant*
Signature of witness _____
Date _____
Day/month/year

I have accurately read or witnessed the accurate reading of the assent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given assent freely.

Name of researcher: **DR.RAAGHUL.C**

**Modified from the Informed Assent form template for children/minors –World Health organization*

PSG Institute of Medical Science and Research, Coimbatore
Institutional Human Ethics Committee
INFORMED CONSENT FORMAT FOR RESEARCH PROJECTS

I **DR.RAAGHUL.C**, am carrying out a study on the topic: **GALLBLADDER CONTRACTILITY IN CHILDREN WITH CHRONIC ABDOMINAL PAIN** as part of my research project being carried out under the aegis of the Department of: **PAEDIATRICSPSGIMSR**

My research guide is: **DR.JOHNMATTHAIMBBSDCH MD PAED. GASTROENTROLOGIST (FELLOWSHIP)**

The justification for this study is: Chronic abdominal pain affects the quality of life in children and identifying gallbladder contractility association in these children by non-invasive technique will help in management of improving their quality of life

The objectives of this study are:

Primary Objective: To assess gallbladder contractility in children with chronic abdominal pain

Secondary Objective: To assess the association between gallbladder contractility and severity, duration of abdominal pain and association of gastro intestinal complaints like dyspepsia, irritable bowel syndrome etc.

Sample size: 60

Study volunteers / participants are (specify population group & age group): children aged 5 to 15years with chronic abdominal pain

Location: Department of PaediatricPSGIMSR Coimbatore 641004.

We request you to kindly cooperate with us in this study. We propose collect background information and other relevant details related to this study. We will be carrying out:

Questionnaire – 20minutes

Radiological Examination: Ultrasound abdomen will be done after 6hours of fasting. Following which child will be fed with fatty meal and repeat ultrasound abdomen at 60 minutes.

No. of times it will be done: Twice

Whether ultrasound abdomen is part of routine procedure or for research (study) purpose:

1. Routine procedure✓ 2. Research purpose ✓

Specify purpose, discomfort likely to be felt and side effects: child may have some physical discomfort during examination.

Data collected will be stored for a period of 5 years. We will not use the data as part of another study.

Benefits from this study: The relation between gallbladder dysfunction and abdominal pain will be found

Risks involved by participating in this study: nil

How the **results** will be used: from the study gallbladder dysfunction and abdominal pain caused by it can be prevented by correcting gallbladder dysfunction

If you are uncomfortable in answering any of our questions during the course of the interview / biological sample collection, **you have the right to withdraw from the interview / study at anytime.** You have the freedom to withdraw from the study at any point of time. Kindly be assured that your refusal to participate or withdrawal at any stage, if you so decide, will not result in any form of compromise or discrimination in the services offered nor would it attract any penalty. You will continue to have access to the regular services offered to a patient. You will **NOT** be paid any remuneration for the time you spend with us for this interview / study. The information provided by you will be kept in strict confidence. Under no circumstances shall we reveal the identity of the respondent or their families to anyone. The information that we collect shall be used for

approved research purposes only. You will be informed about any significant new findings - including adverse events, if any, – whether directly related to you or to other participants of this study, developed during the course of this research which may relate to your willingness to continue participation.

Consent: The above information regarding the study, has been read by me/ read to me, and has been explained to me by the investigator/s. Having understood the same, I hereby give my consent to them to interview me. I am affixing my signature / left thumb impression to indicate my consent and willingness to participate in this study (i.e., willingly abide by the project requirements).

Signature / Left thumb impression of the Study Volunteer / Legal Representative:

Signature of the Interviewer with date:

Witness:

Contact number of PI: 9952665177

Contact number of Ethics Committee Office: During Office hours: 0422 2570170 Extn.: 5818

After Office hours: 9865561463

SOP 03-V 3.0 / ANX10-V 3.0

Institutional Human Ethics Committee
PSG Institute of Medical Sciences and Research, Coimbatore

Parental Consent Form

Title of Study: Gallbladder contractility in children with chronic abdominal pain

Name of the Principal Investigator:Dr.Raaghul.C

Department:

Your (son/daughter/child/infant/adolescent youth) is invited to participate in a study of (describe the study).

My name is **Dr.Raaghul.C**and I am a junior resident at PSG Institute of Medical Sciences and Research, Coimbatore. This study is (state how study relates to your program of work or your supervisor's program of work).

I am asking for permission to include your (son/daughter/child/infant/adolescent youth) in this study because

I expect to have **60** (Number) participants in the study.
If you allow your child to participate, (state who will actually conduct the research) will (describe the procedures to be followed.)

Any information that is obtained in connection with this study and that can be identified with your (son/daughter/child/infant/adolescent youth) will remain confidential and will be disclosed only with your permission. His or her responses will not be linked to his or her name or your name in any written or verbal report of this research project.

Your decision to allow your (son/daughter/child/infant/adolescent youth) to participate will not affect your or his or her present or future relationship with PSGIMS&R or PSGHospitals or (include the name of any other institution connected with this project). If you have any questions about the study, please ask me. If you have any questions later, call me at 09952665177. If you have any questions or concerns about your (son/daughter/child/infant/adolescent youth)'s participation in this study, call……..

You may keep a copy of this consent form.
You are making a decision about allowing your (son/daughter/child/infant/adolescent youth) to participate in this study. Your signature below indicates that you have read the information provided above and have decided to allow him or her to participate in the study. If you later decide that you wish to withdraw your permission for your (son/daughter/child/infant/adolescent youth) to participate in the study, simply tell me.

You may discontinue his or her participation at any time. *This will not affect in any way your future treatment in this hospital.*

Printed Name of (son/daughter/child/infant/adolescent youth)

Signature of Parent(s) or Legal Guardian with Date Signature of Investigator with Date

ஒப்புதல் படிவம்

தேதி :

---------- ஆகிய நான், **PSG** மருத்துவக் கல்லூரியின் ---------- துறையின் கீழ், ----------
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---------- என்ற தலைப்பில் ஆய்வு மேற்கொள்ள உள்ளேன்.

என் ஆய்வு வழிகாட்டி:

ஆய்வு மேற்கொள்வதற்கான அடிப்படை:

ஆய்வின் நோக்கம்:

ஆய்வில் பங்கு பெறும் நபர்களின் எண்ணிக்கை:

ஆய்வு மேற்கொள்ளும் இடம்:

ஆய்வின் பலன்கள்:

ஆய்வினால் ஏற்படும் அசௌகரியங்கள் / பக்க விளைவுகள்:

இந்த ஆய்வில் கிடைக்கும் தகவல்கள் ---------- வருடங்கள் பாதுகாக்கப்படும். இவை வேறு எந்த ஆய்விற்கும் பயன்படுத்தப் பட மாட்டாது. எந்த நிலையிலும் உங்களைப் பற்றிய தகவல்கள் யாருக்கும் தெரிவிக்கப்பட மாட்டாது. அவை இரகசியமாக வைக்கப்படும்.

இந்த ஆய்வில் பங்கேற்க ஒப்புக்கொள்ளுவதால் எந்த விதமான பலனும் உங்களுக்குக் கிடைக்காது. எந்த நேரத்தில் வேண்டுமானாலும் ஆய்விலிருந்து விலகிக்கொள்ளும் உரிமை உங்களுக்கு உண்டு. ஆய்விலிருந்து விலகிக்கொள்வதால் உங்களுக்கு அளிக்கப்படும் சிகிச்சையில் எந்த வித மாற்றமும் இருக்காது.

இந்த ஆராய்ச்சிக்காக உங்களிடம் சில கேள்விகள் கேட்கப்படும் / சில இரத்த மாதிரிகள் அல்லது திசு மாதிரிகள் எடுக்கப்படும்.

மேலும், இந்த ஆய்வில் பங்கு கொள்வது உங்கள் சொந்த விருப்பம். இதில் எந்த விதக் கட்டாயமும் இல்லை. நீங்கள் விருப்பப் பட்டால், இந்த ஆய்வின் முடிவுகள் உங்களுக்குத் தெரியப் படுத்தப்படும்.

ஆய்வாளரின் கையொப்பம் :
தேதி :

<u>ஆய்வுக்குட்படுபவரின் ஒப்புதல்:</u>

நான் இந்த ஆராய்ச்சியின் நோக்கம் மற்றும் அதன் பயன்பாட்டினைப் பற்றி தெளிவாகவும், விளக்கமாகவும் தெரியப்படுத்தப் பட்டுள்ளேன். இந்த ஆராய்ச்சியில் பங்கு கொள்ளவும், இந்த ஆராய்ச்சியின் மருத்துவ ரீதியான குறிப்புகளை வரும் காலத்திலும் உபயோகப்படுத்திக் கொள்ளவும் முழு மனதுடன் சம்மதிக்கிறேன்.

ஆய்வுக்குட்படுபவரின் பெயர், முகவரி :

கையொப்பம் :
தேதி :

ஆய்வாளரின் தொலைபேசி எண்:

மனித நெறிமுறைக் குழு அலுவலகத்தின் தொலைபேசி எண்: 0422 2570170 Extn.: 5818

PROFORMA

Name: Age: Sex:

IP number: OP number:

1. History of any abdominal surgery (YES)/ (NO)

   If yes then specify ……..

2. Previously diagnosed chronic abdominal pathology (YES)/(NO)

   If yes then specify……

3. Does your child have upper abdominal pain or discomfort "Several times a week" or more often (YES) / (NO)

4. Is the duration of upper abdominal pain or discomfort is "2 months" or longer (YES)/(NO)

5. Pain exclusively relieved with defecation ("sometimes" or less often) (YES)/(NO)

6. Periumbilical/lower abdominal pain/discomfort "once a week" or more often (YES)/(NO)

7. Duration of Periumbilical/lower abdominal pain/discomfort is "2 months" or longer (YES)/(NO)

8. Pain associated with change in bowel movement form: softer or harder (YES)/(NO)

9. Pain associated with change in bowel movement frequency: more or fewer (YES)/(NO)

10. In the past year, 2 or more episodes of severe pain lasting 1 hour or longer and causing restriction in daily activities

(YES)/(NO)

11. Two or more of the following in past 2 years when child has abdominal pain

a. No appetite b. Nausea c. Vomiting

d. Pale skin e. Headache f. Eyes sensitive to light

12. Symptom-free periods between pain episodes (YES)/(NO)

13. EITHER Two or more other somatic symptoms “once a week” or more often

A. Headache B. Difficulty sleeping

C. Pain in arms, legs, or back D. Faint or dizzy

OR

14. Misses activities “once in a while” or more often

(YES)/(NO)

Gallbladder Contractility Data Collection Form

Name:Age:Sex:

IP No: OP No:

During ultrasound, the greatest length (L), greatest transverse width (W), and greatest anteroposterior diameter (A) of the gallbladder were measured. The series gallbladder volumes were calculated by the following Dodd's Formula

Gallbladder Volume (V) = 0.52 x L x W x A

	Fasting State	Post Prandial (60min after fatty meal)
Greatest length **L**		
Greatest transverse width **W**		
Greatest anteroposterior diameter **A**		
Volume	V_O =	V_n =

Where V_O = gallbladder volume before the test meal,

Vn = gallbladder volumes 30min after the test meal

Gallbladder EF (Ejection Fraction) (%) = $[(V_o - V_n) / V_o] \times 100\%$

ROME III CRITERIA FOR FUNCTIONAL GASTRO INTESTINAL DISORDER IN CHILDREN

H2. ABDOMINAL PAIN-RELATED FUNCTIONAL GI DISORDERS

H2a. Functional Dyspepsia

*Diagnostic criteria** *Must include **all** of the following:*

1. Persistent or recurrent pain or discomfort centered in the upper abdomen (above the umbilicus)
2. Not relieved by defecation or associated with the onset of a change in stool frequency or stool form (i.e., not irritable bowel syndrome)
3. No evidence of an inflammatory, anatomic, metabolic or neoplastic process that explains the subject's symptoms

* Criteria fulfilled at least once per week for at least 2 months prior to diagnosis

H2b. Irritable Bowel Syndrome

*Diagnostic criteria** *Must include **both** of the following:*

1. Abdominal discomfort** or pain associated with *two or more* of the following at least 25% of the time:
   a. Improvement with defecation
   b. Onset associated with a change in frequency of stool
   c. Onset associated with a change in form (appearance) of stool
2. No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject's symptoms

* Criteria fulfilled at least once per week for at least 2 months prior to diagnosis

** "Discomfort" means an uncomfortable sensation not described as pain.

H2c. Abdominal Migraine

*Diagnostic criteria** *Must include **all** of the following:*

1. Paroxysmal episodes of intense, acute periumbilical pain that lasts for 1 hour or more
2. Intervening periods of usual health lasting weeks to months
3. The pain interferes with normal activities
4. The pain is associated with 2 of the following:
   a. Anorexia
   b. Nausea
   c. Vomiting
   d. Headache
   e. Photophobia
   f. Pallor
5. No evidence of an inflammatory, anatomic, metabolic, or neoplastic process considered that explains the subject's symptoms

* Criteria fulfilled two or more times in the preceding 12 months

H2d. Childhood Functional Abdominal Pain

*Diagnostic criteria** *Must include **all** of the following:*

1. Episodic or continuous abdominal pain
2. Insufficient criteria for other FGIDs
3. No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject's symptoms

* Criteria fulfilled at least once per week for at least 2 months prior to diagnosis

H2d1. Childhood Functional Abdominal Pain Syndrome

*Diagnostic criteria** *Must satisfy criteria for childhood functional abdominal pain and have at least 25% of the time **one or more** of the following:*

1. Some loss of daily functioning
2. Additional somatic symptoms such as headache, limb pain, or difficulty sleeping

* Criteria fulfilled at least once per week for at least 2 months prior to diagnosis

LIST OF ABBREVIATIONS

RAP	–	Recurrent Abdominal Pain
CCK	–	Cholecystokinin
VIP	–	Vasoactive Intestinal Peptide
GB	-	Gallbladder
USG	–	Ultrasonography
IBS	–	Irritable Bowel Syndrome
SO	-	Sphincter of Oddi
ENS	–	Enteric Nervous System
CNS	–	Central Nervous System
TCA	-	Tricyclic Antidepressants
SSRIs	-	Selective Serotonin Reuptake Inhibitors

MASTER CHART

Sl.No.	AGE	Sex	ABDSUR	CHABDPATH	ABDP	UPABDP	UMABDP	DUR	RELDEF	CHANGEFREQ	CHANGPAIN	>2EPI	NOSYM	ACTMISS	FGBVOL	PPGBVOL	EF
1	5 .5	2	2	2	1	2	1	1	2	2	2	1	1	1	6.58	2.9	55
2	10	1	2	2	1	1	2	1	2	2	2	2	1	2	3.5	2.5	28
3	13	2	2	2	1	1	2	1	2	1	1	2	1	1	5.1	2.74	46
4	11	1	2	2	1	1	2	1	2	2	1	1	1	1	10.5	3.9	62
5	11	1	2	2	1	2	1	1	2	2	2	1	1	1	8.9	2.9	67
6	6	2	2	2	1	2	1	1	2	2	2	2	1	2	11.9	2.2	81
7	15	1	2	2	1	1	2	1	2	2	2	2	1	2	8.75	4.5	48
8	6 .5	1	2	2	1	2	1	1	2	2	2	2	1	2	9.38	4.99	46
9	10	1	2	2	1	2	1	1	1	2	2	2	1	2	9	2.5	72
10	7	2	2	2	1	1	2	1	2	2	2	2	1	1	8.7	2.3	73
11	9	2	2	2	1	2	1	1	1	2	2	1	1	2	16.1	3.2	80
12	11	2	2	2	1	2	1	1	1	2	2	2	1	2	4	2.2	45
13	5	2	2	2	1	1	2	1	2	2	2	2	1	2	3.69	1.97	47
14	8	2	2	2	1	1	2	1	2	2	2	2	1	2	5.2	4.2	21
15	9	2	2	2	1	1	2	1	2	2	2	2	1	2	9.36	7.03	24
16	11	1	2	2	1	1	2	1	2	2	2	2	1	2	6	2.6	52
17	9	2	2	2	1	2	1	1	2	2	2	2	1	2	4.7	1.7	63
18	13	2	2	2	1	2	1	1	2	2	2	2	1	2	7.1	2.1	70
19	11	1	2	2	1	2	1	1	2	2	2	2	1	1	10.4	3.9	62.5
20	15	2	2	2	1	1	2	1	2	2	2	2	1	2	13.7	8.7	36
21	13	1	2	2	1	2	1	1	2	2	2	2	1	1	7.41	4.25	42
22	13	1	2	2	1	2	1	1	2	2	2	2	1	2	18.6	5.02	73
23	9	2	2	2	1	2	1	1	2	2	2	2	1	2	16.8	3	82
24	6 .5	2	2	2	1	2	1	1	1	2	2	2	1	1	5	3.2	36
25	7	2	2	2	1	2	1	1	1	2	2	2	1	2	3.9	2.3	41
26	12	1	2	2	1	1	2	1	2	2	2	1	1	1	7	5.4	22
27	13	2	2	2	1	2	2	2	2	2	2	2	2	2	7	2.5	64
28	8	2	2	2	1	2	1	1	1	2	2	2	1	2	3.9	2.4	38
29	5 .5	2	2	2	1	2	1	1	1	2	2	2	1	1	8	4.5	45
30	6	2	2	2	1	2	1	1	2	2	2	2	1	2	6.1	3.8	37
31	9	1	2	2	2	2	2	2	2	2	2	2	2	2	2.02	1.9	4
32	13	2	2	2	2	2	2	2	2	2	2	2	2	2	6.4	1.9	70
33	11	2	2	2	2	2	2	2	2	2	2	2	2	2	4.4	0.15	96
34	13	2	2	2	2	2	2	2	2	2	2	2	2	2	0.72	0.69	4
35	12	2	2	2	2	2	2	2	2	2	2	2	2	2	2.7	0.4	85
36	13	2	2	2	2	2	2	2	2	2	2	2	2	2	8.3	2.2	73
37	13	2	2	2	2	2	2	2	2	2	2	2	2	2	12.6	1.8	85
38	11	2	2	2	2	2	2	2	2	2	2	2	2	2	8.3	1.8	78
39	13	2	2	2	2	2	2	2	2	2	2	2	2	2	11.9	3.8	68
40	13	2	2	2	2	2	2	2	2	2	2	2	2	2	6.7	1.5	77
41	13	2	2	2	2	2	2	2	2	2	2	2	2	2	7.6	1.7	77
42	14	1	2	2	2	2	2	2	2	2	2	2	2	2	4.9	1.9	61

43	14	1	2	2	2	2	2	2	2	2	2	2	2	2	4.95	3.3	32
44	14	1	2	2	2	2	2	2	2	2	2	2	2	2	3.04	2.2	27
45	11	2	2	2	2	2	2	2	2	2	2	2	2	2	4.78	3.1	35
46	14	1	2	2	2	2	2	2	2	2	2	2	2	2	6.9	1.9	72
47	14	1	2	2	2	2	2	2	2	2	2	2	2	2	3.5	1.7	51
48	7	1	2	2	2	2	2	2	2	2	2	2	2	2	5.8	1.04	82
49	12	1	2	2	2	2	2	2	2	2	2	2	2	2	6.8	1.9	72
50	9	2	2	2	1	2	1	2	2	2	2	2	1	2	12.37	6.73	45
51	9	2	2	2	2	2	2	2	2	2	2	2	2	2	6.75	3.97	41
52	8	1	2	2	2	2	2	2	2	2	2	2	2	2	11.22	5.3	52.7
53	13	1	2	2	2	2	2	2	2	2	2	2	2	2	5.84	3.97	32
54	8	1	2	2	2	2	2	2	2	2	2	2	2	2	10	3.58	64.2
55	11	1	2	2	2	2	2	2	2	2	2	2	2	2	9.28	3.49	62.3
56	11	1	2	2	2	2	2	2	2	2	2	2	2	2	12.2	4	67
57	9	1	2	2	2	2	2	2	2	2	2	2	2	2	7.79	5.41	30.5
58	12	1	2	2	2	2	2	2	2	2	2	2	2	2	9.48	2.97	68.6
59	12	1	2	2	2	2	2	2	2	2	2	2	2	2	8.76	3.24	63
60	12	1	2	2	2	2	2	2	2	2	2	2	2	2	7.59	5.17	31.8
61	10	1	2	2	2	2	2	2	2	2	2	2	2	2	7.95	3.12	60.7
62	11	1	2	2	2	2	2	2	2	2	2	2	2	2	7.22	2.6	63.9
63	9	1	2	2	2	2	2	2	2	2	2	2	2	2	12.01	3.24	73
64	10	1	2	2	2	2	2	2	2	2	2	2	2	2	7.74	6.33	18.2
65	13	1	2	2	2	2	2	2	2	2	2	2	2	2	10.83	4.96	54.2
66	12	1	2	2	2	2	2	2	2	2	2	2	2	2	11.56	2.74	76.2