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MINIREVIEWS

Monitoring inflammatory bowel disease during pregnancy: Current literature and future challenges

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Abstract

Inflammatory bowel disease has a high prevalence in women of childbearing age and can have a significant impact on pregnancy, from conceiving to carrying the pregnancy. Active disease during pregnancy is known to have negative effects on pregnancy outcomes; therefore, careful monitoring during this period is an important but challenging aspect of care and is crucial as it affects important management decisions. Recent data seems to suggest that endoscopy is a relatively safe procedure during all trimesters of pregnancy. Serum biomarkers such as C-reactive protein and fecal calprotectin are helpful non-invasive markers, but have shown conflicting results for correlation with disease activity in some initial studies. Further work is necessary to establish standard of care monitoring during pregnancy.

Key words: Inflammatory bowel disease; Crohn's disease; Ulcerative colitis; Pregnancy; Fecal calprotectin

Core tip: This review article fills in the gap in the paucity of literature specifically focusing on the monitoring of inflammatory bowel disease during pregnancy. New and emerging literature on the use of non-invasive biomarkers such as fecal calprotectin is discussed, but classic monitoring techniques such as endoscopy and radiographic imaging are also evaluated within the scope of pregnancy.

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INTRODUCTION

Inflammatory bowel disease (IBD) has a high prevalence in young adults and affects many women of childbearing age. Having IBD has many effects on women who are contemplating having children, ranging from conceiving to carrying the pregnancy, concerns about passing the disease onto children, fetal outcomes, and effects of pregnancy on the disease process itself.

Many women with IBD have poor knowledge about their ability to bear children or the effect that IBD will have on their pregnancy, with a tendency to overestimate the effects of IBD on fertility[1,2]. This has led to the phenomenon of voluntary childlessness, which affects up to 18% of women with IBD as compared to 6% in the general population. Women with IBD have misconceptions about a decreased rate of fertility, fear of passing on the condition onto offspring, and concerns over the effects of the disease on pregnancy outcomes[3]. In fact, multiple studies have shown that overall rates of fertility between the general population and women with IBD in clinical remission are comparable[4]. However, this trend excludes women who had pelvic surgical procedures, and in particular ileal pouch-anal anastomosis (IPAA) procedures for ulcerative colitis (UC), which have a relative risk of infertility of 3.91 as compared to the general population[5].

Most women who have a quiescent disease before pregnancy have normal pregnancy outcomes. However, active disease upon conception or during pregnancy has been shown to increase adverse outcomes such as low birth weight, preterm birth, and fetal loss[6]. In a recent retrospective study following 406 pregnant Indian IBD patients, pregnancies after disease onset were associated with higher number of adverse fetal outcomes and cesarean sections compared to before disease onset[7] . Similarly, a study from Denmark sought to evaluate birth outcomes with a cohort of women on anti-TNF therapy during pregnancy. Disease activity was associated with adjusted odds ratio of 2.05 for low birth weight and 2.64 for preterm birth, with the ratio for preterm birth increasing to 3.60 for patients with clinical moderate to severe disease activity[8]. In addition to disease activity, inadequate gestational weight gain in the IBD population has been shown to have a 2-fold increase in risk of low gestational weight compared with non-IBD patients with inadequate gestational weight gain in a Norwegian cohort study[9]. This finding has been reproduced in a prospective American cohort study for Crohn's disease, but not for ulcerative colitis[10].

Given the adverse effects of active IBD and associated effects on pregnancy outcomes, careful monitoring during this period is an important but challenging aspect of care. Ideally, disease activity should be objectively assessed prior to pregnancy as a part of conception planning. Endoscopy showing histological mucosal healing is an important predictor of clinical outcomes. This is particularly important since the correlation of clinical symptoms and histologic disease can be weak, especially in Crohn's disease. Therefore, having an objective assessment of disease activity during pregnancy is crucial as this directly affects important management decisions, such as medication changes, in order to keep the pregnant patient in remission through the prenatal course.

To this end, the purpose of our review paper is to discuss the current landscape of research on the safety, efficacy and utility of various methods of monitoring IBD activity during pregnancy (Table 1).

LOWER ENDOSCOPY

Endoscopy is the most definitive method of monitoring and evaluating disease activity. However, endoscopic procedures have been theorized to pose a threat to the fetus through the possibility of intra-procedural maternal hypoxia and hypotension, which can cause fetal hypoxia and potential demise[11]. Additionally, sedating medications, prolonged procedure times, and maternal positioning during endoscopy can potentially have significant effects on maternal circulation. Here, we have categorized lower endoscopy into colonoscopy and flexible sigmoidoscopy due to their separate risks and benefits.

Colonoscopy

Colonoscopy may be indicated in a pregnancy state, to evaluate the extent of ulcerative colitis that may determine the need for additional immunosuppressive agents or in small bowel Crohn's disease. A systematic review of lower gastrointestinal endoscopies performed in all three trimesters of pregnancy evaluated any adverse pregnancy outcomes that were noted to be in a temporal or etiological relation with the procedure[12]. This review comprised of 100 endoscopies, with a total of six reported adverse events that were related to the procedure. The authors concluded that colonoscopy is not only a low-risk procedure during pregnancy, but also that there were no significant changes in adverse events between the three trimesters. Furthermore, a prospective study done by de Lima *et al*[13] compared 42 pregnant IBD patients who underwent lower endoscopy (13 colonoscopies and 33 sigmoidoscopies) with case-matched pregnant IBD patients who did not undergo endoscopy. The adverse events were two spontaneous abortions, which were likely related to the endoscopic procedure; however, this was not a statistically significant difference when compared to the control group. There remains a gap of literature on safety of endoscopy in pregnant patients; but early studies appear

Table 1 Overview of various disease monitoring modalities and their pros/cons in pregnant inflammatory bowel disease patients

Monitoring modality	Pros	Cons
Lower endoscopy		
Colonoscopy	Gold standard of disease monitoring	Limited studies
	Early studies show no difference in adverse events between pregnant IBD patients who underwent colonoscopy and who did not undergo colonoscopy	Provider/patient hesitancy due to procedural and anesthetic concerns
Flexible sigmoidoscopy	Can be performed without sedation	Limited studies
	No case reports of any procedure-related complications	
Radiologic studies		
Ultrasound	Safest form of radiologic imaging	Sensitivity in pregnancy unknown
	Contrast-enhanced ultrasound shown to have good results in IBD	
Magnetic resonance imaging	No use of damaging ionizing radiation	Currently no well-controlled studies of the teratogenic effects of gadolinium contrast in pregnant women have been performed and the fetal risk is unknown
	Can detect luminal and extraluminal abnormalities	
	Long-term safety after exposure to MRI trimester of pregnancy showed no increased risk of harm to the fetus or in early childhood	
Biomarkers		
Albumin	Low albumin shown to be predictor of poor outcomes in IBD	Limited utility in pregnancy due to pregnancy-induced hemodilution resulting in lower albumin values
ESR	Generally a good marker of inflammation and reflects disease activity	Limited utility in pregnancy due to physiologic increase in ESR (2-3 x upper limit of normal)
CRP	Levels are only slightly raised in normal pregnancy and are still under the normal limits	May not accurately reflect disease activity in second and third trimester
	CRP higher in clinically active pregnant IBD patients at preconception and first trimester compared to clinically inactive pregnant IBD patients	Limited studies in pregnant IBD population
FCP	Measure of GI mucosal inflammatory activity detected prior to signs of systemic inflammation	Conflicting evidence for utility of FCP in IBD during pregnancy
	Multiple studies showing correlation between FCP levels and non-invasive disease activity scores in CD and UC	Limited studies with actual endoscopic data to evaluate clinical activity

IBD: Inflammatory bowel disease; CD: Crohn's disease; MRI: Magnetic resonance imaging; UC: Ulcerative colitis; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; FCP: Fecal calprotectin.

to suggest that endoscopy when necessary is shown to be a low-risk and safe procedure in any trimester.

Flexible sigmoidoscopy

Unsedated flexible sigmoidoscopy is an alternative approach to evaluate the rectum and left colon, thereby avoiding the risks of anesthesia. It plays an important role in determining the severity of mucosal disease in patients with refractory colitis and to evaluate concomitant infections. Based on reviews of retrospective studies and case series, it seems that performing an unsedated flexible sigmoidoscopy in a pregnant woman is quite safe[14]. None of the studies or case reports indicated any procedure-related complications to either the mother or fetus. In addition, the timing of the procedure did not seem to matter given that sigmoidoscopies were safely performed during all three trimesters.

Safety of anesthetics and colon cleansing agents

According to a joint statement from the American Society of Anesthesiologists and the American College of Obstetrics and Gynecology, none of the currently used anesthetic agents, when used in standard concentrations at any gestational age, have been shown to have any teratogenic effect in humans. There is currently an insufficient amount of data on the safety of colon cleansing agents in the pregnant population. Polyethylene glycol electrolyte isotonic cathartic solutions have not been studied in pregnancy, and are classified as pregnancy category C. Sodium phosphate preparations (category C) may cause fluid and electrolyte abnormalities and should be used with caution. Tap water enemas may be sufficient for flexible sigmoidoscopy in a pregnant patient.

RADIOLOGIC STUDIES

In general, imaging with non-ionizing radiation is preferred over modalities with ionizing radiation in pregnancy. In utero radiation exposure to a developing fetus includes intrauterine growth restriction, microsomia, mental retardation, organ malformation, and childhood cancers. These risks are dependent on the gestational age at the time of exposure and the absorbed radiation dose levels. Traditionally, abdominal plain films and computed tomography (CT) scans are avoided due to their high levels of ionizing radiation. However, consensus statements from the American College of Obstetricians and Gynecologists, American College of Radiology, and International Commission on Radiological Protection have

all concluded that radiation doses less than 50 mGy are shown to have negligible risk to the fetus. Therefore, most properly done diagnostic procedures do not present a measurably increased risk to the fetus and should be performed in cases of diagnostic necessity[15].

Ultrasound

Ultrasound is the safest form of radiologic imaging in pregnancy; it can be used to assess abscess formation along with the location and length of the affected segment of bowel. More recently, contrast enhanced ultrasound has been studied in inflammatory bowel disease with good results. It is an emerging technique to evaluate disease activity, the differentiation between small bowel stricture due to inflammation or mural fibrosis, and for the assessment of response to specific therapies[16]. Its sensitivity in pregnancy needs to be investigated.

Magnetic resonance imaging

The principal advantage of MRI over ultrasonography and CT scan is the ability to image deep soft tissue structures in a manner that is less operator dependent and does not use ionizing radiation. As per the guidelines from the American College of Obstetrics and Gynecologists, there are no precautions or contraindications for MRI specific to the pregnant woman[17]. It is being used now in routine obstetric care. MRI has been used to diagnose terminal ileal CD during pregnancy[18].

Use of gadolinium based contrasts agents (GBCA) in MRI during pregnancy: To date, there have been no known adverse effects to human fetuses reported when clinically recommended dosages of GBCA have been given to pregnant women. A single prospective cohort study of 26 women exposed to gadolinium chelates during the first trimester of pregnancy showed no evidence of teratogenesis or mutagenesis in their progeny[19].

There are no known cases of nephrogenic systemic fibrosis associated to the use of GBCAs in pregnant patients. However, gadolinium chelates may accumulate in the amniotic fluid which has the potential for the dissociation of the toxic free gadolinium ion. This is swallowed by the fetus and enters the fetal circulation possibly conferring risk to the fetus. Currently no well-controlled studies of the teratogenic effects of these media in pregnant women have been performed and the fetal risk is unknown.

Both the American College of Radiology and the American College of Obstetrics and Gynecology conclude that gadolinium contrast with MRI should be used with caution; it may be used as a contrast agent in a pregnant woman only if it significantly improves diagnostic performance and is expected to improve fetal or maternal outcome, outweighing the possible but unknown risk of fetal exposure to free gadolinium ions. Lowest possible dose should be used to achieve diagnostic results. Contrast enhanced MRI may be useful to evaluate for abscess or fistulas.

Abdominal X ray

Traditionally X-rays are avoided in pregnancy due to fear of fetal risks from ionizing radiation. The maximal risk attributed to a 1-rad exposure, approximately 0.003%, is thousands of times smaller than the spontaneous risks of malformations, abortion, or genetic disease[20]. One abdominal X ray results in fetal exposure to radiation to 0.1 rad[21]. Therefore, in diagnosis of toxic megacolon, the risks to the fetus of an abdominal X-ray (1 in 30000) compared to the condition being poorly managed (60% fetal mortality rate) indicate that the patient should be imaged as would a non-pregnant patient. In conclusion, in cases of emergent situation or when other modalities are not available, an abdominal X ray would prove to be an important test.

BIOMARKERS

Serum and fecal biomarkers play an important role in non-invasive monitoring of the disease activity in IBD patients.

Albumin

Albumin is routinely used to assess overall disease activity state and its impact on the body. Patients with active disease may lose protein/albumin from the inflamed mucosa. Low albumin has shown to be a predictor of poor outcomes in inflammatory bowel disease. However, there are normal physiological changes in some laboratory parameters in pregnancy that should not be attributed to disease activity. Pregnancy causes hemodilution, resulting in fall in albumin by about 1 mg/dL by the end of 1st trimester. Hence, albumin of 2 mg/L during the third trimester in a patient with baseline albumin of 3 mg/L may not reflect worsening disease activity.

Erythrocyte sedimentation rate

Erythrocyte sedimentation rate (ESR) is a marker of inflammation and reflects disease activity. Pregnancy causes a physiological increase in ESR from increase fibrinogen levels. The increase is about 2 to 3 times upper limit of normal by the first trimester. Hence an elevated ESR of 40 mm/h may reflect normal health in a third trimester pregnancy female. Thus, ESR values merit careful interpretation in evaluation of the disease activity in pregnant state.

C-reactive protein

C-reactive protein (CRP) is another marker of inflammation and reflects disease activity. Its levels are usually unaltered or possibly only slightly raised in normal pregnancy compared to a non-pregnant state, however the levels are still under the normal limits[22]. In a prospective study, Bal *et al*[23] evaluated the association of elevated CRP with clinical disease activity during pregnancy among women with IBD. The median CRP was numerically higher in women with clinically active disease

compared to those with clinically inactive disease at preconception (6.95 *vs* 2.80 mg/L, *P* = 0.559) and first trimester (24.75 *vs* 6.00 mg/L, *P* = 1.000), respectively. However, surprisingly the median CRP was lower in women with clinically active disease compared to those with clinically inactive disease at second trimester (8.85 *vs* 12.40 mg/L, *P* = 0.5923), and third trimester (5.45 *vs* 11.90 mg/L, *P* = 0.592), respectively. Their study shows that CRP remains a potential tool for assessing IBD disease activity in the early trimesters of pregnancy; however, it may not accurately reflect the disease activity in later trimesters. It is possible that in their study, concomitant minor infections in later trimesters might have increased CRP in healthy pregnancy patients with silent IBD. More research is needed to clearly identify the response of CRP in pregnancy state with IBD. At present, most physicians consider CRP as a useful tool in monitoring disease activity during pregnancy.

Fecal calprotectin

Among various different biological markers, fecal calprotectin (FCP) has emerged as the most superior marker to diagnose or monitor inflammatory bowel disease. Calprotectin is a heterodimer of two S100 proteins (S100A8 and S100A9), which are a family of calcium-binding proteins that are linked to innate immune functions through their expression in macrophages, monocytes, phagocytes, and granulocytes[24]. These proteins are released during periods of inflammation from gastrointestinal epithelial cells. Therefore, fecal calprotectin can be used as a measure of gastrointestinal mucosal inflammatory activity that is detected prior to signs of systemic inflammation, such as elevations in CRP or ESR[25].

Elevation of fecal calprotectin concentrations is shown to predict disease relapse in the next 12 mo in IBD, although this association is stronger in UC than in CD[26,27]. A recent prospective study showed that fecal calprotectin level below 50 ug/g is predictive of histologic remission in quiescent UC[28]. While there are a multitude of studies that have successfully shown the use of fecal calprotectin in monitoring IBD, its utility in pregnancy has not been fully elucidated yet.

Does pregnancy affect FCP levels?

To evaluate the utility of FCP as marker for active IBD disease during pregnancy, the effects of normal pregnancy on FCP need to be established. A recent prospective study involving 135 patients compared the concentrations of FCP in healthy non-pregnant and pregnant women and in patients with inflammatory bowel disease[29]. Stool samples were taken during each trimester, and there were no significant difference ($P < 0.092$) between FCP concentrations during each trimester. The mean FCP concentration between pregnant and non-pregnant health women showed no statistically significant difference, suggesting that pregnancy itself does not cause an elevation in FCP markers. While the FCP concentrations between patients with IBD and healthy controls were statistically different, no pregnant patients with IBD were included in this study; therefore, it is difficult to draw a conclusion on the combined influence of IBD and pregnancy on FCP levels.

Evidence for utility of FCP in IBD during pregnancy

To date, there have been a few recent studies assessing the utility of FCP in IBD during pregnancy. Initial results have been conflicting, with some showing good correlation between FCP levels and non-invasive disease activity score in CD and UC, while others showed that it is a poor predictor of IBD relapse during pregnancy. Huang *et al* enrolled seventeen pregnant IBD patients in a prospective study, in which fecal calprotectin was monitored at pre-conception and at each trimester along with modified Harvey Bradshaw Index (mHBI) for Crohn's disease and partial Mayo score for ulcerative colitis patients. The median FCP values for women with clinically active disease (as measured by mHBI $\geqslant$ 5 and partial Mayo score $\geqslant$ 2) were numerically higher than women with clinically inactive disease, but did not reach statistical significance at all-time points[30].

A prospective study by Shitrit *et al*[31] enrolled 33 pregnant women with IBD, and compared fecal calprotectin levels with partial Mayo and Harvey Bradshaw index scores, along with serum ESR, CRP, and albumin levels. No correlation was noted between FCP and clinical scores, albumin, and inflammatory serum markers, although a subsequent study by the same group using 80 samples from 57 pregnant patients did show a positive correlation between stool calprotectin and Crohn's disease activity index and partial Mayo scores (r = 0.60 and r = 0.77, respectively)[32]. FCP showed a high sensitivity and specificity in the occurrence of disease activity (as determined by the clinician) at 81.8% and 80.7% in a prospective study by Kanis *et al*[33]; however, there was no correlation between an elevated FCP and subsequent disease relapse. Ultimately, there is no clear consensus at this time with these small prospective studies showing conflicting results. FCP should be used in conjunction with clinical judgment, and appears to be an unreliable predictor of IBD relapse in the setting of pregnancy.

DISCUSSION

Monitoring IBD during pregnancy continues to be an important challenge for clinicians. Recent data seems to suggest that endoscopy, both colonoscopy and flexible sigmoidoscopy, is a relatively safe procedure during all trimesters of pregnancy. MRI and ultrasound remain the safest methods of imaging during pregnancy. Serum biomarkers such as CRP and fecal calprotectin are helpful non-invasive markers, but have shown conflicting results for correlation with disease activity in some initial studies. Further investigation into these non-invasive biomarkers is necessary. Careful monitoring during this period remains a crucial component for important management

decisions to keep the patient in remission throughout the prenatal course.

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ORIGINAL ARTICLE

Retrospective Study

Declining use of combination infliximab and immunomodulator for inflammatory bowel disease in the community setting

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Abstract

AIM

To describe trends of combination therapy (CT) of infliximab (IFX) and immunomodulator (IMM) for inflammatory bowel disease (IBD) in the community setting.

METHODS

A retrospective study was conducted of all IBD patients referred for IFX infusion to our community infusion center between 04/01/01 and 12/31/14. CT was defined as use of IFX with either azathioprine, 6-mercaptopurine, or methotrexate. We analyzed trends of CT usage overall, for Crohn's disease (CD) and ulcerative colitis (UC), and for the subgroups of induction patients. We also analyzed the trends of CT use in these groups over the study period, and compared the rates of CT use prior to and after publication of the landmark SONIC trial.

RESULTS

Of 258 IBD patients identified during the 12 year study period, 60 (23.3%) received CT, including 35 of 133 (26.3%) induction patients. Based on the Cochran-Armitage trend test, we observed decreasing CT use for IBD patients overall ($P < 0.0001$) and IBD induction patients, ($P = 0.0024$). Of 154 CD patients, 37 (24.68%) had CT, including 20 of 77 (26%) induction patients.

The Cochran Armitage test showed a trend towards decreasing CT use for CD overall ($P < 0.0001$) and CD induction, ($P = 0.0024$). Overall, 43.8% of CD patients received CT pre-SONIC *vs* 7.4% post-SONIC ($P < 0.0001$). For CD induction, 40.0% received CT pre-SONIC *vs* 10.8% post-SONIC ($P = 0.0035$). Among the 93 patients with UC, 19 (20.4%) received CT. Of 50 induction patients, 14 (28.0%) received CT. The trend test of the 49 patients with a known year of induction again failed to demonstrate any significant trends in the use of CT ($P = 0.6$).

CONCLUSION

We observed a trend away from CT use in IBD. A disconnect appears to exist between expert opinion and evidence favoring CT with IFX and IMM, and evolving community practice.

Key words: Crohn's disease; Ulcerative colitis; Infliximab; Azathioprine; Inflammatory bowel disease

Core tip: In our 13 year experience at a community hospital infusion center, approximately 26% of inflammatory bowel disease patients receiving infliximab infusions received concomitant immunomodulator therapy. This is comparable to rates of combination therapy (CT) at major tertiary referral centers. However, there was a trend of decreased utilization of CT over the study period, even following the publication of SONIC. This suggests a need for further study to define the population with the most favorable risk-benefit ratio from CT, as well as the need for more direct guidelines from major societies.

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INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) together comprise most cases of inflammatory bowel disease (IBD). The prevalence of IBD in the United States appears to be increasing, and it is currently estimated at 1 in 300 individuals, or roughly 1.5 million members of the population[1]. For both CD and UC, treatment of moderate to severe disease often includes the use of corticosteroids for induction of clinical remission, with guidelines recommending transitioning patients off corticosteroids and using an immunomodulator (IM) such as 6-mercaptupurine (6-MP), azathioprine (AZA) for either CD or UC, or methotrexate (MTX) for CD, to maintain remission[2] For those failing to maintain steroid free clinical response or remission with IM, the addition or substitution of the newer biologic therapies comprise the next step in what is now commonly referred to as a "step up" approach to IBD therapy.

Infliximab (IFX) was introduced as the first biologic therapy targeting TNF-α. Initially approved in the United States for CD in 1997, approval for UC followed in 2005[3]. Though IFX has been followed by other TNF-α inhibitors, and newer biologics targeting alternate pathways, IFX is still among the most widely used biologic therapies[4]. IFX and the other biologics are increasingly viewed as an alternative to steroid and IM therapy as part of a "top down" therapeutic approach, which has been shown to reduce patients' steroid exposure as well as potentially improving overall clinical outcomes[5].

Early studies suggested a potential therapeutic benefit to combination therapy (CT) utilizing both IFX and IM, mainly through reduction of antibodies to IFX (ATI), reduced infusion reactions and higher IFX trough levels[6]. A major turning point was the SONIC study. While earlier work examined the role of IM combined with anti TNF-α mostly in those with IM exposure and failure prior to stepping up to IFX, SONIC focused on induction therapy among patients naïve to both biologic and IM with CD. Patients were randomized to receive either IFX, AZA or CT with both agents. CT was found to be superior to monotherapy with either IFX or AZA for the induction of steroid free clinical remission, without any increase in adverse events[7]. More recently the UC SUCCESS trial has demonstrated a similar benefit to combing AZA with IFX in those with UC[8].

Since the publication of SONIC, key thought leaders[9] and major society guidelines[10] have increasingly advocated for the use of CT, but it is unclear to what extent community practice has changed, balanced against reports of opportunistic infections[11], and cases of hepatosplenic T-cell lymphoma (HSTCL) with CT[12,13]. Currently, little is known regarding the adoption of CT in the community setting. Our main goal was to analyze the trends over time of CT usage for IBD overall, CD and UC. As a secondary goal we sought to examine whether the publication of the SONIC trial has had any impact on the proportion of CT use for CD in the community setting.

MATERIALS AND METHODS

The Northwell Health Center for Infusion Medicine, part of the Division of Rheumatology, provides IFX infusion services on behalf of both Northwell Health faculty and community gastroenterologists. Patients referred for IFX include both those beginning therapy at the center, as well as those switching their infusion therapy from another location. Center protocol requires that all physician referrals must include the completed standardized medical history form specifying IBD type, along with signed orders for IFX dose, schedule and pre-infusion medications. The standardized form includes a medication history section which specifically asks the

Table 1 Patient demographics *n* (%)

	IBD[1]	CD	UC
Total	258	154	93
Male	127 (49.2)	78 (50.6)	48 (51.6)
Mean age, yr	40.88 ± 16.67	39.59 ± 16.28	43.66 ± 17.04
IFX Pre-SONIC	111 (43.0)	73 (47.4)	30 (32.2)
6-MP/AZA use	56 (21.7)	35 (22.7)	18 (19.4)
MTX use	4 (1.6)	3 (1.9)	1 (1.1)

[1]The "IBD Total" group includes the "CD Total" and "UC Total" groups, as well as 11 patients with indeterminate colitis. IBD: Inflammatory bowel disease; CD: Crohn's disease; UC: Ulcerative colitis; IFX: Infliximab; 6-MP: 6-mercaptupurine; AZA: Azathioprine; MTX: Methotrexate.

referring physician to record either past or current use of AZA, 6-MP, MTX, without specifying dose, as well as other commonly used IBD medications. Following the initiation of IFX, updated versions of the standardized medical history are not performed.

We conducted a retrospective chart review of all patients receiving IFX infusions at the center from 01/01/2002 until 12/31/2014. Inclusion criteria required a diagnosis of CD, UC or indeterminate colitis (IC), receipt of at least 1 IFX infusion at the center, age of 18 years or greater, and availability of a completed standardized medical history form.

In addition to IBD type, patients were subcategorized as induction or maintenance patients based on the schedule of the infusions they received. Induction patients were those whose first infusion was part of a documented standard week 0, 2, and 6 induction regimen. All other patients were grouped in the maintenance cohort. CT for both induction and maintenance patients was defined by IM use at first IFX dose at the infusion center. Descriptive analysis was performed of the overall group including both induction and maintenance IBD patients, as well as for the subgroup limited to induction patients. Similar analyses were performed by CD and UC subgroups. For the secondary analysis comparing usage of CT therapy pre *vs* post SONIC, a patient was considered a pre-SONIC patient if they presented to the infusion center before April 2010.

The proportions of CT use in the induction and maintenance groups were calculated for all patients as well as for CD and UC separately. In secondary analyses we stratified patients based on years of age (< 35, 35-60, > 60), diagnosis (UC *vs* CD), gender and faculty status of the prescribing physician (faculty *vs* community) to investigate for any disparities in CT utilization between subgroups.

RESULTS

The infusion records of 293 IBD patients were reviewed. Of these, 10 were excluded due to incompleteness of the infusion record, and 25 were excluded due to a missing record of concurrent medications, leaving 258 for analysis. The patients were referred by 57 gastroenterologists (mean and median patients per gastroenterologist of 4.54 and 2 respectively). Patient demographics are detailed in Table 1. 154 (59.7%) had CD, 93 (36.1%) had UC. Eleven patients had IC, and these patients were included in the overall analysis but excluded from the disease-specific analyses. For two subjects, one each with CD and UC, infusion pre *vs* post April 2010 was confirmed without exact date of first dose. These patients were excluded from the analyses of trends in CT use over time.

All IBD patients

Among the total group of 258 patients with IBD, 60 (23.3%) received CT at the time of first IFX infusion at our center. The Cochran-Armitage trend test of the 256 patients with a known year of first infusion demonstrated a significant decrease in the use of CT for all IBD patients over the 13 year period, from 2002 to 2014, $P < 0.0001$ (see Figure 1A). The IBD induction group included 133 patients of whom 35 (26.3%) received CT. The trend test of the 131 subjects in the IBD induction group with a known year of induction again demonstrated a significant decreasing trend in the use of CT, $P = 0.0024$.

For the 258 total IBD group 111 (43.0%) had their induction or maintenance regimen start pre-SONIC compared with 147 (57.0%) post-SONIC. Due to evidence of effect modification (EM) of the patient's IBD diagnosis type on the relationship between induction time period (pre *vs* post-SONIC trial) and use of CT ($P = 0.01$), analyses comparing pre *vs* post-SONIC trial were stratified by disease type. Stratum-specific results for CD are reported below.

CD patients

Among the 154 patients with CD, 37 (24.0%) received CT at the time of first infusion. The Cochran-Armitage trend test of the 153 patients with a known year of first infusion demonstrated a significant decrease in the use of CT over the 13 year period, from 2002 to 2014, $P < 0.0001$ (see Figure 1B). The CD induction group included 77 patients of whom 20 (26.0%) received CT. The trend test of the 76 subjects with a known year of induction again demonstrated a significant decreasing trend in the use of CT, $P = 0.0024$. The proportion of all CD patients receiving CT was greater pre *vs* post-SONIC (43.8% *vs* 7.4%, respectively, $P < 0.0001$) as well as for the induction only group (40.0% *vs* 10.8%, respectively, $P = 0.0035$).

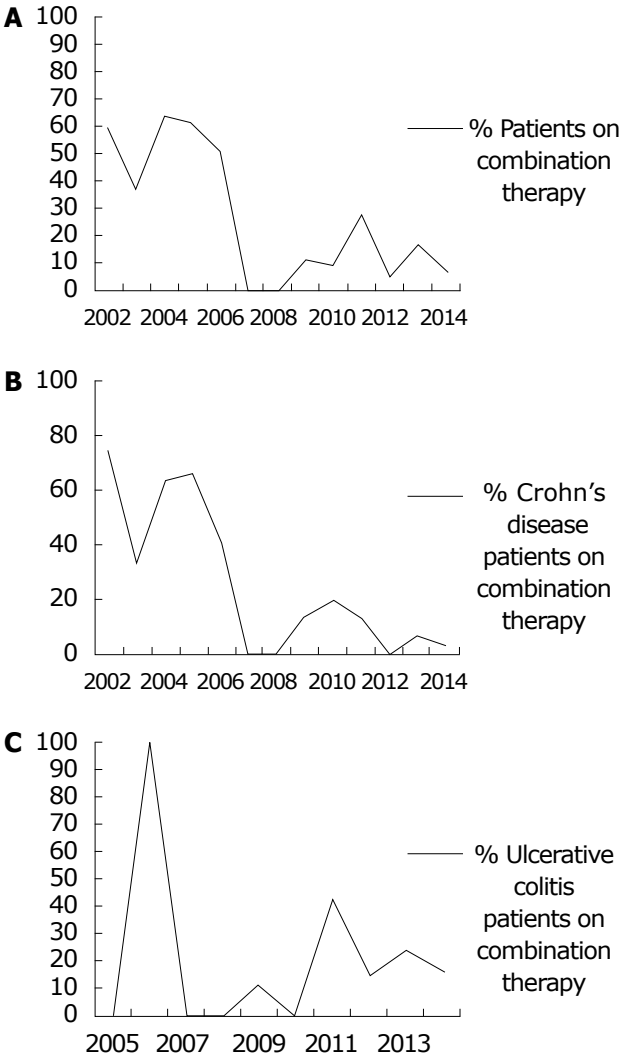

Figure 1 Percentage of inflammatory bowel disease (A), Crohn's disease (B), and ulcerative colitis (C) patients on combination therapy. Y axis: Percentage of infusion patients receiving combination therapy (0-100%); X axis: Year for which data is being reported (2002-2014). A: Percentage of inflammatory bowel disease patients receiving combination therapy over time; B: Percentage of Crohn's disease patients receiving combination therapy over time; C: Percentage of ulcerative colitis patients receiving combination therapy over time.

UC patients

Among the 93 patients with UC, 19 (20.4%) received CT at the time of first infusion. The Cochran-Armitage trend test of the 92 patients with a known year of first infusion did not demonstrate any significant trends in the use of CT over time, $P = 0.9$ (see Figure 1C). The UC induction group included 50 patients of whom 14 (28.0%) received CT. The trend test of the 49 patients with a known year of induction again failed to demonstrate any significant trends in the use of CT, $P = 0.6$.

There were no statistically significant differences in the proportions of CT use across the study period, among CD patients or UC patients, according to age group, gender, faculty status of the referring gastroenterologist, use of other agent or steroid use ($P > 0.05$ for all tests); results not shown.

DISCUSSION

Despite the positive effects offered by CT for CD in the SONIC population, and for UC by UC SUCCESS, it is unclear to what degree the use of CT has been adopted into clinical practice. A recent review from 7 high volume IBD referral centers, comprising 1659 patients with CD and 946 with UC, showed a wide range of adoption of CT. Among CD patients the use CT overall was 21%. There was a significant variation of usage across all centers ranging between 8% and 32%, with a 95%CI: 3.15 (1.79-5.56). Among UC patients the use of CT overall was 9%, with no significant variation of usage seen, ranging between 6% and 13%, CI 1.14 (0.48-2.78)[14].

Our findings offer a different perspective by which to view the question of CT usage, by providing 13 years of follow up data addressing the adoption of CT in the community setting. Examining a mixed cohort of 258 patients of whom 154 had CD, all receiving IFX, we found that CT was employed at the beginning of therapy in 23.3% of patients overall. Notably, we observed a significant trend of decreasing use of CT for IBD generally, in the CD cohort, as well as for the subgroup of CD patients receiving induction therapy.

Much like the findings from the referral center consortium, we suspect that these findings do not reflect a lack of awareness on the part of community gastroenterologists with the SONIC trial. More likely, it reflects a deeper understanding of what the SONIC results specifically support; the value of CT in a subset of treatment naïve patients. It is also likely that persistent concerns regarding adverse events with CT exert a strong pull away from CT even in cases where it may be appropriate. Though it is still uncertain if CT increases Non-Hodgkin's Lymphoma rates overall as compared to thiopurine monotherapy[15], it is now accepted that CT increases the risk of Hepatosplenic T Cell Lymphoma (HSTCL). While exceedingly rare, a recent systematic review found that 20 of 36 documented cases of HSTCL occurred in patients with a history of CT use[13]. Evidence of this association began to accumulate in 2007, which coincides with the temporary disappearance of CT use for our patients at that time[16]. Despite risk-benefit analyses favorable to CT accounting for lymphoma[17] - the preferences of physicians and/or patients have likely been impacted, particularly when faced with a black box warning addressing HSTCL found in the IFX packaging insert. Even if one is to accept the benefit of CT for induction, there is still uncertainty regarding the appropriate duration of IMM for maintenance[18]. This uncertainty may itself serve as a barrier to choosing CT over anti-TNF-α monotherapy.

The main weaknesses of our findings are mainly those which are inseparable from the retrospective study design. While our primary aim was simply observational, examining trends of CT usage over time, we specifically singled out the publication of SONIC as a time point for analysis and comparison. Given the

impact of SONIC on clinical thinking we believe this to be fair, but since we did not have data on disease duration or history of prior IMM use, it is unknown how our study population compared to those in SONIC. Especially for those patients infused during the earlier years of the analysis, it is very likely that many had a longer disease duration and past IMM use, unlike those patients in the SONIC cohort. A history of failure or intolerance to prior IMM could not be accounted for, and would tend to lower the use of CT for those beginning IFX. Also, as we defined induction by a specific schedule of IFX infusions at 0, 2, and 6 wk, we were unable to account for those receiving induction therapy with a non standard regimen, nor were we able to differentiate those receiving a first time induction regimen verses those who may have been receiving re-induction with IFX. Also, our inability to track medication changes other than IFX over time prevents us from observing the rate of CT usage at any time point during IFX therapy. I.e. we have no way of knowing how many of our patients beginning IFX mono-therapy may have "stepped up" to CT over time. Also, while we did a pre *vs* post SONIC analysis for IBD overall, this result of course included patients with UC, which the SONIC trial did not address. Finally, with 57 prescribing gastroenterologists identified it would appear that we have a fair overview of local community practice, but the community itself is narrowly defined and may not be reflective of prescribing trends in other regions.

In summary, we present the results of our analysis of community prescribing trends of CT with IFX and IMM for IBD overall, CD and UC. Over the 13 year period examined we observed a significant trend away from usage of CT with IFX and IMM for IBD overall and for CD patients specifically. It is likely that balanced against the benefit of CT observed in the SONIC cohort are the daily concerns of both patients and their physicians regarding HSTCL risk and the uncertainty of optimal duration of IMM use along with IFX. Further investigation regarding these issues, as well as a clearer demonstration of benefit in non treatment native patients, will be needed to support any future expanded use of CT.

ARTICLE HIGHLIGHTS

Background

The SONIC trial demonstrated the superiority of combination immunomodulator and biologic therapy for Crohn's disease (CD). Further studies evaluated the efficacy of combination therapy (CT) in ulcerative colitis. There are concerns regarding the safety of CT, specifically the risks of infection and malignancy.

Research frontiers

Little is known about the degree of utilization of CT in the community setting. It is also unknown whether the publication of the SONIC trial impacted rates of CT usage.

Innovations and breakthrough

This study demonstrates that the utilization of CT has generally trended down over the past decade. It also demonstrates that the publication of the SONIC study did not lead to an increase in the utilization of CT.

Applications

The decline in CT utilization highlights the need for further studies to define the ideal patient population for CT, as well as the need for more definitive guidelines from professional societies.

Terminology

Combination therapy refers to the concurrent use of an immunomodulator, such as azathioprine, with a biologic drug, such as infliximab, in the treatment of inflammatory bowel disease.

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CORRECTION

Erratum for factors associated with visceral fat accumulation in the general population in Okinawa, Japan (*World J Gastrointest Pharmacol Ther* 2016; 7: 261-267)

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Arakaki S, Maeshiro T, Hokama A, Fujita J. Erratum for Factors associated with visceral fat accumulation in the general population in Okinawa, Japan (*World J Gastrointest Pharmacol Ther* 2016; 7: 261-267). *World J Gastrointest Pharmacol Ther* 2018; 9(1): 14-15 Available from: URL: http://www.wjgnet.com/2150-5349/full/v9/i1/14.htm DOI: http://dx.doi.org/10.4292/wjgpt.v9.i1.14

CORRECTION

Correction to: Arakaki S, Maeshiro T, Hokama A, Hoshino K, Maruwaka S, Higashiarakawa M, Parrott G, Hirata T, Kinjo K, Fujita J. Factors associated with visceral fat accumulation in the general population in Okinawa, Japan. *World J Gastrointest Pharmacol Ther* 2016; 7(2): 261-267 PMID: 27158542 DOI: 10.4292/wjgpt.v7.i2.261[1].

Erratum 1

In the Results and Discussion, the description regarding the relationship between several parameters and VFA is lacking. In the Results (page 263) within the right side column, after "...(P < 0.05, Table 4).", "Although statistically not significant, a univariate analysis also indicated that FPG and HbA1c were slightly higher and HDL-C was slightly lower in males with low VFA group (Table 3)." should be added.

In the Discussion (page 266), after the first sentence (...related diseases[14].) in the left side column, "In the present univariate analysis, in contrast to most prior reports, although statistically not significant, HDL-C was slightly lower and FPG and HbA1c were slightly higher in males with low VFA group. The precise reasons for this discrepancy have not been revealed, however, the lack of data, including medication, lifestyle behaviors, smoking status, and chronic disease status, may have influenced the discrepancy. These characteristics have

been known as strong modifiers to these variables. Further work is needed to clarify this issue." should be added.

Erratum 2

In the Discussion, the description regarding the reason for gender differences in VFA by current drinking is lacking. In the Discussion (page 266), after "….such as beer *vs* liquor." in the left side column, "Other possible factors have been considered, including the differences among ethanol metabolizing enzyme genes, diet factors, smoking, and amount of exercise. These factors need to be further investigated." should be added.

Erratum 3

In the Results (page 263), in the last sentence of right side column, "significant lower" should have been "significantly higher".

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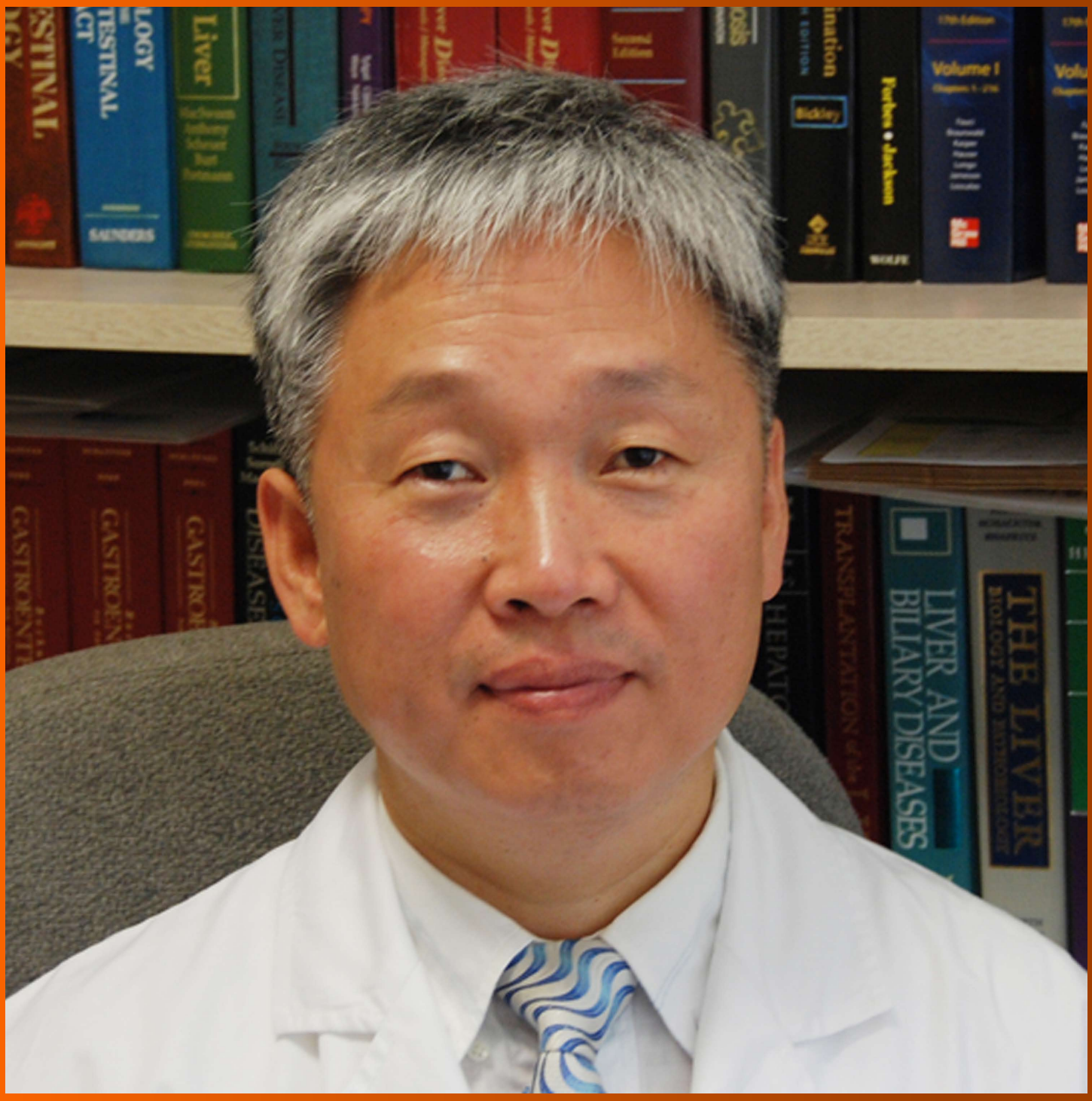

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ORIGINAL ARTICLE

Retrospective Study

Hypothyroidism in patients with autoimmune pancreatitis

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Author contributions: All authors helped to perform the research; Shimizuguchi R and Kamisawa T wrote manuscript, collected and analyzed data; Endo Y, Kikuyama M, Kuruma S, Chiba K, Tabata T and Koizumi S collected data.

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Abstract

AIM

To examine thyroid function and clinical features of hypothyroidism in autoimmune pancreatitis (AIP) patients.

METHODS

We examined thyroid function in 77 patients with type 1 AIP (50 males, 27 females; median age 68 years, range 33-85) diagnosed according to the Japanese diagnostic criteria for AIP 2011. We compared clinical and serological findings between patients with and without various categories of hypothyroidism. The change in hypothyroidism after steroid therapy was also examined.

RESULTS

Eight patients (10%) had hypothyroidism of 6 patients had subclinical hypothyroidism with a normal serum free thyroxine (FT4) and high thyroid stimulating hormone (TSH) level, and 2 patients had central hypothyroidism with low serum free triiodothyronine (FT3), FT4 and TSH levels. A significant goiter of the thyroid was not observed in any patient. There were no significant differences in age; male to female ratio; serum concentrations of IgG and IgG4-related disease (IgG4-RD); presence of anti-thyroglobulin antibody, antinuclear antigen or rheumatoid factor; or presence of extrapancreatic lesions between the 6 patients with subclinical hypothyroidism and patients

with euthyroidism. After steroid therapy, both subclinical and central hypothyroidism improved with improvement of the AIP.

CONCLUSION

Hypothyroidism was observed in 8 (10%) of 77 AIP patients and was subclinical in 6 patients and central in 2 patients. Further studies are necessary to clarify whether this subclinical hypothyroidism is another manifestation of IgG4-RD.

Key words: Autoimmune pancreatitis; Hypothyroidism; IgG4-related disease

Core tip: Autoimmune pancreatitis (AIP) is a pancreatic manifestation of IgG4-related disease (IgG4-RD) and is frequently associated with other IgG4-RDs. The aim of this study was to examine thyroid function and clinical features of hypothyroidism in AIP patients. Hypothyroidism was observed in 8 (10%) of 77 AIP patients and was subclinical in 6 patients and central in 2 patients. After steroid therapy, both subclinical and central hypothyroidism improved with improvement of the AIP.

Shimizuguchi R, Kamisawa T, Endo Y, Kikuyama M, Kuruma S, Chiba K, Tabata T, Koizumi S. Hypothyroidism in patients with autoimmune pancreatitis. *World J Gastrointest Pharmacol Ther* 2018; 9(2): 16-21 Available from: URL: http://www.wjgnet.com/2150-5349/full/v9/i2/16.htm DOI: http://dx.doi.org/10.4292/wjgpt.v9.i2.16

INTRODUCTION

IgG4-related disease (RD) is a systemic inflammatory disorder that was first proposed following the observation of patients with autoimmune pancreatitis (AIP) in 2003[1]. IgG4-RD is characterized by infiltration of IgG4-positive plasma cell and lymphocyte and an elevated serum IgG4 concentration. AIP is currently divided into type 1 and type 2; type 1 AIP is recognized as a pancreatic manifestation of IgG4-RD[2]. AIP has been reported to be complicated with various other IgG4-RDs such as sclerosing cholangitis, sialadenitis, dacryoadenitis, retroperitoneal fibrosis, interstitial lung disease, and tubulointerstitial nephritis[3]. Komatsu *et al*[4] first reported in 2005 that 26.8% of 41 AIP patients showed hypothyroidism; however, there are only a few reports regarding thyroid function in AIP patients[4-6]. In this study, we examined thyroid function in 77 AIP patients and the change in hypothyroidism after steroid therapy.

MATERIALS AND METHODS

Patients

A total of 77 patients with type 1 AIP (50 males, 27 females; median age 68 years, range 33-85) who had been examined and treated at Tokyo Metropolitan Komagome Hospital, were enrolled in this study. The diagnosis of type 1 AIP was based on the Japanese diagnostic criteria for AIP 2011[7].

Study design

In all AIP patients, antinuclear antibody (ANA) and rheumatoid factor (RF) were assayed, and the serum concentrations of IgG and IgG4 as well as the serum levels of free triiodothyronine (FT3), free thyroxine (FT4), and thyroid stimulating hormone (TSH), were measured. Anti-thyroglobulin antibodies (TgAb) and anti-thyroid peroxidase antibodies (TPOAb) were measured in 41 and 6 of the patients. Extrapancreatic lesions of AIP were defined as sclerosing cholangitis of the hilar or intrahepatic bile duct, sialadenitis/dacryoadenitis, retroperitoneal fibrosis and renal lesions. Contrast-enhanced computed tomography (CT) of neck or chest was performed for screening of other lesions of IgG4-RD in 65 patients. Ultrasonography of the thyroid was done only in 2 patients.

We classified hypothyroidism into two groups according to the following conditions: Clinical hypothyroidism with high TSH and low FT4 levels, and subclinical hypothyroidism with high TSH levels and normal FT4 levels. Hypothyroidism induced by hypophysitis, which showed low FT3, FT4 and TSH levels, was termed central hypothyroidism. Clinical and serological findings and extrapancreatic lesions were compared between patients with and without these various hypothyroidisms.

Steroid therapy was administered to 70 AIP patients and consisted of initial prednisolone (0.6 mg/kg per day) for 2-4 wk that was gradually tapered to a maintenance dose of 2.5-5 mg/d over a period of 2-3 mo. Maintenance therapy was administered for 1-2 years to prevent relapse. The serum levels of FT3, FT4, and TSH in the 6 patients with subclinical hypothyroidism and the 2 patients with central hypothyroidism were measured after treatment with prednisolone.

This study was approved by the institutional review board. Informed consent for invasive modalities had been obtained prior to performance from all study participants.

Statistical analysis

Statistical analyses were performed using paired *t*-test in Figure 1 and Fisher's exact test and the Mann-Whitney *U*-test in Table 1. A *P* value of less than 0.05 was regarded as indicating a statistically significant difference. The statistical methods of this study were reviewed by a biostatistician.

RESULTS

Of the 77 study patients with AIP, 8 (10%) had hypothyroidism. Of these 8 patients, 6 patients had subclinical hypothyroidism with a normal FT4 and a high TSH level, and 2 patients had central hypothyroidism with low FT3, FT4 and TSH levels. There were no

Table 1 Clinical and serological differences in autoimmune pancreatitis patients with hypothyroidism and euthyroidism

	Hypothyroidism (n = 8)	Euthyroidism (n = 69)	P value
Age	70 (58-85)[1]	66 (63-68)	0.421
Sex (M/F)	6/2	44/25	0.571
IgG (mg/dL)	2315 (961-4557)	1829 (883-4135)	0.487
IgG4 (mg/dL)	366 (26-715)	304 (11-2490)	0.482
Rheumatoid factor (+)	1/6	21/65	0.324
Antinuclear antibody (+)	2/7	32/69	0.242
Anti-thyroglobulin antibody (+)	0/7	3/36	-
Anti-thyroidperoxidase antibody (+)	1/6	0/0	-
Extrapancreatic lesions (+)	2/8	27/69	0.912

[1]Median (range). M: Male; F: Female; IgG4: IgG4-related disease.

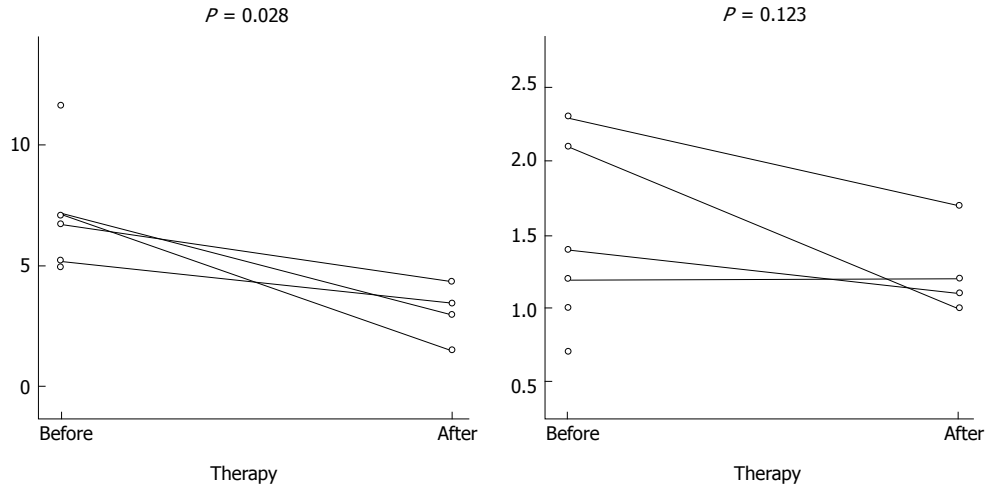

Figure 1 Changes in thyroid stimulating hormone and free thyroxine levels after steroid therapy of autoimmune pancreatitis patients with subclinical hypothyroidism.

patients with clinical hypothyroidism who required thyroid hormone supplements. The remaining 69 patients had euthyroidism with normal FT4 and TSH levels (Table 2). A past history of hypothyroidism had not been identified for any patient. A significant goiter of the thyroid was not observed in any patient. Enlargement of the pituitary stalk was observed on CT and MRI and decreased levels of other pituitary hormones (adrenocorticotropic hormone (ACTH), luteinizing hormone (LH), and follicle-stimulating hormone (FSH) were observed in the 2 patients with central hypothyroidism.

There were no significant differences in age; male to female ratio; serum concentrations of IgG and IgG4; the presence of anti-thyroglobulin antibody, RF, or ANA; or presence of extrapancreatic lesions between the 6 patients with subclinical hypothyroidism and the patients with euthyroidism. Male preponderance was at comparable levels in patients with hypothyroidism and in those with euthyroidism (Table 1).

The AIP of all patients responded well to steroids. After steroid therapy, serum TSH values had decreased significantly from a median value of 6.95 μIU/mL to a value of 3.24 mIU/mL (P = 0.029) and the FT4 values had decreased from a median value of 1.3 ng/dL to a value of 1.15 ng/dL (P = 0.146) in the 6 patients with subclinical hypothyroidism (Figure 1).

In the 2 patients with central hypothyroidism, the TSH and FT4 values had increased to the normal range one month after starting corticosteroid therapy (Figure 2). The enlargement of the pituitary stalk and decreased levels of other pituitary hormones had also improved.

One patient with normal FT4 and TSH levels had a benign cyst in the thyroid on ultrasonography, and low density areas suggesting adenomas in the thyroid were pointed out on CT.

DISCUSSION

AIP is now recognized as a pancreatic manifestation of IgG4-RD. IgG4-RD is a systemic disease that is characterized by organ enlargement, male preponderance, elevated serum IgG4 levels, marked infiltration of IgG4-positive plasma cells and lymphocytes with fibrosis, and steroid responsiveness. Many patients with IgG4-RD have lesions in several organs, synchronously or metachronously, and various other IgG4-RDs are frequently associated with AIP[2,3].

In the present study, hypothyroidism was observed in 8 (10%) of 77 AIP patients of whom 6 (8%) patients had subclinical hypothyroidism with a normal

Table 2 Free T3, free T4 and thyroid stimulating hormone levels in autoimmune pancreatitis patients with subclinical hypothyroidism, central hypothyroidism and euthyroidism

	Subclinical hypothyroidism (n = 6)	Central hypothyroidism (n = 2)	Euthyroidism (n = 69)
Free T3 (2.0-3.8 pg/mL)	1.5 (1.1-2.0)[1]	1.6 (1.6-1.7)	2.1 (0.7-3.2)
Free T4 (0.7-1.5 ng/dL)	1.3 (0.7-2.3)	0.5 (0.5-0.6)	1.1 (0.9-1.5)
TSH (0.4-4.80 μIU/mL)	6.95 (5.04-11.6)	0.19 (0.04-0.34)	1.60 (0.48-4.46)

[1]Median (range).

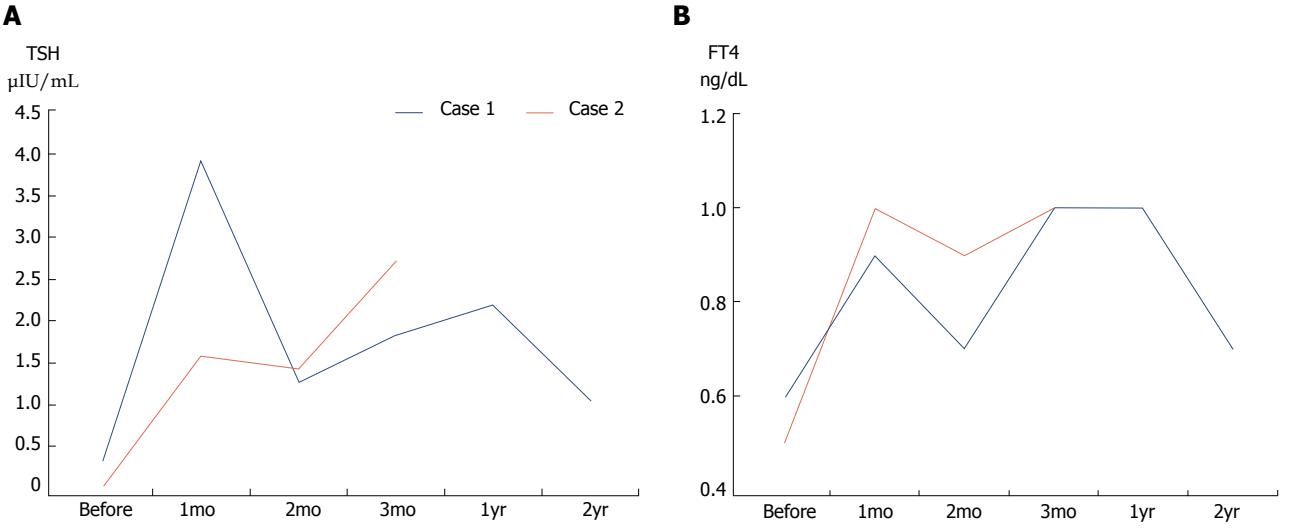

Figure 2 Changes in (A) thyroid stimulating hormone and (B) free thyroxine levels after steroid therapy of autoimmune pancreatitis patients with central hypothyroidism. TSH: Thyroid stimulating hormone; FT4: Free thyroxine.

FT4 and a high TSH level, and 2 patients had central hypothyroidism with low FT3, FT4 and TSH levels. In a study by Komatsu *et al*[4], the prevalence of hypothyroidism in AIP patients was reported as 26.8% (11/41), and 6 patients had clinical hypothyroidism with a low FT4 level of whom 5 patients were treated with thyroid hormone supplements. Sah *et al*[5] reported the detection of clinical hypothyroidism requiring thyroxine supplementation in 14 (14.4%) of 97 AIP patients. In a study by Abraham *et al*[6], the prevalence of AIP patients with hypothyroidism was 18.2% (2/11). Watanabe *et al*[8] reported that hypothyroidism was found in 22 (19%) of 114 patients with IgG4-RD. The prevalence of hypothyroidism in our AIP patients was lower than those reported in the literature, but the prevalence in the general population has been reported as 4.6%[9].

The AIP patients with and without hypothyroidism in the present study were predominantly elderly males. Although these findings were similar to those of Komatsu's report[4], they differed from the findings of Sah's report[5], in which the AIP patients with hypothyroidism (71 ± 8 years) were older than those without hypothyroidism (57 ± 16 years). However, in Sah's[5] report, 11 of the 14 AIP patients with hypothyroidism were already on thyroxine supplementation at the time of presentation with AIP. In Komatsu's[4] report, AIP patients with hypothyroidism showed a significantly higher frequency of anti-thyroglobulin antibody (63.6%) than euthyroid subjects (20.0%). However, in our study only 3 euthyroid AIP patients were positive for anti-thyroglobulin antibody. There were no differences in serum IgG4 levels or in the prevalence of other organ involvement between AIP patients with and without hypothyroidism in the present study. These findings were similar to the data reported in the studies of both Komatsu *et al*[4] and Sah *et al*[5]. In terms of therapy, the AIP patients with hypothyroidism in our study responded well to steroids, whereas the two other studies[4,5] reported that steroid therapy could not ameliorate hypothyroidism. In summary, many of the findings in our study differed from those in the previously reported studies including our findings that the prevalence of hypothyroidism in AIP patients was twice that in the general population but was lower than reported data; the hypothyroidism in AIP patients was relatively mild without need of thyroxine supplementation; only 1 anti-thyroidperoxidase antibody and no anti-thyroglobulin antibody was detected in our AIP patients with hypothyroidism; and our hypothyroid AIP patients showed a good response to steroids. However, we cannot explain the reasons behind these discrepancies.

Riedel's thyroiditis is a rare disease that has been described as a part of multifocal fibrosclerosis involving sclerosing cholangitis, retroperitoneal fibrosis, and chronic pancreatitis. However, it is now recognized

clinicopathologically as a thyroid lesion of IgG4-RD[2,10,11]. In our cohort, only 1 patient was diagnosed as Riedel's thyroiditis based on histological examination of the resected specimen, while this case did not have AIP and was not included in this study.

Hashimoto's thyroiditis is an autoimmune thyroiditis that is almost always associated with diffuse goiter[12]. In 2009, Li *et al*[13] first described a unique subtype of Hashimoto's disease, known as IgG4-related Hashimoto's disease. They classified Hashimoto's thyroiditis into two groups: IgG4-related Hashimoto's thyroiditis with abundant infiltration of IgG4-positive plasma cells, and non-IgG4 Hashimoto's thyroiditis without infiltration of IgG4-positive cells based on IgG4-immunostaining[13]. Patients with IgG4-related Hashimoto's thyroiditis tended to be younger and male; were more likely to have a shorter duration of disease; and had higher level of anti-thyroglobulin antibodies than patients with non-IgG4 Hashimoto's thyroiditis[14]. The AIP patients with hypothyroidism in our study showed no goiter, a preponderance of elderly males, and no presence of anti-thyroglobulin antibodies. Since histological examination of the thyroid was not done in any of our cases, a precise judgement regarding whether these cases were IgG4-related Hashimoto's thyroiditis or not could not be made; however, our cases of subclinical hypothyroidism appeared to be different from the so-called IgG4-related Hashimoto's thyroiditis.

Good responsiveness to steroids is one of the major characteristics of IgG4-RD, and the hypothyroidism in our AIP patients improved after steroid administration and was accompanied by improvement of AIP. Thus, this hypothyroidism appeared to be a thyroid lesion associated with AIP. However, it was reported that AIP patients with associated renal lesions or sialadenitis or dacryoadenitis show higher serum IgG4 levels and have more extrapancreatic lesions than those without these lesions, which may suggest higher disease activity[15,16]. In the present cases, there were no significant differences in serum IgG4 levels or extrapancreatic lesions between AIP patients with and without hypothyroidism. Ultimately, we cannot judge whether the hypothyroidism observed in our AIP patients is a thyroid lesion involved in IgG4-RD from these findings due to lack of evidence of histology and imaging of the thyroid.

In the present study, we experienced two cases of central hypothyroidism that was induced by hypophysitis. Although IgG4-related hypophysitis is a rare lesion of IgG4-RD[17], we showed that this lesion is one of the causes of hypothyroidism in AIP patients.

There are some limitations to this study. First, due to the retrospective nature of the study, anti-thyroglobulin antibodies and anti-thyroidperoxidase antibody were measured in only 41 and 6 patients. Second, a radiological study of the thyroid was not systemically performed. Third, histology of the thyroid was not examined in any of the patients with hypothyroidism.

In conclusion, the hypothyroidism detected in the AIP patients of this study was present to a mild degree and was less frequent compared to previously reported cases. Further studies are necessary to clarify whether this hypothyroidism is another manifestation of IgG4-RD.

ARTICLE HIGHLIGHTS

Research background

Autoimmune pancreatitis (AIP) is a pancreatic manifestation of IgG4-related disease (IgG4-RD) and is frequently associated with other IgG4-RDs. AIP has been reported to be complicated with various other IgG4-RDs such as sclerosing cholangitis, sialadenitis, dacryoadenitis, retroperitoneal fibrosis, interstitial lung disease, and tubulointerstitial nephritis.

Research motivation

It was reported for the first time that 26.8% of 41 AIP patients showed hypothyroidism in 2005. However, there are only a few reports regarding thyroid function in AIP patients.

Research objective

The objective of this study was to examine thyroid function and clinical features of hypothyroidism in AIP patients.

Research methods

We examined thyroid function in 77 patients with type 1 AIP (50 males, 27 females; median age 68 years, range 33-85) diagnosed according to the Japanese diagnostic criteria for AIP 2011. We compared clinical and serological findings between patients with and without various categories of hypothyroidism. The change in hypothyroidism after steroid therapy was also examined.

Research results

Eight patients (10%) had hypothyroidism of 6 patients had subclinical hypothyroidism with a normal serum free thyroxine (FT4) and high thyroid stimulating hormone (TSH) level, and 2 patients had central hypothyroidism with low serum free triiodothyronine (FT3), FT4 and TSH levels. A significant goiter of the thyroid was not observed in any patient. There were no significant differences in age; male to female ratio; serum concentrations of IgG and IgG4; presence of anti-thyroglobulin antibody, antinuclear antigen or rheumatoid factor; or presence of extrapancreatic lesions between the 6 patients with subclinical hypothyroidism and patients with euthyroidism. After steroid therapy, both subclinical and central hypothyroidism improved with improvement of the AIP.

Research conclusions

Hypothyroidism was observed in 8 (10%) of 77 AIP patients and was subclinical in 6 patients and central in 2 patients. Further studies are necessary to clarify whether this subclinical hypothyroidism is another manifestation of IgG4-RD.

Research perspectives

Further studies are necessary to clarify whether this hypothyroidism is another manifestation of IgG4-RD.

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ORIGINAL ARTICLE

Randomized Controlled Trial

Blood glucose response after oral intake of lactulose in healthy volunteers: A randomized, controlled, cross-over study

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Author contributions: Steudle J and Schön C designed this study; the study was performed at the study site of BioTeSys under the supervision of Steudle J and Schön C; Wargenau M planned and performed statistical analysis; Steudle J and Schön C drafted the manuscript and made the final approval of the version to be published; Pauly L, Schwejda-Güttes S, Gaigg B, Kuchinka-Koch A and Stover JF planned and supervised this study, reviewed and approved the manuscript.

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Abstract

AIM

To investigate possible changes of blood glucose levels after oral intake of lactulose in healthy subjects.

METHODS

The study was performed as prospective, randomized, two-part study with 4-way cross-over design with n = 12 in each study arm. Capillary blood glucose levels were determined over a time period of 180 min after intake of a single dose of 10 g or 20 g lactulose provided as crystal or liquid formulation. During the manufacturing process of lactulose, impurities with sugars (*e.g.,* lactose, fructose, galactose) occur. Water and 20 g glucose were used as control and reference. Because lactulose is used as a functional food ingredient, it may also be consumed by people with impaired glucose tolerance, including diabetics. Therefore, it is of interest to determine whether the described carbohydrate impurities may increase blood glucose levels after ingestion.

RESULTS

The blood glucose concentration-time curves after intake of 10 g lactulose, 20 g lactulose, and water were almost identical. None of the three applications showed any changes in blood glucose levels. After intake of 20 g glucose, blood glucose concentration increased by approximately 3 mmol/L (mean C_{max} = 8.3 mmol/L), reaching maximum levels after approximately 30 min and returning to baseline within approximately 90 min, which was significantly different to the corresponding 20 g lactulose formulations (P < 0.0001). Comparing the two lactulose formulations, crystals and liquid, in the dosage of 10 g and 20 g, there was no difference in the blood glucose profile and calculated pharmacokinetic parameters despite the different amounts of carbohydrate impurities (1.5% for crystals and 26.45% for liquid). Anyhow, the absolute amount of single sugars was low with 0.3 g in crystals and 5.29 g in liquid formulation in the 20 g dosages. Lactulose was well tolerated by most volunteers, and only some reported mild to moderate mainly gastrointestinal side effects.

CONCLUSION

The unchanged blood glucose levels after lactulose intake in healthy subjects suggest its safe use in subjects with impaired glucose tolerance.

Key words: Lactulose; Functional food ingredient; Sugar substitute; Blood glucose concentration

Core tip: Lactulose can be used as a functional food ingredient. During manufacturing as liquid or crystalline formulation, impurities with different sugars occur. Lactulose may also be consumed by people with impaired glucose tolerance, including diabetics. For these consumers, it is of interest whether the described carbohydrate impurities may increase blood glucose levels after ingestion. This study was performed to investigate possible changes of blood glucose levels after oral intake of 10 g and 20 g of liquid and crystalline lactulose in healthy subjects. The small amounts of carbohydrate impurities did not influence blood glucose levels, indicating potential applicability to people with impaired glucose tolerance.

Steudle J, Schön C, Wargenau M, Pauly L, Schwejda-Güttes S, Gaigg B, Kuchinka-Koch A, Stover JF. Blood glucose response after oral intake of lactulose in healthy volunteers: A randomized, controlled, cross-over study. *World J Gastrointest Pharmacol Ther* 2018; 9(3): 22-30 Available from: URL: http://www.wjgnet.com/2150-5349/full/v9/i3/22.htm DOI: http://dx.doi.org/10.4292/wjgpt.v9.i3.22

INTRODUCTION

The undigestible lactulose (galacto-fructose) is a semi-synthetic product made by isomerization from lactose (galacto-glucose). Lactulose does occur in very small amounts in heated milk but is not present in nature. In contrast to its substrate lactose, the β-glycosidic linkage of lactulose can not be split by human digestive enzymes. Reaching the colon, lactulose is mainly metabolized by saccharolytic intestinal bacteria[1]. Lactulose has been used as food ingredient, *e.g.,* as a sugar substitute or functional food ingredient with prebiotic effects for human consumption[2,3]. Changes in gut microbiota composition and health-promoting effects due to its bifidogenic effects were described. Furthermore, the growth of pathogenic bacteria, *e.g.,* Salmonella, could be inhibited. Moreover, lactulose improves the survival of probiotic strains like *Lactobacillus rhamnosus* and *Bifidobacterium bifidum* in yogurt[4].

The particularly gentle and natural laxative action of lactulose at dosages of 10 g and more result from its prebiotic, osmotic, and peristalsis-activating effects. This is also reflected in the European Food Safety Authority (EFSA)-approved health claim that "Lactulose contributes to an acceleration of intestinal transit"[5]. Furthermore, lactulose is also marketed as a drug to treat constipation, hepatic encephalopathy and dysbacteria[1]. Besides these health benefits, lactulose has some desirable properties like taste improvement, favorable browning behavior and excellent solubility in water for the development and manufacture of functional food products[4]. Lactulose is produced from lactose. During manufacturing impurities, including epilactose, lactose, galactose, fructose, tagatose and small amounts of unspecified or unknown sugars, occur[4]. Lactulose is available in two formulations: Crystals (powder to be dissolved in water) and liquid syrup (solution). Carbohydrate impurities are found up to 3% in the crystalline and approximately 30% in the liquid form. The amount and the pattern of related substances of the carbohydrate impurities varies depending on the conditions during the manufacturing process used to produce lactulose.

Because lactulose is used as a functional food ingredient, it may also be consumed by people with impaired glucose tolerance, including diabetics. For these consumers, it is of interest whether the described carbohydrate impurities may increase blood glucose levels after ingestion. A case report showed higher blood glucose levels in a diabetic patient after changing the lactulose syrup brand[6]. In previous human studies, only slight or no increases in

blood glucose concentrations were observed with single doses of 20-25 g of lactulose[7-9].

In this study, possible changes in blood glucose levels after oral intake of lactulose products from Fresenius Kabi were investigated in healthy volunteers. Because of the small amounts of impurities, particularly in lactulose crystals, no or only small changes in blood glucose levels were expected. In future studies, the results of this study need to be confirmed for a diabetic collective.

MATERIALS AND METHODS

Study design

The study was performed as a prospective, open, mono-center, randomized, two-part study with 4-way cross-over design in each study arm. BioTeSys GmbH, Esslingen, was charged as a contract research organization (CRO) for study coordination, product supply and data collection. The study was performed in the study center of BioTeSys. The protocol followed the Declaration of Helsinki guidelines and was approved by the Ethics Committee of the Landesärztekammer Baden-Württemberg.

The study consisted of a screening visit and four study visits. After inclusion, subjects, who gave their written informed consent to participate, were stratified by gender and randomized to study arm (intervention with crystals or liquid) and sequence group 1-4 (random order of 10 g or 20 g lactulose either as crystal or liquid, water or 20 g glucose, according to Williams design). Randomization of volunteers was performed by means of the computer program DatInf® RandList, version 1.2.

Volunteers were instructed to have an individually standardized meal composed of farmhouse bread, cream cheese and cucumber in the evening prior to study visit 1-4. Furthermore, volunteers were not allowed to consume food or drink other than water for at least 10 h before the tests. In the morning of study visits, volunteers were instructed to drink 1-2 glasses (minimum 200 mL) of water after sleep before coming to the study site. Consumption of alcohol, as well as intensive exercise, was not allowed 24 h prior to all visits. Furthermore, in the morning of all visits, volunteers were not allowed to use means of transport accompanied with vigorous exercise (*e.g.,* jogging, cycling).

Study population

Subjects were recruited by advertisement in local newspapers and a database of the study site. Eligible subjects were healthy Caucasian men and women, aged ⩾ 18 and ⩽ 65 years, without known (family) history of diabetes mellitus or use of anti-hyperglycemic drugs or insulin, having approximately 3-5 bowel movements per week. The blood routine parameters were determined in venous blood samples at screening and judged by the investigator according to the exclusion criteria. Main criteria for exclusion were clinically relevant renal or hepatic disease, liver enzymes > 10% above reference range, fasting blood glucose > 100 mg/dL or glycated hemoglobin (HbA1c) > 5.7%, total cholesterol > 250 mg/dL or triglycerides > 150 mg/dL, hemoglobin < 11 g/dL (women); < 12.5 g/dL (men), body mass index (BMI) < 19 kg/m² and ⩾ 30 kg/m², intentional and unintentional weight loss > 5% in the previous 6 mon, smoker, major medical or surgical event requiring hospitalization within the previous 3 mo, presence of disease or drugs influencing digestion and absorption of nutrients or bowel habits, intake of medications known to affect glucose tolerance, *e.g.*, steroids, protease inhibitors or antipsychotics, chronic intake of substances affecting blood coagulation, which in the investigator's opinion would impact volunteer safety, hereditary galactose or fructose intolerance, lactase deficiency or glucose-galactose malabsorption.

Sample size

For sample size estimation, the precision of the estimate for the absolute difference between interventions concerning incremental area under the curve (iAUC) was considered, which was expressed as half of the width of the 95% confidence interval (CI) for the mean difference. The precision was regarded as sufficient if half of the width of the 95%CI did not exceed one (intra-subject) standard deviation. Based on this approach, 11 evaluable subjects would have been required. To consider the 4-way cross-over in each group, including four intervention sequences, the final sample size should have been a multiple of four to be able to adjust for potential period effects. Therefore, 12 subjects in each study arm were enrolled (*i.e.,* 24 subjects in total).

Study products

Lactulose crystals were produced by S.C.M., Società Chimica Mugello, S.r.l., a Fresenius Kabi Company in Vicchio, Italy, and lactulose liquid was produced by Fresenius Kabi Austria GmbH in Linz, Austria. Maximum carbohydrate impurities of both lactulose formulations according to the European Pharmacopoeia monographs are listed in Table 1. The total impurities of the study products were 1.5% in lactulose crystals and 26.45% in lactulose liquid.

Subjects received study products in a single dose at the study site under fasting conditions. Despite the open nature of the study, volunteers were kept blinded on the dosage of study products (10 g or 20 g lactulose or 20 g glucose) as well as on the formulation (lactulose crystals and liquid). Study products were provided by study staff dissolved in 250 mL water, ready for consumption.

Data collection

Blood glucose levels were measured in capillary whole blood obtained by finger prick. For analysis of glucose levels, the HemoCue Glucose 201+ Analyzer (Ängelholm, Sweden) was used, and glucose was determined photometrically using a modified glucose dehydrogenase method. Blood glucose concentrations were monitored over a period of 180 min at specified time points (0, 15, 30, 45, 60, 90, 120, 150, 180 min post-intake). From the boundary conditions including the methodology of blood

Table 1 Limits for carbohydrate impurities in Lactulose formulations according to monographs in the European Pharmacopoeia

	Lactulose crystals	Lactulose liquid[1]
Epilactose	⩽ 0.5%	⩽ 10.0%
Galactose	⩽ 0.5%	⩽ 15.0%
Lactose	⩽ 3.0%	⩽ 10.0%
Fructose	⩽ 0.5%	⩽ 1.0%
Tagatose	⩽ 0.5%	⩽ 4.0%
3-Deoxy-D-glyceropentulose	-	⩽ 4.0%
Total impurities	⩽ 3.0%	⩽ 12.0% (excluding galactose and lactose)

[1]Values relative to lactulose.

Table 2 Demographic and baseline data

Variable	mean	SD
Age (yr)	35.4	13.11
BMI (kg/m²)	22.71	2.202
Venous fasting glucose level (mg/dL)	85.0	5.63
HbA1c (%)	4.98	0.297

glucose device, the study was performed in compliance with ISO 26642:2010 for determination of glycemic index (GI) of foods[10].

Paper CRFs served as source documents and were transferred into an electronic database (ALPHADAS®, an electronic data capturing system from Instem plc, Stone, Staffordshire, United Kingdom, ensuring full audit trail). Trial on-site monitoring verified the accurateness of source data transfer into electronic database as well as Good Clinical Practices compliance. Data were transferred to Biostatistics contract research organization M.A.R.C.O. GmbH and Co. KG, Düsseldorf, for statistical analysis. Statistical analysis was performed with SAS software (Version 9.3).

Data analysis

The primary endpoint was iAUC, *i.e.,* above baseline levels for blood glucose concentration after oral intake of lactulose products compared to water (negative control). Secondary efficacy endpoints were: The maximum blood glucose concentration (C_{max}), the time to reach maximum blood glucose concentration (T_{max}), the maximum blood glucose concentration minus baseline value ($Max_{\_increase}$), the total area under the curve (AUC) from 0 to 180 min for blood glucose concentration ($AUC_{(0\text{-}180min)}$), the baseline corrected AUC from 0 to 180 min for blood glucose concentration (AUC_{base} = AUC from 0 to 180 min - baseline*180 min). After glucose intake, the parameter $T_{baseline}$, the first time to reach baseline again after increase in blood was evaluated. The following comparisons were done: (1) lactulose with negative control (water); (2) 20 g lactulose products with 20 g glucose; and (3) lactulose crystals and liquid.

Untransformed endpoints were analyzed separately for the two study arms using a mixed analysis-of-variance model with intervention (4 levels), period (4 levels), and baseline blood glucose level within study periods as fixed effects and subject as random effect. Group means were calculated from the model ("LS Means"). Data are presented for the Intention-to-treat (ITT) population which, however, was identical with the Per-Protocol (PP) population in this study. Due to the 7 d wash-out period, an examination of possible carry-over effects was not necessary. There were only minor time deviations for the wash-out period, which were discussed during data review meetings and judged to have no impact on study results.

Subjects were instructed to document any adverse events (AEs) and concomitant medication in diaries, starting after screening and ending with 24 h tolerability assessment at visit 4. All AEs were followed until resolution. During visits, all AEs were asked and reviewed by an investigator and reported on the CRF.

RESULTS

From November 2016 to January 2017, a total of 24 (of 35 screened) volunteers were included, as shown in Figure 1. The main reasons for non-inclusion were relevant findings of blood routine parameters. All 24 volunteers (12 women and 12 men) completed the study successfully without major protocol deviations. Only small deviations occurred, *e.g.,* in the standardized dinner in the evening or amount of water in the morning before visits, which were judged as minor with no impact on study results. Participants were 20 to 62 years old. Table 2 shows the demographic data of the volunteers. The study product was administered to all subjects under supervision of study staff after at least 10 h of fasting. Despite the open nature of the study, volunteers were kept blinded on the dosage of study products (10 g or 20 g lactulose or 20 g glucose, water) as well as on the formulation (lactulose crystals and liquid). All study products were provided dissolved in a total volume of 250 mL water, equivalent to the negative control. The intake was complete with no residual amounts, resulting in 100% compliance.

Figures 2 and 3 show the blood glucose concentration-time curves for the different applications. In both study arms (crystals and liquid), the glucose concentration-time curves after intake of 10 g lactulose, 20 g lactulose, and water were almost identical. None of the three applications showed any influence on the blood glucose levels.

As expected, there was a distinct increase in blood glucose concentration of approximately 3 mmol/L [mean Max_increase: 3.2 mmol/L (crystal arm); 3.1 mmol/L

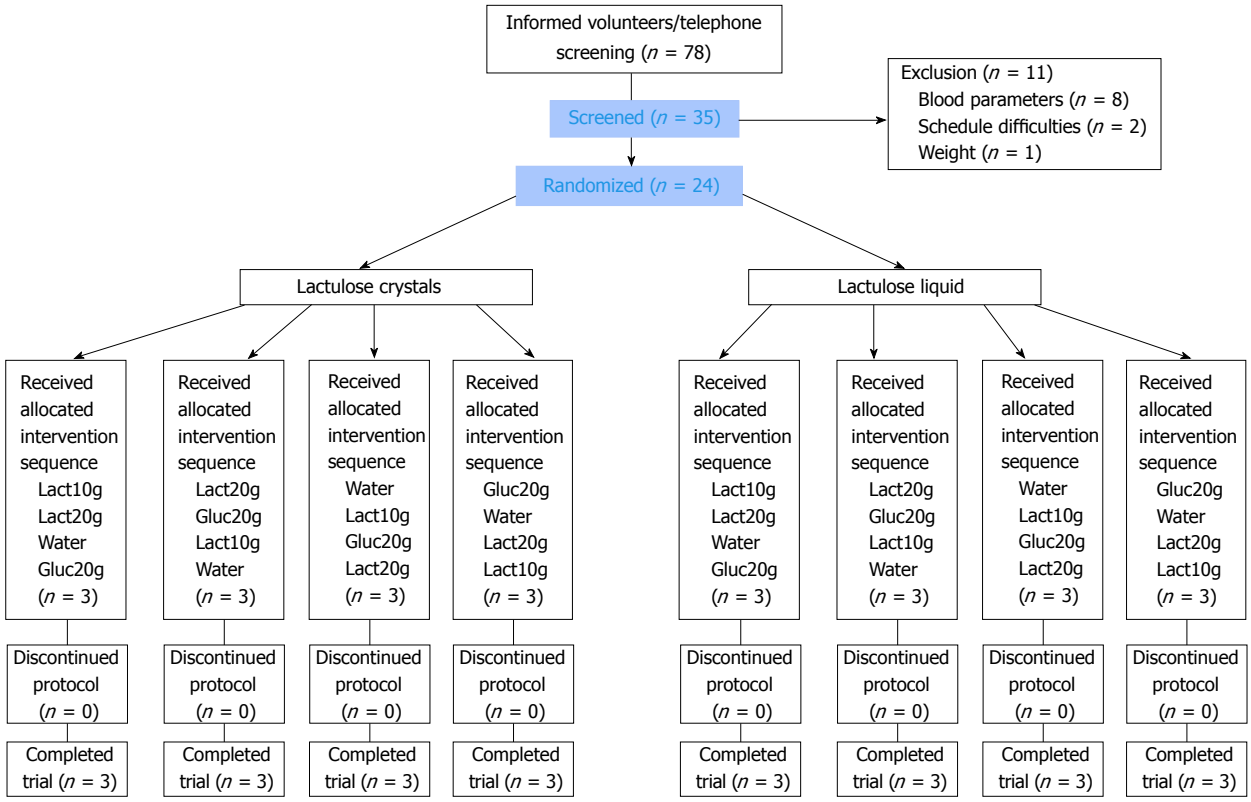

Figure 1 Flowchart demonstrating patient recruitment. Lact10g: Lactulose 10 g; Lact20g: Lactulose 20 g; Gluc20g: Glucose 20 g.

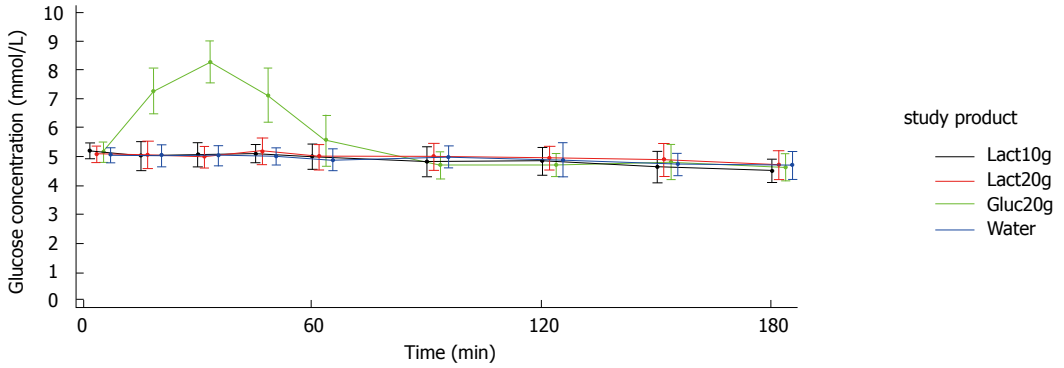

Figure 2 Display of mean ± SD glucose concentration - time curves. Study arm: Crystals. Lact10g: Lactulose 10 g; Lact20g: Lactulose 20 g; Gluc20g: Glucose 20 g; Water: Water 250 mL; SD: standard deviation.

(liquid arm)] after intake of 20 g glucose (mean C_{max} = 8.3 mmol/L in both study arms), reaching its maximum after approx. 30 min [T_{max}: 30.6 min (crystal arm), 37.5 min (liquid arm)] and returning to baseline within approx. 90 min [$T_{baseline}$: 76.8 min (crystal arm), 90.2 min (liquid arm)]. Mean baseline values (*i.e.,* pre-dose values in each study period) were very similar for the four treatments within each study arm.

Lactulose vs negative control (water)

When taking lactulose as crystals or as liquid up to a dosage of 20 g, no differences on blood glucose concentration were observed over a time period of 180 min in comparison to water. iAUCs after the intake of lactulose were comparable with the control group receiving water. LS means are summarized in Tables 3-6. The findings were also confirmed for the secondary endpoints for which no treatment difference compared to water could be identified. T_{max} for lactulose and water were not reported, as there were no glucose concentration peaks, which are necessary to define a distinct time to reach maximum glucose concentration.

20 g lactulose vs 20 g glucose

The estimated treatment difference of iAUC with 95%CIs for lactulose crystals 20 g *vs* glucose 20 g was -109.58 (95%CI: -128.03; -91.13). The estimated treatment difference of iAUC with 95%CIs for lactulose

Table 3 Summary of results of pharmacokinetic variables from analyses-of-variance: Lactulose 10 g (crystals) *vs* Water

Crystals	Lactulose 10 g			Water 250 mL			Treatment difference	
Variable	*n*	LS mean	95%CI	*n*	LS mean	95%CI	Difference	95%CI
iAUC (mmol/L*min)	12	6.91	(-7.41; 21.24)	12	7.74	(-6.57; 22.05)	-0.822	(-19.50; 17.85)
AUC (mmol/L*min)	12	873.11	(841.26; 904.97)	12	896.86	(865.03; 928.70)	-23.75	(-51.80; 4.30)
AUC_base (mmol/L*min)	12	-50.14	(-81.99; -18.28)	12	-26.39	(-58.22; 5.45)	-23.75	(-51.80; 4.30)
C_max (mmol/L)	12	5.32	(5.12; 5.53)	12	5.36	(5.16; 5.57)	-0.04	(-0.30; 0.22)
Max_increase (mmol/L)	12	0.20	(-0.01; 0.40)	12	0.24	(0.03; 0.44)	-0.04	(-0.30; 0.22)

Table 4 Summary of results of pharmacokinetic variables from analyses-of-variance; Lactulose 20 g (crystals) *vs* Water

Crystals	Lactulose 20 g			Water 250 mL			Treatment difference	
Variable	*n*	LS mean	95%CI	*n*	LS mean	95%CI	Difference	95%CI
iAUC (mmol/L*min)	12	12.51	(-1.74; 26.76)	12	7.74	(-6.57; 22.05)	4.772	(-13.58; 23.12)
AUC (mmol/L*min)	12	902.78	(871.02; 934.53)	12	896.86	(865.03; 928.70)	5.912	(-21.48; 33.30)
AUC_base (mmol/L*min)	12	-20.47	(-52.23; 11.28)	12	-26.39	(-58.22; 5.45)	5.912	(-21.48; 33.30)
C_max (mmol/L)	12	5.41	(5.21; 5.62)	12	5.36	(5.16; 5.57)	0.049	(-0.20; 0.30)
Max_increase (mmol/L)	12	0.28	(0.08; 0.49)	12	0.24	(0.03; 0.44)	0.049	(-0.20; 0.30)

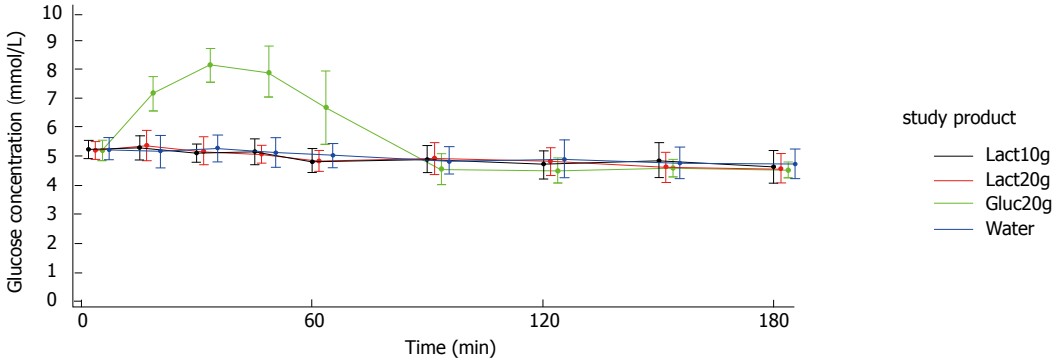

Figure 3 Display of mean ± SD glucose concentration - time curves. Study arm: Liquid. Lact10g: Lactulose 10 g; Lact20g: Lactulose 20 g; Gluc20g: Glucose 20 g; Water: Water 250 mL; SD: standard deviation.

liquid 20 g *vs* glucose 20 g was -130.94 (95%CI: -147.87; -114.00). Thus, a very large difference was observed between glucose and both lactulose formulations (P < 0.0001). The same applies to AUC and AUC_{base}, which were much smaller for 20 g of both lactulose formulations compared to 20 g glucose (P < 0.0001).

The maximum blood glucose concentrations (C_{max}) and the maximum increase of blood glucose ($Max_{\_increase}$) after intake of both lactulose formulations were also significantly lower in comparison to glucose (P < 0.0001).

Lactulose crystals vs lactulose liquid

For the 10 g lactulose dose, the mean iAUC after intake of crystals was 5.12 ± 6.63 mmol/L*min, and after intake of liquid 5.80 ± 8.47 mmol/L*min.

The mean iAUC of blood glucose concentrations after application of 20 g lactulose was 13.56 ± 17.60 mmol/L*min for crystals and 11.74 ± 13.33 mmol/L*min for liquid. As reference, the mean iAUC of water in the crystals study arm was 9.42 ± 8.87 mmol/L*min and 9.76 ± 14.80 mmol/L*min in the liquid study arm. No differences in blood glucose concentration profiles after administration were identified between the two lactulose formulations.

For the AUC and AUC_{base} of blood glucose concentration after intake of 10 g and 20 g lactulose, very similar results for both formulations were observed (data not shown). As there were no distinct glucose concentration peaks after intake of lactulose secondary endpoints, C_{max} and T_{max} were not appropriate to add findings next to the AUC data.

AEs and tolerability

In total, 19 AEs were reported by 11 volunteers, of which three AEs occurred between the screening visit and study visit 1. During the intervention phase (study visit 1-4) in each study arm, eight AEs occurred, which were reported by six subjects in the crystals study arm and five subjects in the liquid study arm. Overall, none of the AEs were serious and all AEs resolved at the end of the study. No AE led to discontinuation or modification of study product dosage.

Of these 16 AEs, seven possibly related AEs [digestive system (6 ×), headache (1 ×)] were reported and rated 6 × as mild and 1 × as moderate (heartburn). These AEs occurred after the intake of lactulose. Frequencies

Table 5 Summary of results of pharmacokinetic variables from analyses-of-variance: Lactulose 10 g (liquid) *vs* Water

Liquid	Lactulose 10 g			Water 250 mL			Treatment difference	
Variable	*n*	LS mean	95%CI	*n*	LS mean	95%CI	Difference	95%CI
iAUC (mmol/L*min)	12	5.89	(-8.94; 20.72)	12	9.92	(-4.92; 24.77)	-4.029	(-20.97; 12.91)
AUC (mmol/L*min)	12	886.19	(852.75; 919.64)	12	890.45	(856.97; 923.93)	-4.258	(-33.36; 24.85)
AUC_base (mmol/L*min)	12	-53.93	(-87.38; -20.48)	12	-49.67	(-83.15; -16.19)	-4.258	(-33.36; 24.85)
C_max (mmol/L)	12	5.41	(5.17; 5.66)	12	5.49	(5.24; 5.73)	-0.073	(-0.35; 0.20)
Max_increase (mmol/L)	12	0.19	(-0.05; 0.43)	12	0.26	(0.02; 0.51)	-0.073	(-0.35; 0.20)

Table 6 Summary of results of pharmacokinetic variables from analyses-of-variance: Lactulose 20 g (liquid) *vs* Water

Liquid	Lactulose 20 g			Water 250 mL			Treatment difference	
Variable	*n*	LS mean	95%CI	*n*	LS mean	95%CI	Difference	95%CI
iAUC (mmol/L*min)	12	11.62	(-3.21; 26.46)	12	9.92	(-4.92; 24.77)	1.701	(-15.29; 18.69)
AUC (mmol/L*min)	12	886.03	(852.58; 919.49)	12	890.45	(856.97; 923.93)	-4.419	(-33.65; 24.82)
AUC_base (mmol/L*min)	12	-54.09	(-87.55; -20.64)	12	-49.67	(-83.15; -16.19)	-4.419	(-33.65; 24.82)
C_max (mmol/L)	12	5.57	(5.33; 5.81)	12	5.49	(5.24; 5.73)	0.083	(-0.19; 0.36)
Max_increase (mmol/L)	12	0.35	(0.10; 0.59)	12	0.26	(0.02; 0.51)	0.083	(-0.19; 0.36)

of reported possibly related AEs attributed to the digestive system were higher in the liquid study arm (five AEs reported by three subjects) compared to the crystals study arm (one AE); especially stomach ache was reported [3 × liquid study arm (2 × 10 g + 1 × 20 g)]. Furthermore, flatulence (1 × 10 g liquid), diarrhea (1 × 20 g liquid) and heartburn (1 × 20 g crystals) were reported. All other AEs were not related [six AEs: rhinitis, running nose, cough, migraine, headache (2 ×)] or unlikely related [three AEs: one subject after 10 g crystals (headache) and two AEs: one subject after intake of 20 g glucose (nausea and headache)].

Tolerability was assessed directly after the end of the blood glucose concentration assessment period (after 180 min) and 24 h after intake of study products after each intervention phase. The majority of subjects judged the tolerability at the single assessment time points as "well tolerated". Only twice at the 180 min time point (1 × glucose; 1× lactulose 20 g liquid) and five times 24 h after intake, the product was rated as slightly unpleasant (after 10 g lactulose: 1 × crystal arm, 2 × liquid arm; 2 × after 20 g lactulose liquid). Very unpleasant tolerability was only rated 1 × after 20 g lactulose crystals. The tolerance assessment by subjects reflects the occurrence of AEs.

DISCUSSION

This study was performed as a prospective, open, mono-center, randomized, two-part study with 4-way cross-over design in each study arm to investigate blood glucose levels after oral intake of lactulose.

Due to the small amounts of carbohydrate impurities, up to 3% in lactulose crystals and approximately 30% in the liquid formulation, no or only small changes in blood glucose levels were expected. These expectations were confirmed by all primary and secondary endpoints. The glucose concentration-time curves showed that there was no difference after intake of lactulose (crystals or liquid) and water. iAUCs, AUCs and AUC_{base} after intake of lactulose were comparable with the control assessment with water. The intake of the two single lactulose dosages 10 g and 20 g did not affect blood glucose levels. This is in accordance with previous studies showing that 25 g lactulose did not increase blood glucose concentration in female lactose digesters and maldigesters[9] or diabetic subjects[8]. Hoffmann *et al*[7] showed only a slight increase of blood glucose level after intake of 36.4 g lactulose syrup containing 8.4 g of sugars and 20 g of lactulose. The dose of lactulose and accompanying sugars in the case report published by Kirkman *et al*[6] was higher compared to this study (daily intake 3 × 30 mL lactulose syrup, containing 24 g of simple sugars). However, the increase in blood glucose after changing the lactulose brand (3 × 30 mL lactulose syrup, containing 27.6 g of simple sugars) could not be explained by sugar impurities because the difference in daily intake was only 3.6 g. Normal food may cause much higher differences in daily sugar intake.

Furthermore, investigating AUC_{base} indicated an overall negative area for all lactulose administrations and water. This means that blood glucose concentrations tended to decrease over time. Of note, these changes over time during/after lactulose administration occurred within a tight range and within the normal limits of fasting blood glucose and were comparable with water. Consequently, no hypoglycemic values were observed during and after lactulose administration. The decrease expressed as AUC_{base} was to the same extent as with water and only reflects the normal physiologic metabolism. One should bear in mind that at the end of the intervention phase, subjects were fasting for at least 13 h.

The analysis of blood glucose levels was performed in capillary blood to also enable the determination of minor changes. Capillary measurement reflects changes in blood glucose more readily at finger sites than at the forearm[10,11]. This approach is also used for the determination of the GI. In this context, analysis in

capillary finger-prick samples is discussed to be less variable and more sensitive to postprandial changes compared to venous blood samplings[12,13]. As expected, there was a significant difference for iAUC, AUC, AUC_{base} and C_{max} after the intake of lactulose (crystals or liquid) compared to glucose. Interestingly, there was a decrease in blood glucose concentrations below baseline 90 min and 120 min after intake of glucose in both study arms. This minor decrease was counteracted by the body returning to baseline concentrations after 150 and 180 min. This profile reflects the regulation of the body by a normal slight overcompensation in the management of blood glucose concentration and is also described in GI determinations for various foods containing simple sugars[14].

Despite the higher concentration of carbohydrate impurities in the used lactulose liquid formulation with 26.45% in comparison to only 1.5% in crystals, both formulations showed similar blood glucose curves with no differences when evaluating primary and secondary endpoints. In both study arms, a difference between lactulose dosages was not apparent. This can be explained by the low total amount of sugars in both lactulose products (*i.e.,* 0.3 g in crystals and 5.29 g in liquid formulation in the 20 g dosages). Furthermore, not all sugars may affect blood glucose to the same extent as glucose[15]. Even comparable decreases in blood glucose concentrations over time (expressed as baseline corrected AUC) were observed for the 10 g and 20 g dosages as well as for water.

This study adds data for currently marketed lactulose products to available data published between 1964 and 1999. For the first time, two doses of two lactulose formulations (crystals and liquid) were compared in a cross-over design ensuring high credibility and power of the study since expected high variation between subjects is of no concern in cross-over settings. Furthermore, older studies included less subjects[7,8] or women only[9]. The study was performed in compliance with ISO 26642:2010.

One limitation of the study might be the open design. Despite subjects being blinded on the dosage of study products (10 g or 20 g lactulose or 20 g glucose) as well as on the formulation (crystal or liquid), subjects could possibly distinguish between water as control and the study products due to the slight sweet taste of lactulose. Anyhow, it is expected that the impact of such a confounding factor on the objective measure of blood glucose level is rather limited, and placebo effects on blood glucose level were not identified from the study results.

These results clearly demonstrate that the carbohydrate impurities in 10-20 g of lactulose preparations have no impact on the glucose metabolism in healthy adults. As a next step, data should be confirmed in a study collective with impaired glucose tolerance. Overall, tolerability was good. Some volunteers reported mild and one volunteer reported moderate gastrointestinal side effects of lactulose, which are known[16,17].

In summary, a single dose administration of 10 g and 20 g of lactulose as crystals or liquid with their small amounts of carbohydrate impurities had no impact on blood glucose concentration in healthy subjects. Comparable to water, there was no glycemic response. Taken together, these data suggest that lactulose used as a functional food ingredient may also be consumed by people with impaired glucose tolerance.

ARTICLE HIGHLIGHTS

Research background

During the manufacturing process of lactulose, impurities with sugars (*e.g.,* lactose, fructose, galactose) occur. Because lactulose is used as a functional food ingredient, it may also be consumed by people with impaired glucose tolerance, including diabetics. Therefore, it is of interest whether the described carbohydrate impurities may increase blood glucose levels after ingestion.

Research motivation

There is only limited information if lactulose and especially the currently marketed formulations (liquid formulation and crystals) influence the blood glucose level.

Research objectives

The main objective was to investigate possible changes of blood glucose levels after oral intake of lactulose in healthy subjects.

Research methods

The study was performed as a prospective, randomized, two-part study with a 4-way cross-over design with $n = 12$ in each study arm. Capillary blood glucose levels were determined over a time period of 180 min after intake of a single dose of 10 g or 20 g lactulose provided as crystal or liquid formulation. Water and 20 g glucose were used as control and reference, respectively.

Research results

The blood glucose concentration-time curves after intake of 10 g lactulose, 20 g lactulose, and water were almost identical. The three applications did not show any changes in the blood glucose levels. There was no difference between lactulose liquid and crystals. After intake of 20 g glucose, blood glucose concentration increased by approximately 3 mmol/L (mean C_{max} = 8.3 mmol/L), reaching maximum levels after approximately 30 minutes and returning to baseline within approximately 90 minutes, which was significantly different to the corresponding 20 g lactulose formulations ($P < 0.0001$).

Research conclusions

The unchanged blood glucose levels after lactulose intake in healthy subjects suggest its safe use in subjects with impaired glucose tolerance.

Research perspectives

As a next step, data should be confirmed in a study collective with impaired glucose tolerance.

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ORIGINAL ARTICLE

Observational Study

Colorectal cancer screening use among insured adults: Is out-of-pocket cost a barrier to routine screening?

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Abstract

AIM

To describe the characteristics of adults who needed to see a doctor in the past year but could not due to the extra cost and assess the impact of limited financial resources on the receipt of routine fecal occult blood test, sigmoidoscopy, or colonoscopy for colon cancer screening among insured patients.

METHODS

Data obtained from the 2012 Behavioral Risk Factor Surveillance System included 215436 insured adults age 50-75 years. We computed frequencies, adjusted odds ratios (aORs), and 95%CIs using SAS v9.3 software.

RESULTS

Nine percent of the study population needed to see a

doctor in the past year but could not because of cost. The numbers were significantly higher among those aged 50-64 ($P < 0.0001$), Non-Hispanic Whites ($P < 0.0001$), and those with a primary care physician ($P < 0.0001$) among other factors. Adjusting for possible confounders, aORs for not seeing the doctor in the past year because of cost were: stool occult blood test within last year aOR = 0.88; 95%CI: 0.76-1.02, sigmoidoscopy within last year aOR = 0.72; 95%CI: 0.48-1.07, colonoscopy within the last year aOR = 0.91; 95%CI: 0.81-1.02.

CONCLUSION

We found that the limited financial resources within the past 12 mo were significantly associated with colorectal cancer (CRC) non-screening. Patients with risk factors identified in this study should adhere to CRC guidelines and should receive financial help if needed.

Key words: Fecal occult blood; Healthcare delivery; Sigmoidoscopy; Colorectal cancer; Screening; Access to care; Behavioral Risk Factor Surveillance System

Core tip: There is scarcity of data about role of "out-of-pocket costs" among insured patients. From a prospectively collected database of more than 200000 insured individuals, we found that almost 9% of the population could not see a doctor due to an out-of-pocket cost issue. This occurrence was significantly higher in African-Americans, and those without primary care physicians. Undergoing the stool occult blood test, sigmoidoscopy, or colonoscopy in past one-year was significantly associated with not following up with a physician because of cost. The results of our study show that limited financial resources are significantly associated with colorectal cancer non-screening in the insured Americans.

Perisetti A, Khan H, George NE, Yendala R, Rafiq A, Blakely S, Rasmussen D, Villalpando N, Goyal H. Colorectal cancer screening use among insured adults: Is out-of-pocket cost a barrier to routine screening? *World J Gastrointest Pharmacol Ther* 2018; 9(4): 31-38 Available from: URL: http://www.wjgnet.com/2150-5349/full/v9/i4/31.htm DOI: http://dx.doi.org/10.4292/wjgpt.v9.i4.31

INTRODUCTION

Colorectal cancer (CRC) is the leading cause of cancer-related mortality in the United States after breast and lung cancer[1]. According to the National Cancer Institute (NCI), the five-year survival rate for CRC patients between the years 2007 and 2013 was only 64.9%[2]. As per the American Cancer Society (ACS, 2017), approximately 135430 patients would be diagnosed with CRC, representing 8% of all new cancer cases[3]. The mortality rates have been declining in the past decades which is thought to be mainly due to the widespread use of CRC screening[3]. The rate of decline in the CRC-related mortality has accelerated slightly; from 2005 to 2014, with rates decreased by an average of 2.5% per year[3]. However, this progress has lagged in the high-poverty and rural areas of the United States, including the lower Mississippi Delta and parts of Appalachia[2]. In the National Colorectal Cancer Roundtable (NCCRT), almost 1500 organizations have committed to reducing CRC as a significant public health problem and are working toward an ambitious goal of reaching 80% screening rate for CRC by 2018[4].

The screening rate for CRC was 52.1% in 2008 and 62.6% in 2015[5]. Colonoscopy can reduce CRC mortality by almost 50%[6]. Screening rates are known to be higher among individuals with high income and higher education[7]. Unfortunately, for many individuals, CRC screening is not a priority due to multiple possible reasons. Over the past decade, intense research has been focused on predictors of CRC screening to improve the screening rates[8]. Availability of health insurance, the level of income, educational status, and access to a personal doctor, obesity, and race were significant predictors of CRC non-screening rates[9-11]. Though uninsured individuals are at high-risk for non-screening, studies related to the barriers to CRC screening among insured individuals are scarce[9].

The financial burden of CRC screening is huge in the United States[3]. In a comparative effectiveness study on CRC screening procedures, the yearly cost for providing fecal immunochemical tests (FITs) to 5863 patients was estimated to be $1.47 million whereas the annual cost for providing colonoscopies for 4869 patients was expected to be $5.17 million[12]. However, the adenoma detection rate with FIT's was only 1.6% as compared to the colonoscopies, which detected 23.6% of adenoma[12]. Therefore, while costs vary considerably, the differences between the tests' sensitivities are worth the extra cost. Beyond screening costs, medical costs of treatment were even more extreme in the United States In 2014, the direct medical costs of CRC added up to roughly $14 billion[3].

With the introduction of the Patient Protection and Affordable Care Act (ACA), a larger percentage of adults obtained health insurance[13]. We studied the barriers to routine CRC screening in an "insured population" which might predict who will be screened in the future. Even though a larger percentage of adults are becoming "insured", the "out-of-pocket" costs for CRC screening might also affect the screening rate[14]. There is a limited data on the barriers to screening in insured adults, but "out-of-pocket costs" appear to be emerging as an essential factor in the prediction of screening[15]. Despite having health insurance, the out-of-pocket cost might be an important variable for potential recipients of the screening and hence could be a target for future research. Several studies have studied the effects of out-of-pocket costs on uninsured individuals, but there is a huge gap in the research about these effects on insured individuals.

MATERIALS AND METHODS

We utilized the Behavioral Risk Factor Surveillance System

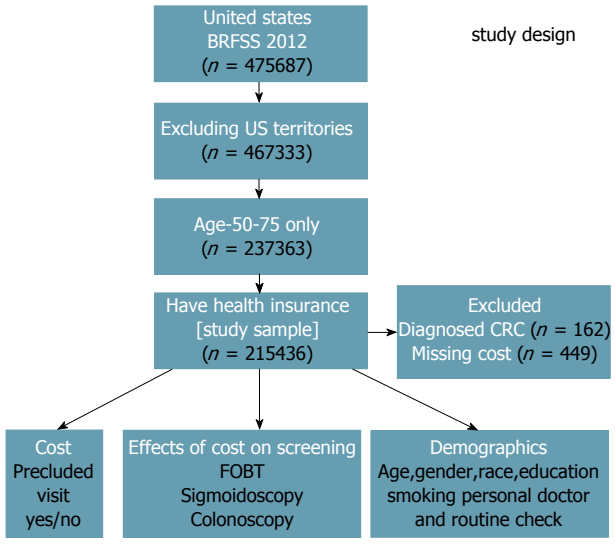

Figure 1 Study design. CRC: Colorectal cancer; BRFSS: Behavioral Risk Factor Surveillance System; FOBT: Fecal Occult Blood testing.

(BRFSS) 2012, a United States national database, to apply individual predictors affecting the CRC screening. BRFSS is a random-digit-dialed telephone survey of the noninstitutionalized United States civilian population aged 18 and older. Individuals were asked the demographic and health-related questions such as the insurance status, visits to doctors in specified time periods, screenings received, and influence of "out-of-pocket" visiting a physician and getting screened. Initially, 475687 individuals were surveyed in the BRFSS 2012 (Figure 1). Excluding United States territories (Guam, Puerto Rico, American Samoa, Northern Mariana Islands, and United States Virgin Islands), 467333 individuals were evaluated. Of these individuals, 237363 were aged between 50 to 75 years, and 216047 had health insurance. Financial data was not available regarding 449 people, and 162 were already diagnosed with CRC. Excluding these, a study sample of 215436 was obtained.

Demographic characteristics of the population are described in Table 1. Among these individuals with cost constraints, subjects were divided into an age 50-64 year group (10%, early CRC screening) and age 60-75 year group (5%, late CRC screening). We applied United States Preventive Service Task Force (USPSTF), Centers for Disease Control and Prevention (CDC), and ACS recommendations to assess the CRC screening rates among individuals who could and could not see a doctor due to cost (out-of-pocket) constraints. We computed frequencies, adjusted odds ratios (aORs), and 95% confidence intervals (CIs) using Surveyfreq and Surveylogistic. SAS v.9.3 (SAS Institute, Cary, NC) was used to analyze the data in a manner that accounts for the BRFSS's complex sample survey design.

RESULTS

Out of 215436 adults aged between 50 and 75 years, 9% (16517) individuals could not see a doctor due to out-of-pocket cost constraints even when in need of screening (Table 1). The prevalence of adults who could not afford to visit a doctor in the last 12 mo because of "out-of-pocket cost" was significantly higher among 50-64 years old individuals than 65-75 year ($P < 0.0001$); men compared to females ($P < 0.0001$); Non-Hispanic Whites in comparison to Non-Hispanic Blacks ($P < 0.0001$); those who were college graduates compared to those who did not graduate from high school ($P < 0.0001$). The prevalence of "unable to see a doctor due to cost constraint" in the past 12 mo was unusually high among respondents who were: Healthy adults in comparison to the adults with fair or poor health ($P < 0.0001$), non-smokers versus current smokers ($P < 0.0001$), and the individuals with a doctor compared to those without a personal doctor ($P < 0.0001$).

Among adults aged 50-75 years, 5913 individuals who never received a colonoscopy screening due to out-of-pocket cost constraints were lower than those without cost constraint (OR = 0.72). Similar observations were noted for the use of sigmoidoscopy and FOBT (Table 2). To assess the trend of CRC screening, we used the data from BRFSS 2008 and 2010 together with that for 2012. We compared adults with out-of-pocket cost constraint to adults who did not report a cost constraint, and found a significant association in receipt of a colonoscopy within the last 12 months for BRFSS 2008, 2010, and 2012 [aOR = 0.77; 95%CI: 0.69-0.85, 0.90 (0.82-0.99), 0.90 (0.80-1.00); respectively]. This was adjusted for age, gender, race, education level, general health status, having a personal doctor, the length of time since the last routine checkup, and per capita primary care physicians with a univariate logistic model (Figure 2). The odds of getting a colonoscopy screening in the past 12 months improved from 2008 to 2012 [aOR = 0.77; 95%CI: 0.69-0.85; 2008 *vs* 0.90 (0.80-1.00); 2012]. However, this was not seen with FOBT [aOR = 0.93; 95%CI: 0.83-1.05; 2008 *vs* 0.88 (0.77-1.01), 2012] or sigmoidoscopy [aOR = 0.72; 95%CI: 0.49-1.04; 2008 *vs* 0.69 (0.46-1.03), 2012], indicating there might be a paradigm shift towards colonoscopy as a preferred way of CRC screening compared to FOBT or sigmoidoscopy in recent years.

DISCUSSION

Our study indicates that out-of-pocket cost is a potential barrier in the colonoscopy for colon cancer screening among the insured population. Studies identifying barriers to CRC screening among insured adults are rare. Our study focuses on the "insured adults" compared to other studies that target the uninsured groups[16]. While the need to look at the uninsured population is essential, this study indicates that the same factors that limit screening colonoscopy in uninsured also affect many of the insured. With more adults obtaining health insurance due to the expanded ACA, concern about the out-of-pocket costs is increasing. Despite the expansion of health insurance, there are potential hidden costs that remain a barrier to the screening process[16-18]. Understanding the specifics

Table 1 Characteristics of 2012 Behavioral Risk Factor Surveillance System respondents ages 50-75 years old who had health insurance by the affordability of doctor visit *n* (%)

Variables	Cost precluded a doctor visit[1]	Cost did not affect a doctor visit	*P*-value	Odds ratio (99%CI)
Total (*n* = 215436)	16517 (9)	198919 (91)		
Age group (*n*)				
50-64 (127569)	12149 (73.6)	115420 (58.0)	< 0.0001	
65-75 (87867)	4368 (26.4)	83499 (42.0)		2.01 (1.92, 2.11)
Gender (*n*)				
Male (86028)	5442 (32.9)	80586 (40.5)	< 0.0001	
Female (129408)	11075 (67.1)	118333 (59.5)		0.72 (0.69-0.75)
Race/ethnicity (*n*)				
White, non-Hispanic (177916)	11806 (71.5)	166110 (83.5)	< 0.0001	
Black, non-Hispanic (16861)	2107 (12.8)	14754 (7.4)		0.50 (0.47-0.53)
Hispanic (7847)	1049 (6.4)	6798 (3.4)		0.46 (0.41-0.51)
Others (10314)	1321 (8.0)	8993 (4.5)		0.48 (0.43-0.54)
Education attainment (*n*)				
Did not Graduate High School (15280)	2367 (14.3)	12,913 (6.5)	< 0.0001	
Graduated High School (62826)	5439 (32.9)	57387 (28.8)		0.75 (0.70-0.80)
Attended College/Technical School (58305)	4852 (29.4)	53453 (26.9)		0.78 (0.74-0.83)
Graduated College/Technical School (78388)	3795 (23.0)	74593 (37.5)		1.40 (1.32-1.48)
Health status (*n*)				
Excellent/very good/good (169114)	8841 (53.5)	160273 (80.6)	< 0.0001	
Fair/poor (45648)	7594 (46.0)	38054 (19.1)		0.28 (0.26-0.29)
Body mass index (kg/m^2)				
Normal (2666)	280 (1.7)	2386 (1.2)	0.0205	
Overweight (60265)	4099 (24.8)	56166 (28.2)		0.97 (0.82-1.15)
Obese (77582)	5177 (31.3)	72405 (36.4)		0.99 (0.94-1.05)
Current smokers (*n*)				
Yes (31599)	4119 (24.9)	27480 (13.8)	< 0.0001	2.09 (1.99-2.20)
No (179993)	12034 (72.9)	167959 (84.4)		
Binge drinkers[2] (*n*)				
Yes (18355)	1349 (8.2)	17006 (8.5)	0.9101	
No (189647)	14486 (87.7)	175161 (88.1)		0.96 (0.89-2.20)
Have a personal doctor or health care, provider				
Yes, at least one (200482)	14657 (88.7)	185825 (93.4)	< 0.0001	
No (14554)	1801 (10.9)	12753 (6.4)		0.56 (0.52-0.60)

Missing not included; therefore, some variables' total percentages do not meet 100%. [1]Adults who could not see a doctor in the last 12 mo because of cost; [2]Males having five or more drinks on one occasion, females having four or more drinks on one occasion.

of a health care plan might delineate some of the costs involved in the process.

The USPSTF recommends the use of either FOBT, sigmoidoscopy, or colonoscopy as the approved CRC screening methods beginning at the age of 50 years in average-risk individuals[19]. Colonoscopy is the most preferred and accurate of all the screening methods but is also the most expensive[19-21]. FOBT can reduce the number of deaths from CRC by approximately 15% to 33%[21]. FOBT is a non-invasive test and can be easily done at home[21]. For patients avoiding screening due to embarrassment, social stigma, or lack of financial resources, FOBT can be a great solution to raise screening rates. People aged 50 to 60 years who are screened with sigmoidoscopy have a 70% lower risk of death due to CRC compared to those not screened[22]. Sigmoidoscopy is only needed every 5-years, making it convenient for patients living in the rural areas with limited transportation and medical care[23]. Lastly, screening colonoscopies have been shown to reduce the risk of death by 60% to 70%[20]. Colonoscopies are needed every ten years as recommended by the USPSTF, which helps to counteract its high cost[23]. While endoscopy procedures are invasive, the time and money spent on fewer screenings overall can be a great motivator for rural patients to increase their screening rate for CRC[22]. In the recent years, the virtual colonoscopy has been developed, which is performed via CT scan but in much less invasive fashion[24]. With this test, there are fewer risks of complications as well[24]. However, due to the lack of evidence for assessing the effectiveness of virtual colonoscopy due to the limited number of studies, it has not been accepted as a mainstream screening method. Moreover, extracolonic incidental findings on virtual colonoscopy can lead to over diagnosis and over treatment[23]. Some insurance companies including Medicare still do not cover this procedure making it a high out-of-pocket cost screening method not only for those who are uninsured but also for

Table 2 Colorectal cancer screening of the 20122 Behavioral Risk Factor Surveillance System respondents ages 50-75 years old *n* (%)

Variables	Cost precluded a doctor visit	Cost did not preclude a doctor visit	*P*-value	Odds ratio (99%CI)
Time since last blood stool test (*n*)				
Within the past year (20496)	1420 (9.1)	19076 (10.0)	< 0.0001	
Within the past 2 to < 5 yr (29863)	1838 (11.8)	28025 (14.9)		1.25 (1.14-1.38)
5 or more years (25290)	1569 (10.1)	23721 (12.6)		1.24 (1.13-1.36)
Never (128556)	10717 (68.9)	117839 (62.5)		0.90 (0.84-0.97)
Time since last sigmoidoscopy (*n*)				
Within the past year (1053)	80 (0.5)	973 (0.5)	< 0.0001	
Within the past 2 to < 5 yr (2645)	172 (1.0)	2473 (1.2)		1.18 (0.82-1.70)
5 or more years (2888)	238 (1.4)	2650 (1.3)		1.24 (1.13-1.36)
Never (57443)	5913 (35.8)	51530 (25.9)		0.90 (0.84-0.97)
Time since last colonoscopy (*n*)				
Within the past year (33454)	2316 (14.0)	31138 (15.7)	< 0.0001	
Within past 2 to < 5 yr (77619)	4634 (28.1)	72985 (36.7)		1.29 (1.21-1.39)
5 or more years (28253)	1931 (11.7)	26322 (13.2)		1.12 (1.04-1.20)
Never (57443)	5913 (35.8)	51530 (25.9)		0.72 (0.67-0.77)

Missing values not included; therefore, some variables' total percentages do not meet 100%.

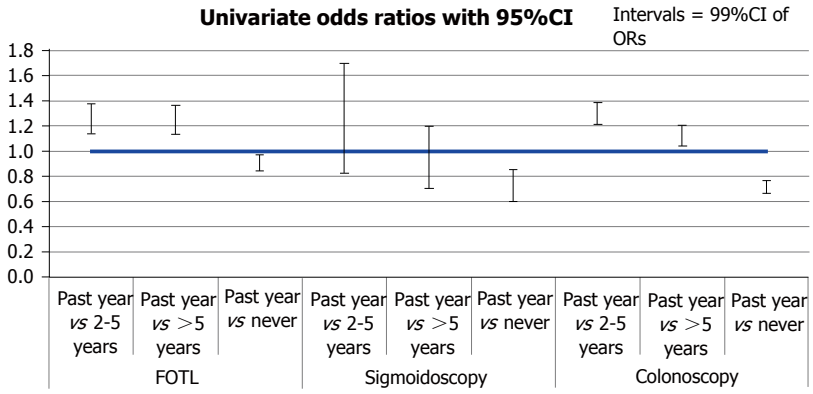

Figure 2 Odds ratios for fecal occult testing, sigmoidoscopy and colonoscopy. FOTL: Fecal occult testing (same as FOBT: Fecal occult blood testing).

insured individuals. As one could expect, out-of-pocket costs affect all everyone in the population, and thus, all sectors of the population need to be studied in regards to this particular barrier to investigating whether this barrier is a significant driver of low CRC screening rates.

The ACS reports that disparities in CRC survival time are predominantly due to socioeconomic variables such as race/ethnicity, insurance coverage, and income[3]. These disparities also drive the access to early screening procedures, which influence the patients' prognosis ultimately[3]. For instance, Non-Hispanic Blacks and American Indians or Alaskan Natives are the most likely to be diagnosed with metastatic CRC[3]. Non-Hispanic Whites, as well as Asian and Pacific Islanders, are most likely to be diagnosed with the local CRC, which is much easier to treat and cure[3]. Also, 5-year survival rates also indicate disparities[3]. For instance, only 11% of Non-Hispanic Blacks versus 14% of Non-Hispanic Whites live for 5-years after diagnosis of metastatic CRC[3].

Health insurance related barriers to screening

Most healthcare insurance carriers divide the costs between premium (monthly fee to the insurance carrier), deductible (initial payment by beneficiary before insurance payment), cost-sharing (percentage of cost shared by insurance carrier and beneficiary), co-payment (cost for routine services which is not paid by deductible) and out-of-pocket cost (which is the absolute payment for healthcare cost annually). ACA recommends zero cost-sharing and zero co-payment (which includes screening colonoscopy)[13]. However, the amount of deductible and out-of-pocket cost remains unclear. Although out-of-pocket costs and co-payments are useful in a more meaningful utilization of the health care system, their use in screening procedures is debatable[17].

Screening colonoscopy is traditionally covered by most of the insurance carriers. However, if during the screening procedure, a lesion is identified, removed, and biopsied, it is termed as "diagnostic or therapeutic" colonoscopy. In most events, there would be additional costs related to pathology, anesthesia and facility fees. This leads to an ill-defined area, where screening colonoscopies turn into a diagnostic and may result in high co-payment and out-of-pocket cost to the patient[17]. These costs are difficult

to predict, given that different insurance carriers charge differently (including within or out of network groups) which leads to varying costs for colonoscopies in the United States[14]. Also, state-specific rules apply with regards to the extent of coverage for the screening procedures[18]. It was previously reported that health insurance plans with high deductibles have a lower percentage of screening colonoscopy[15]. These hidden costs make the receipt of colonoscopy a costly affair for the beneficiary and might prevent the widespread screening of CRC[14].

The lack of health insurance, educational level, smoking, alcohol intake, non-availability of a personal doctor, race, and employment status are among some of the important barriers to routine CRC screening[9-11,25]. These barriers could be divided into provider, practice, or patient based[1,16]. In recent years there has been an increased need for the system-based methods to promote screening explicitly targeting patient-related barriers[26]. Among the obstacles which could potentially be reversible, lack of insurance coverage remains an important one[11,13,16]. Among barriers to colonoscopy, lack of a personal doctor, ethnicity, low socioeconomic status, lack of education, rural location and non-availability of health care coverage constitutes a vulnerable section[8-10,22,27]. Over the last few years, there has been a push to find an answer on how to raise the low CRC screening rates. Use of health information technologies, computerized reminders, mailed letters, clinician feedback, narrative interventions, a culturally targeted navigation system, care plan, clear goal setting, performance-based financial incentive, and personal telephone outreach has been found to increase the adherence to CRC screening[26,28-33]. Patients undergoing screening for other cancers like prostate, breast, or cervical are usually more adherent to CRC screening which indicates overall health as a variable for screening. This might be utilized by the health care providers to discuss the CRC screening during patient visits for other cancer screening[34]. Also, an active discussion about health care reforms and coverage with the patient and physician could probably help. An interactive multimedia computer program (IMCP) to expand psychosocial factors for promoting CRC screening was tried, but with limited success[35].

Strengths and limitations

One of the strengths of this study is the inclusion of a large random sample. Furthermore, information about confounding variables affecting the colorectal screening helped in effective comparison. Availability of BRFSS data over 2008, 2010 and 2012 helped in predicting a trend. Also, the unique aspect of our focus on the insured individuals' sheds light on an aspect of out-of-pocket barriers to screening that has not been explored prior to this study.

There are some potential limitations to our study. BRFSS is based on non-institutionalized adults and not patient-based data. However, as screening involves adults without symptoms, this is being of low significance. There are some missing data in the BRFSS that could limit our study interpretation. Subjects with precluded visits were more likely to have missed FOBT ($P < 0.0001$) as well as sigmoidoscopy and colonoscopy ($P < 0.0001$) than individuals without a precluded visit. This is expected, given that adults who cannot afford to get screening due to the cost are more likely not to report or do not recall any screening events. Our data predominately includes white non-Hispanics population that could limit the validity of results. Given the one-time telephonic survey and cross-sectional causality could not be determined. Adults without access to a landline or cell phone are excluded from this survey. It is limited to adults speaking English or Spanish language. It is also obvious that some respondents may not give the information in its entirety during the self-reporting telephonic conversation. The results are limited to the US healthcare system, therefore, might not apply to other countries because of variation in colon cancer screening guidelines.

Our findings that out-of-pocket cost may be a barrier to the receipt of colonoscopy might have a potential role in future, larger studies. As we see the trend of increased recognition of colonoscopy as a CRC screening option compared to FOBT or sigmoidoscopy, the rate of receipt of colonoscopies is expected to rise in the future. This would probably be a paradigm shift with colonoscopy taking over as a predominant screening for CRC screening. Given the reversible nature of insurance coverage issues, a payment program targeting the vulnerable population either federal or state-funded among the insured adults might reduce the bridge between the target and current screening rate. Formulating designs and protocols to isolate the vulnerable adults from the impact of high out-of-pocket costs for screening might decrease the CRC mortality. Use of health savings accounts and access to insurance plans, which cover a large portion of the out-of-pocket costs, educating individuals and discussing these models probably will move closer to the targeted screening rate.

ARTICLE HIGHLIGHTS

Research background

Over the past decade, intense research has been focused on predictors of colorectal cancer (CRC) screening to improve the screening rates. Availability of health insurance, the level of income, educational status, and access to a personal doctor, obesity, and race were found to be significant predictors of CRC non-screening rates in the past. Though uninsured individuals are at high-risk for non-screening, studies related to the barriers to CRC screening among insured individuals are scarce.

Research motivation

There is only limited information if out-of-pocket cost restraints in the insured population affect the receipt of coloscopy for CRC screening.

Research objectives

The main objective was to investigate if out-of-pocket cost restraint plays a part in not getting the screening colonoscopy.

Research methods

The study was performed from a prospectively collected telephone database named Behavioral Risk Factor Surveillance System (BRFSS) (2012) included

215,436 insured adults age 50-75 years. We computed frequencies, adjusted odds ratios (aORs), and 95%CIs using SAS v9.3 software.

Research results

Nine percent of the insured population needed to see a doctor in the past year but could not because of cost. The numbers were significantly higher among those aged 50-64 ($P < 0.0001$), Non-Hispanic Whites ($P < 0.0001$), and those with a primary care physician ($P < 0.0001$) among other factors. Adjusting for possible confounders, aORs for not seeing the doctor in the past year because of cost were: stool occult blood test within last year aOR = 0.88; 95%CI: 0.76-1.02, sigmoidoscopy within last year aOR = 0.72; 95%CI: 0.48-1.07, colonoscopy within the last year aOR = 0.91; 95%CI: 0.81-1.02.

Research conclusions

Out-of-pocket cost is a barrier to the receipt of colonoscopy in the insured population.

Research perspectives

Further steps should be taken to target the insured population to increase the colon cancer screening.

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EDITORIAL

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EDITORIAL

Challenges in the management of pancreatic exocrine insufficiency

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Abstract

Pancreatic exocrine insufficiency (PEI) occurs when the insufficient secretion or function of pancreatic enzymes leads to maldigestion, most commonly as a result of chronic pancreatitis and pancreatic cancer. The condition is associated with significant morbidity and reductions in quality of life, even in milder forms. The challenges in approaching this condition include the non-specific presentation of mild to moderate PEI, and the lack of a convenient, accurate diagnostic test in this cohort. Classical symptoms appear late in the disease, and the diagnosis should be considered before steatorrhoea develops. Direct pancreatic function tests are the reference standard for diagnosis, but are invasive and not widely available. The faecal elastase-1 (FE-1) stool test is widely available and has been shown to be as effective as the ^{13}C-mixed triglyceride breath test in more advanced disease. We recommend a pragmatic diagnostic approach that combines clinical history, assessment of nutritional status and measurement of FE-1. The critical first step is to consider the diagnosis. Once the diagnosis is confirmed, pancreatic enzyme replacement therapy should be initiated. The variety of enzyme preparations and recommended dosing regimens can present a challenge when selecting an adequate initial dose. Non-response should be actively sought and addressed in a systematic manner. This article discusses these challenges, and presents a practical approach to the diagnosis and management of PEI.

Key words: Pancreatic exocrine insufficiency; Chronic pancreatitis; Steatorrhoea; Pancreatic function tests; Pancreatic enzyme replacement therapy

Core tip: Pancreatic exocrine insufficiency (PEI) is common, and the prevalence is likely to increase in line

with global trends in associated conditions (notably increasing age and diabetes mellitus). The classical symptom of steatorrhoea is a late presentation of PEI. The diagnosis should be considered far earlier, based on risk factors and clinical history. A current, pragmatic approach to diagnosis combines clinical history, assessment of nutritional status and measurement of faecal elastase-1. Treatment with pancreatic enzyme replacement therapy (PERT) is safe and effective. PERT must be adequately dosed, monitored, and optimized to ensure its benefits are realized.

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INTRODUCTION

Pancreatic exocrine insufficiency (PEI) is defined by insufficient secretion or function of pancreatic enzymes or sodium bicarbonate for normal digestion. It is commonly caused by a reduction in functioning pancreatic tissue or ductal disease, such as in chronic pancreatitis and pancreatic malignancy. It can also result from reduced enterohormonal stimulation of the pancreas in severe duodenal mucosal disease, and from anatomical changes following gastrointestinal surgery[1].

The prevalence of PEI in the general population has not been established, and is problematic owing to a lack of a suitable screening test. It is accepted that the prevalence of PEI increases with age, and it is estimated to be as high as 11.5%-20% in apparently healthy older individuals[2,3]. Studies of selected populations estimate the prevalence of PEI to be 85% in advanced chronic pancreatitis, 50%-100% in inoperable pancreatic cancer, 56%-98% following pancreaticoduodenectomy, 85% in cystic fibrosis, 30% in coeliac disease, and 40% in diabetes mellitus[1]. The aging population and increasing incidence of diabetes mellitus worldwide suggest that PEI will be a more commonly encountered clinical problem in the future.

There are multiple diagnostic tests for PEI, and a balance between diagnostic accuracy and feasibility has not yet been achieved, particularly for milder disease. The cornerstone of treatment is pancreatic enzyme replacement therapy (PERT), but studies suggest that treatment is sub-optimal in more than half of patients[4].

This narrative article will explore the challenges that arise in the diagnosis and management of PEI.

DIAGNOSIS OF PANCREATIC EXOCRINE INSUFFICIENCY

PEI initially presents with symptoms of bloating, excessive flatulence, abdominal discomfort and diarrhoea, which are common to many other gastrointestinal conditions[1]. The classical symptoms of steatorrhoea and weight loss develop late in the course of PEI, when the secretion of pancreatic lipase is less than 10% of normal[5]. However, even patients with mild or moderate PEI are at risk of nutritional deficiencies, particularly of fat-soluble vitamins, and their consequences, including osteoporosis, renal insufficiency, and reduced quality of life[6,7]. As such, early consideration of PEI, based on risk factors and non-specific symptoms, is vital.

Direct Tests

The gold standard test for the diagnosis of PEI is said to be direct pancreatic function testing, where pancreatic secretions are measured in the duodenum or pancreatic duct following the administration of a secretagogue. Although direct tests are considered the most sensitive tests for PEI, multiple techniques exist and there is a lack of standardisation across the few centres that offer them. In addition, direct pancreatic function testing is expensive, invasive, and technically challenging[6]. As a result, invasive direct tests lack clinical application.

There has been interest in non-invasive direct pancreatic function testing using secretin-stimulated magnetic resonance cholangiopancreatography (S-MRCP). One study comparing this technique to the intra-ductal secretin test demonstrated a sensitivity of 72% and specificity of 87%[8], whilst another comparing S-MRCP to the secretin endoscopic pancreatic function test found 100% sensitivity and specificity[9]. Both studies are limited by small patient numbers. There is a lack of robust evidence to recommend this as a single diagnostic test for PEI, but it can provide additional information on pancreatic exocrine function whilst assessing the structure of the pancreas.

Indirect tests

Quantitative faecal fat estimation: The 72-h faecal fat test is considered the gold standard for the diagnosis of fat malabsorption, and can also be used to assess the adequacy of PERT. Stool is collected for 72 h whilst the patient consumes 100 g of fat per day. Steatorrhoea is defined by > 7 g of fat per 100 g of stool per day, or a calculated co-efficient of fat absorption < 90%[10]. However, the test is not specific for PEI, and false negatives may occur where there is poor adherence to, or reporting of, dietary fat intake. The test is time consuming and unpleasant for both the patient and laboratory staff. In our experience few centres offer this test routinely.

^{13}C-mixed triglyceride breathe test: The use of stable isotope breath testing of metabolic and physiological function is well established in gastroenterology. The ^{13}C-mixed triglyceride (^{13}C-MTG) breath test is a study of the digestion of an isotope-labelled fat meal that has emerged as an indirect measure of pancreatic exocrine

function that is accurate, simple, repeatable, and non-invasive. Studies comparing the ^{13}C-MTG breath test to endoscopic secretin studies and 72-h faecal fat measurement demonstrate a sensitivity of 90%-100% and a specificity of 90%-92%[11,12]. An additional strength is that it can be used to assess response to treatment, with normalisation of ^{13}C-MTG breath test results correlating with weight gain and the normalisation of faecal fat and nutritional deficiencies[13].

The length of time over which excreted CO_2 is measured, the constituents of the test-meal, and physical exercise may affect results[14]. An attempt to simplify the ^{13}C-MTG breath test showed that when cumulative CO_2 excretion is measured over less than 4 h the test loses its specificity, although it remains highly sensitive[15]. The test may generate false positives in patients with steatorrhoea of non-pancreatic origin, such as those with severe duodenal mucosal disease[16]. These limitations can be addressed by standardising test protocols and excluding duodenal mucosal disease as part of a considered diagnostic work-up for patients with diarrhoea. The main limitation of the ^{13}C-MTG breath test is that it is more costly and time-consuming than alternatives, namely faecal elastase-1 (FE-1), without convincing evidence of superiority. Furthermore, it is not yet widely available, having not been commercialised in many countries at time of publication. Therefore in many countries it cannot yet be incorporated into clinical practice.

Faecal elastase-1: FE-1 measures a protease, secreted only by the pancreas, that has been shown to be stable during intestinal transit and correlate well with duodenal levels of lipase and bicarbonate[17]. An FE-1 value of < 200 μg/g is used as a conventional cut-off for diagnosing PEI, but the result should be viewed as a continuum.

A recent meta-analysis demonstrated a pooled sensitivity of 77% and specificity of 88%, when compared to the secretin stimulation test, and 96% and 88% when compared to quantitative faecal fat estimation[18]. It compares favourably with, and has largely replaced, previous indirect tests such as faecal chymotrypsin estimation and the pancreolauryl test[19,20]. Concerns over the lack of sensitivity in mild PEI persist, however FE-1 was found to be more sensitive and specific than the ^{13}C-MTG breath test in a direct comparison study that included patients with both mild and severe PEI[20].

FE-1 is measured from a single, solid stool sample, and does not degrade if the sample is stored for several days[17]. As a result it is a cheap and practical test, and has been adopted as the primary diagnostic test for PEI in most centres. FE-1 is not affected by PERT therefore it cannot be used to monitor response to therapy[21].

Assessment of nutritional status: Malnutrition is common in PEI, though non-specific, and established markers of malnutrition can be used as part of the diagnostic approach[6]. Anthropometric measurements such as body mass index and muscle stores are lower in patients with PEI than in controls[22]. Vitamin D deficiency is found in 53% of patients with PEI[23], and a retrospective study found that hypomagnesaemia detects PEI with a sensitivity of 88% and specificity of 66%[24].

Recommended approach

Our current, pragmatic approach is to combine clinical history, assessment of nutritional status, tests to exclude other causes of malabsorption, and FE-1 to determine the likelihood of PEI in an individual patient. Imaging to assess the structure of the pancreas and exclude pancreatic carcinoma should be carried out in all patients diagnosed with PEI in adulthood. Where it is available, S-MRCP is the logical imaging modality of choice, given the additional functional information gained[6].

MANAGEMENT OF PANCREATIC EXOCRINE INSUFFICIENCY

The overall aim of treating PEI must be to normalise digestion to improve the quality and longevity of life. PERT is the cornerstone of the management of PEI. It has been shown to improve weight, reduce faecal fat excretion, ameliorate abdominal pain and improve quality of life, without significant side effects[25]. Although its impact on long-term survival in chronic pancreatitis has not been studied, PERT has been shown to improve survival rates in patients with unresectable pancreatic cancer and following pancreatic surgery[26,27].

Despite these benefits, evidence suggests that clinicians are not initiating treatment often enough, nor replacing enzymes adequately. A recent study showed that only 21% of patients with pancreatic cancer received PERT, despite 70% reporting symptoms consistent with fat maldigestion[28]. A Northern European cross sectional survey of patients receiving PERT found 68% had steatorrhoea and 39% had weight loss. Nearly half were needlessly restricting their fat intake and only 36% had seen a dietitian[4]. Similar findings emerged from a Dutch National survey[29].

This suggests that there is a great deal of room for improvement in our management of PEI, particularly in terms of initiating and optimising PERT. Challenges in achieving this include the availability of multiple different enzyme preparations, the need to individualise dosing and timing of PERT, and uncertainty about how to monitor and optimise treatment in non-responders.

Pancreatic enzyme replacement therapy

Enzyme preparations: An effective PERT preparation should intersperse well with chyme, resist denaturation by gastric juices, empty from the stomach simultaneously with nutrients, and release enzymes quickly in the proximal small intestine.

Conventional (uncoated) preparations are vulnerable

to denaturing by gastric acid. However, most modern preparations are pH-sensitive, enteric-coated mini-microspheres, enclosed within a gelatine capsule shell. The enteric coating of the microspheres is acid resistant and dissolves in the duodenum at a pH of around 5.5.

There are marked differences in the rate of release of lipase between preparations *in vitro*, but little clinical data supports any specific preparation over another[30,31]. The size of the microspheres is important, however, as this determines the rate at which they empty into the small bowel. Spheres of 2.4 and 3.2 mm diameter empty more slowly than 1 mm spheres, and may not enter the small bowel at the same time as ingested food[32].

In current practice, enteric-coated microspheres or mini-microspheres of < 2 mm in size are the preparation of choice[6].

Dosing: If chyme stays within the duodenum for four hours, physiological lipase output is between 480000 and 960000 units after a standard meal[33]. As steatorrhoea only occurs when lipase output falls to < 10% of normal[5], the minimum number of lipase units required for normal digestion would be 24000 to 48000[33]. However, exogenous lipase is only one third as effective endogenous lipase[6], probably owing to partial denaturing by gastric acid and late release in the distal small bowel[33].

There is a lack of consensus on the optimum dose of PERT. Randomised controlled trials have shown that PERT is effective at doses of 72000-75000 IU with main meals, and 36000-50000 IU with snacks[34,35]. Recent European guidelines recommend a minimum starting dose of 40000-50000 IU with main meals for adults with chronic pancreatitis, and half that dose with snacks[6]. The Australasian Pancreatic Club suggests a starting dose of 25000-40000 lipase units with food[36].

For adults with cystic fibrosis, Australia and New Zealand guidelines recommend PERT dosing based on grams of dietary fat: 500-4000 lipase units per gram of fat consumed[37]. This equates to 12000-92000 lipase units for a 600-calorie meal in which 35% of calories are from fat. The ESPEN-ESPGHAN-ECFS guidelines for cystic fibrosis suggest PERT supplementation in lipase units per kilogram body weight per meal. They propose an initial dose of 500 lipase units/kg/meal[38]. This equates to approximately 30000 lipase units for a 60 kg adult eating a normal meal. The requirement to quantify dietary fat requires highly motivated patients and adds to the challenge of managing PEI in this population.

A patient's PERT requirements vary according to aetiology of PEI, residual pancreatic function and dietary intake, and may change over time. Larger or fattier meals will require more enzymes than a small, low fat one so the dose of PERT should reflect this[39]. Clinical experience demonstrates that a doubling or tripling of initial dose is needed in some patients, however, robust evidence is lacking[6]. The need for an individualised approach to PERT may explain the discrepancy between dosing guidelines. Where there is consensus is on the need to review and titrate PERT according to the degree of malabsorption[39].

We recommend that PERT be initiated at 50000-75000 lipase units with meals and 25000-50000 lipase units with snacks, and that dosing is reviewed regularly. In patients with pancreatic cancer it is prudent to initiate a dose at the upper end of the recommended range, as prompt, adequate PERT has been shown to improve survival and quality of life[26,27].

Timing: The efficacy of PERT requires the mixing of enzymes with chyme, and their synchronised arrival in to the duodenum. The timing of PERT administration therefore influences clinical outcomes. A randomised three way cross over study evaluated the effect of giving enteric-coated mini-microspheres before, during, or after meals in 24 patients with chronic pancreatitis. The percentage of patients who achieved normal fat digestion was highest in patients taking PERT during meals (63%), compared to before or after meals (50% and 54%)[40]. Therefore it is recommended to give PERT during meals, distributed evenly across the meal if more than one capsule is taken[6,25,39].

Side effects: PERT is generally well tolerated[41]. Fibrosing colonopathy is a much discussed but rarely seen complication that has been reported in children with cystic fibrosis using large doses of PERT[42-45]. As a result it is recommended that enzyme dose does not exceed 10000 lipase units per kg per day[46,47]. Assuming three meals and two snacks a day, this equates to 150000 lipase units with meals and 75000 lipase units with snacks for a 60 kg adult.

Religious or ethical constraints: All PERT preparations available in the United Kingdom are of porcine origin. This challenges individuals from certain religions, including Judaism and Islam, as well as vegetarians and vegans. Where religious or ethical beliefs are at odds with PERT, our experience is of non-adherence. Religious patients can be referred to their religious leaders for guidance. Imams or Rabbis usually grant special exemptions where no suitable alternative medication exists and non-adherence poses a threat to health. A novel, non-porcine, PERT is in development, which should improve adherence in these populations[48].

Monitoring response: Commencement of PERT is associated with a relatively quick improvement in symptoms of maldigestion, such as steatorrhoea and weight loss. However, adequacy of PERT should not be assessed based on clinical signs and symptoms alone, as serum markers of nutrition can be low in asymptomatic patients[49]. Therefore response to PERT should also be assessed by normalisation of serum nutritional markers, including fat soluble vitamins, retinol-binding protein, albumin, pre-albumin and minerals/trace elements

(including serum iron, zinc and magnesium)[6,24].

Management of non-response

An inadequate response to PERT should be assessed in a systematic manner. The expiry date and mode of storage of PERT preparations should be checked. Patient compliance should be assessed, particularly regarding the timing of PERT in relation to meals and snacks. Where compliance is poor, a higher strength capsule may help to reduce the pill burden. A dietary history may identify opportunities to individualise PERT according to the size and fat content of each meal, which may be more effective than a fixed dose regimen.

If these factors have been addressed, consider increasing the enzyme dose (by two or three times, to a maximum of 10000 lipase units per kg body weight)[6]. Failing this, adjunctive acid suppression therapy may help.

A significant proportion of patients with PEI demonstrate an inadequate response to enteric-coated enzyme therapy alone[50]. One possible explanation is reduced pancreatic bicarbonate secretion, impairing neutralisation of acidic chyme[51]. If the intra-duodenal pH is lower than 5.0, the enteric coating will not dissolve on time and enzyme release will happen in the distal small bowel[52].

The use of acid suppression with enteric-coated PERT may increase gastric pH and enhance PERT efficacy. In a prospective, open, comparative study, 21 patients with newly diagnosed PEI were treated with enteric-coated mini-microspheres (40000 IU) three times a day, with the addition of esomeprazole after 3 mo. ^{13}C-MTG breath tests normalised in 57% of patients with PERT monotherapy. In non-responders, the addition of esomeprazole normalised fat digestion in an additional 29% of participants[50].

Although data is of only moderate quality and large multicentre trials are still required, the combined use of acid suppression and PERT is considered appropriate when the response to PERT alone is suboptimal[6,25,37-39]. It should be noted that there is limited evidence to support adjuvant acid suppression in PEI caused by cystic fibrosis[53-56].

If maldigestion does not respond to patient education, optimisation of PERT dose and adjuvant acid suppression, then other causes, such as small intestinal bacterial overgrowth, bile acid malabsorption, coeliac disease, inflammatory bowel disease, and lactose intolerance should be investigated and treated[6,37,39].

Quantitative faecal fat estimation or the ^{13}C-MTG breath test can be used to evaluate adequacy of PERT in problematic non-responders, although neither test is widely available[6].

Management of diet and lifestyle

Dietary modification: Patients with PEI may self-restrict fat intake to minimise symptoms. Fats and oils are convenient energy sources and are especially useful for PEI patients, who may have raised energy requirements and/or poor appetite. Reduced fat diets are not recommended for people with PEI[6]. A low-fat diet may further compromise endogenous enzyme secretion[57], and was associated with poorer outcomes in children with cystic fibrosis compared to a normal diet with adequate PERT[58]. Medium-chain triglycerides, which do not require bile or lipase for absorption, do not seem to offer an advantage over a long-chain fat if PERT is used[59].

There is widespread agreement that with adequate PERT, patients should be able to maintain a normal diet. A specialist dietitian can help prevent needless dietary restrictions related to patient anxiety about maldigestion-related symptoms.

Lifestyle modification: Referrals for alcohol cessation are recommended. Alcohol consumption is the most important risk factor for chronic pancreatitis[60], with a three-fold increase in the risk of transitioning from acute to chronic pancreatitis in patients with ongoing alcohol consumption[61]. Smoking is an independent risk factor for both acute and chronic pancreatitis, and may produce a synergistic effect with alcohol[60]. Therefore, all patients should be counselled to abstain from smoking and consuming alcohol.

Recommended approach

Our practice is to use an initial dose of 50000-75000 lipase units with meals and 25000-50000 lipase units with snacks, administered over the duration of the meal, rather than just at the start. A normal diet is recommended, as is the cessation of smoking and alcohol consumption. In non-responders, patient education, flexible dosing of PERT, increasing the dose of PERT, and adjunctive acid suppression can be attempted, and achieves a response in most patients.

CONCLUSION

PEI is an important clinical entity that is often under recognised and undertreated. The symptoms of PEI generally appear late in the disease course and are non-specific. Clinically important nutritional deficiencies precede symptoms and contribute to significant morbidity and mortality. Unfortunately there is no widely available non-invasive test that is accurate in the early stages of PEI, and this should be a priority for future research.

Invasive direct pancreatic function tests are the reference standard, especially in mild PEI, but are unavailable outside of research centres. A combination of clinical history, nutritional assessment and measurement of FE-1 is a pragmatic but imperfect approach.

In PERT we have an effective and safe treatment for PEI that improves symptoms and nutritional status in the majority patients, and improves survival in patients with pancreatic carcinoma. Although the variety of PERT preparations and recommended dosing regimens can

be intimidating to practising clinicians, international consensus is now emerging.

There are opportunities for further research and developments in diagnostics that should be explored, but first we must do the simple things well. This is a condition with significant morbidity that has an effective treatment. The critical step in making the diagnosis of PEI is to consider it.

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EDITORIAL

Endoscopic ultrasound guided gallbladder drainage - is it ready for prime time?

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Abstract

Management of acute cholecystitis includes initial stabilization and antibiotics. However, the most definitive treatment is cholecystectomy. A small percentage of patients who are not suitable for surgery due to the severity of cholecystitis or comorbidities will require a temporary measure as a bridge to surgery or permanent nonoperative management to decrease the mortality and morbidity. Most of these patients who require conservative management were managed with percutaneous transhepatic cholecystostomy or trans-papillary drainage of gallbladder drainage with cystic duct stenting through endoscopic retrograde cholangiopancreaticography (ERCP). Although, these conservative measures are effective, they can cause significant discomfort to the patients especially if used as a long-term measure. In view of this, there is a need for further minimally invasive procedures, which is safe, effective and comfortable to patients. Endoscopic ultrasound (EUS) guided gallbladder drainage is a novel method of gallbladder drainage first described in 2007[1]. Over the last decade, EUS guided gallbladder drainage has evolved as an effective alternative to percutaneous

cholecystostomy and trans-papillary gallbladder drainage. Our goal is to review available literature regarding the scope of EUS guided gallbladder drainage as a viable alternative to percutaneous cholecystostomy or cystic duct stenting through ERCP among patients who are not suitable for cholecystectomy.

Key words: Acute cholecystitis; Acute acalculous cholecystitis; Endoscopic ultrasound guided gallbladder drainage; Percutaneous cholecystostomy; Trans-papillary gallbladder drainage

Core tip: Acute cholecystitis can be a medical emergency if not treated. The definitive treatment for it is cholecystectomy. However, some patients are not surgically fit and will need to be managed conservatively. Endoscopic ultrasound guided gall bladder drainage is a novel technique and is a means to manage these patients conservatively either as a bridge to surgery until they become surgically fit or a long term management. We discuss the advantages and disadvantages of this technique as an alternative to other known conservative measures.

Boregowda U, Umapathy C, Nanjappa A, Wong H, Desai M, Roytman M, Theethira T, Saligram S. Endoscopic ultrasound guided gallbladder drainage - is it ready for prime time? *World J Gastrointest Pharmacol Ther* 2018; 9(6): 47-54 Available from: URL: http://www.wjgnet.com/2150-5349/full/v9/i6/47.htm DOI: http://dx.doi.org/10.4292/wjgpt.v9.i6.47

INTRODUCTION

Acute cholecystitis is a life-threatening inflammatory condition of the gallbladder usually presents with nausea, vomiting, fever and right upper quadrant abdominal pain[2]. Acute cholecystitis is classified into two broad categories based on etiological factors. That is calculous cholecystitis and acalculous cholecystitis.

Gallstones cause more than 90% of the acute cholecystitis, and acalculous cholecystitis accounts for the remaining 5%-10% of the acute cholecystitis. Nearly 10% of the western population is estimated to have gallstones, and 1%-3% of these patients develop symptomatic gallstones. Only 20% of the symptomatic patients eventually develop acute gallstone cholecystitis[3]. Mortality due to acute cholecystitis is approximately 1%-10%[4]. The rate of mortality goes much higher (30% to 90%) depending on the timing of diagnosis[5]. Gallstones cholecystitis is three times more common among women compared to men under age fifty[6].

Acalculous cholecystitis occurs commonly among patients who are on prolonged parenteral nutrition and intensive care stay, trauma, and burns. Other risk factors include uncontrolled diabetes, congestive heart failure, vascular disease, acquired immune deficiency syndrome, drugs (oral contraceptive pills, thiazides) and elderly male patients[7].

SURGICAL MANAGEMENT

Definitive treatment for acute cholecystitis is cholecystectomy. Risk of systemic infection is high if untreated. Complications of acute cholecystitis include gangrenous cholecystitis, gallbladder perforation, biliary peritonitis, cholecystoenteric fistula, pericholecystic abscess, and biliary ileus. The timing of cholecystectomy is usually dependent on the clinical condition of the patient and comorbidities. Approximately 20% of the patients require emergent cholecystectomy. Early laparoscopic cholecystectomy less than 48 h from the time of presentation reduces morbidity, mortality, hospital stay, and costs[8].

Patients with multiple medical comorbidities not suitable for surgery are managed conservatively with gallbladder drainage through cholecystostomy or cystic duct stenting. Early cholecystostomy within 24 h from the time of presentation has shown to reduce hospital stay and procedure related bleeding[9]. Endoscopic ultrasound (EUS) guided gallbladder drainage has created a new paradigm in treating patients with acute cholecystitis who have a contraindication for surgery.

PERCUTANEOUS CHOLECYSTOSTOMY

Percutaneous cholecystostomy is a minimally invasive and safe procedure performed to provide immediate decompression of the distended gallbladder using ultrasound or computed tomography guidance. It can be used as a bridge to elective cholecystectomy or as a definitive treatment in severely ill patients who are not candidates for elective cholecystectomy[10-12]. It allows further evaluation of etiology of acute cholecystitis through cholangiogram. Cystic duct or common bile duct stones could be managed through a percutaneous approach.

Common adverse events due to percutaneous cholecystostomy include bleeding, tube dislodgement, bile leak and peritonitis in approximately 12% of the patients[13]. Percutaneous cholecystostomy is contraindicated in patients with massive ascites, intervening bowel loop, uncorrected coagulopathy or those who require anticoagulation. Intrahepatic gallbladder, shrunken/thick-walled gallbladder or concern for patient's non-adherence is considered as relative contraindications.

ENDOSCOPIC TRANS-PAPILLARY GALLBLADDER DRAINAGE

Gallbladder decompression through trans-papillary cystic duct stenting with the help of endoscopic retrograde

Table 1 Endoscopic ultrasound guided gallbladder drainage using plastic stent

Author	Study design	Year of publication	Number of patients	Technical success	Clinical success	Adverse event rate
Baron *et al*	Case report	2007	1	1 (100%)	1 (100%)	0 (0%)
Kwan *et al*	Case series	2007	3	3 (100%)	3 (100%)	1 (33.3%)
Kamala *et al*	Case report	2009	1	1 (100%)	1 (100%)	0 (0%)
Takasawa *et al*	Case report	2009	1	1 (100%)	1 (100%)	0 (0%)
Subtil *et al*	Case series	2010	4	4 (100%)	4 (100%)	0 (0%)
Song *et al*	Prospective	2010	8	8 (100%)	8 (100%)	2 (25%)
Itoi *et al*	Case series	2011	2	2 (100%)	2 (100%)	0 (0%)

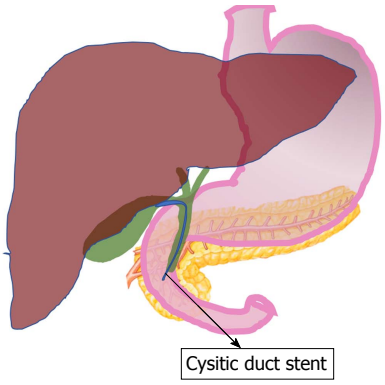


Figure 1 Schematic diagram of trans-papillary cystic duct stenting.

pancreatography and cholangiography (ERCP) can be used to manage acalculous cholecystitis. After cannulating the common bile duct, a guidewire is passed, and the cystic duct is then selectively cannulated. Cystic duct stent is placed to drain the gallbladder content (Figure 1).

In a retrospective case study on 43 patients who underwent ERCP and cystic duct stent for cholecystitis, 83.7% patients had technical success, and 97% had a clinical success of whom 91.7% improved within 72 h[14]. There were no significant adverse events, and 9% of the patients had an elevated amylase level without abdominal pain.

A retrospective study compared percutaneous cholecystostomy (n = 38) and trans-papillary gallbladder drainage (n = 57) using plastic cystic duct stent with ERCP. Technical success of trans-papillary drainage (89% *vs* 93%) was lower compared to percutaneous cholecystostomy. However, recurrent cholecystitis in trans-papillary drainage (2%) group was lower compared to percutaneous cholecystostomy (11%) with similar adverse events (8% *vs* 4%). Patients who underwent cystic duct stenting had the stent in place much longer compared to percutaneous cholecystostomy (three months *vs* one month)[15].

The role of trans-papillary drainage is limited since it is restricted to patients with acalculous cholecystitis.

EUS-GUIDED GALLBLADDER DRAINAGE

The procedure is usually performed using therapeutic linear array echoendoscope. A trans-gastric or trans-duodenal gallbladder puncture is performed under the EUS guidance using a 19-gauge needle. After removing the stylet biliary aspiration and cholecystography are performed in sequence. A 0.035 or 0.025-inch guidewire is introduced through the cannula and coiled in the gallbladder. The gallbladder puncture site is dilated with a Cystotome or needle, and a stent is introduced into the gallbladder. Various types of stents have been used in the past including plastic stent, a self-expandable metal stent and recently lumen apposing metal stents (LAMS). The technical and clinical success of EUS guided drainage by plastic stents is 100%, and pooled analysis showed the adverse events occurred in 5.4% of the patients (Table 1). The technical and clinical success of EUS guided drainage by Naso-biliary drainage is 95.2% and 73.7% respectively, and pooled analysis showed the adverse events occurred in 27.2% of the patients (Table 2). The technical and clinical success of EUS guided drainage by the self-expandable metal stent is 97.5% and 98.5% respectively, and pooled analysis showed the adverse events occurred in 10.4% of the patients (Table 3).

EUS guided gall bladder drainage with LAMS

The recent success of LAMS in the drainage of pancreatic pseudocyst and walled off pancreatic necrosis lead to the development of similar LAMS for gallbladder drainage. An electrocautery-enhanced LAMS (EC-LAMS) has made the procedure simpler and reduced the number of instrument exchanges (Figure 2 and Figure 3). The stent can be delivered in a single step[16].

A meta-analysis included 13 studies (7 retrospective studies, five prospective studies, and 1 case-control study) using LAMS involving 233 patients showed EUS guided gallbladder drainage to be an effective, safe and viable alternative to percutaneous cholecystostomy. Technical success and clinical success were 93.86%, and 92.48% respectively. Overall procedure related adverse events were 18.31% and stent-related adverse events were 8.16%[16]. In most cases the stent was left in situ permanently since patients were not suitable for surgery. Outcomes of prior studies on EUS guided gallbladder drainage by LAMS is shown in Table 4.

Advantages of LAMS

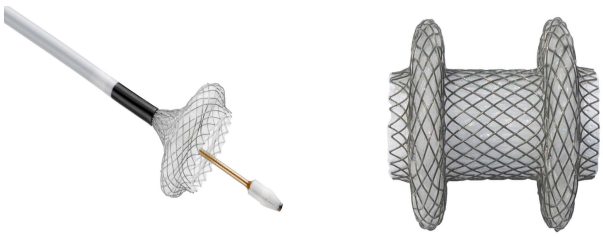
Electrocautery enhanced LAMS can be placed in a single step using EUS scope alone without the need for fluoroscopy, guidewire placement, and tract dilation. LAMS provides better tissue apposition at both the ends

Table 2 Endoscopic ultrasound guided gall bladder drainage using naso-biliary drainage

Author	Study design	Year of publication	Number of patients	Technical success	Clinical success	Adverse event rate
Lee *et al*	Prospective	2007	9	9 (100%)	9 (100%)	0 (0%)
Hikichi *et al*	Retrospective	2007	1	1 (100%)		1 (100%)
Jang *et al*	Prospective	2012	30	29 (97%)	29 (100%)	0 (0%)
Itoi *et al*	Retrospective	2008	43	36 (84%)	35 (95%)	4 (9%)

Table 3 Endoscopic ultrasound guided gall bladder drainage using self-expanding metal stents

Author	Type of study	Year of publication	Number of patients included in the study	Technical success (%)	Clinical success (%)	Adverse events (%)
Widmer *et al*	Retrospective	2015	11	100	100	8
Choi *et al*	Retrospective	2017	14	85.7	91.7	28.5
Jang *et al*	Prospective	2011	15	100	100	13
Moon *et al*	Prospective	2014	7	100	100	0
Takagi *et al*	Retrospective	2016	16	100	100	6
Ahmed *et al*	Retrospective	2017	13	100	92.3	7.7
Oh *et al*	Retrospective	2018	76	99.3	99.3	7.1



Lumen-apposing metal stent (LAMS)

Figure 2 Lumen apposing metal stent.

and reduces the risk of stent migration. Presence of silicon lining reduces the risk of leakage and prevents tissue ingrowth, which can aid in the removal of the stent once the fistula matures. The large diameter of the LAMS reduces the risk of stent stenosis or obstruction and allows extraction of gallstones or cholecystography.

Patients with EUS gallbladder drainage procedure have a lower rate of post-procedure pain and the stent can remain patent for a prolonged period. It also adds to the patient's comfort since there is no need for external drainage to be carried around and mimics natural drainage of biliary secretions into the duodenum. LAMS can be potentially left in situ indefinitely, according to the published literature the longest period of follow up of 3 years, stent patency of 86% was noted[17].

One recent retrospective analysis of long-term outcomes in 21 patients who had documented follow up for more than 12 mo, there were no significant adverse events. Only two patients required repeat endoscopy and found to have tissue overgrowth in one and patent fistula in the other[18].

Complications

Most common complications of EUS guided gallbladder drainage are transient abdominal pain, pneumoperitoneum, biliary peritonitis, and stent migration requiring repeat intervention[19]. Bleeding occurs in up to 13% and stent migration in up to 8% of the patients[20]. Other complications include fever, duodenal perforation, stent occlusion, and hematochezia without anemia. Late complications due to EUS guided gallbladder drainage include recurrent cholecystitis in up to 3.2% of the patients and abscess formation[21,22].

Technical approach

Gallbladder drainage with LAMS can be performed though trans-duodenal or trans-gastric approach. Though there is no clear evidence to show that one is better than the other, most endoscopists prefer trans-duodenal approach since the duodenum is retroperitoneal and has minimal peristaltic movements compared to the stomach, which has stronger peristaltic movements. It reduces the chance of stent migration[23]. Due to the presence of larger food particles, stent occlusion is likely to be more in common in the stomach compared the duodenum.

Large multicenter studies are required to define the advantages and disadvantages of each approach. The invention of electrocautery-enhanced LAMS has reduced the need for instrumentation, the time needed for the procedure, and the stent can be delivered in one step.

EUS guided gallbladder drainage and future surgery

EUS guided gallbladder drainage can complicate future cholecystectomy and may not be used as bridge therapy. Previous studies have reported up to 79% of the patients who underwent EUS guided gallbladder drainage had successful cholecystectomy[24]. Remaining patients who did not have surgery were either nonsurgical or refused the procedure. However, the real concern is a permanent fistula could have been created due to EUS guided gallbladder drainage, which could have prevented definitive surgery. While most fistulas can close on their own, it is unclear from prior literature the exact number

Table 4 Endoscopic ultrasound guided gallbladder drainage using lumen apposing metal stents

Author	Type of study	Year of publication	Number of patients	Technical success (%)	Clinical success (%)	Adverse events (%)
de la Serna-Higuera *et al*	Retrospective	2013	13	86.4	100	18
Irani *et al*	Retrospective	2015	15	93	100	13
Walter *et al*	Prospective	2016	30	90	96	Not available
Law *et al*	Retrospective	2016	7	100	100	0
Kahaleh *et al*	Retrospective	2016	35	91.4	89	11
Irani *et al*	Retrospective	2017	45	98	96	11
Dollhopf *et al*	Retrospective	2017	75	98.7	95.9	10.7
Teoh *et al*	Prospective	2017	59	100	100	23.7

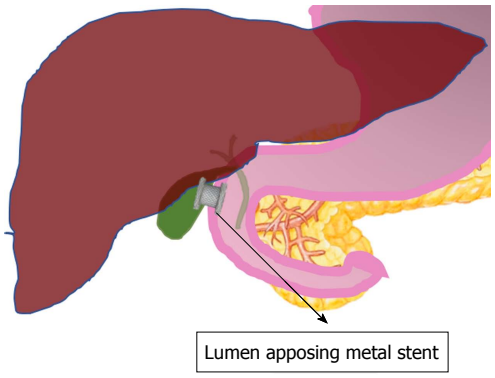


Figure 3 Endoscopic ultrasound guided gallbladder drainage.

of the fistulas that can close spontaneously.

A recent multicenter study on 34 patients showed that 21 patients with percutaneous cholecystostomy tube and 13 patients who had undergone EUS guided gallbladder drainage by LAMS as a bridge therapy all successfully underwent cholecystectomy[25]. There was no difference in the comorbidity index or post-surgical adverse events. However, data on large multicenter studies are still lacking. The areas that need further research are the technique (trans-gastric *vs* trans-duodenal) that creates fewer fistulas and the exact rate of spontaneous closure of the fistula so that it can be used a bridge therapy prior to surgery.

Percutaneous cholecystostomy vs EUS guided gallbladder drainage

In a prospective study, Jang *et al*[24] compared percutaneous cholecystostomy and EUS guided gallbladder drainage as an alternative for acute cholecystitis in patients who are not candidates for cholecystectomy. A total of 59 patients were randomized into either percutaneous cholecystostomy (n = 29) or EUS guided gallbladder drainage (n = 30) after the failure of medical treatment. Both EUS guided gallbladder drainage and percutaneous cholecystostomy had comparable technical success (97% *vs* 97%, P = 0.001 for non-inferiority margin of 15%), clinical success (96% *vs* 100%, P = 0.0001 for non-inferiority margin of 15%), and complications (7% *vs* 3%, P = 0.999 in the Fisher exact test) rates. The rate of conversion to open cholecystectomy was 9% and 12% respectively. Post-procedure pain score was significantly low among patients who underwent EUS guided drainage compared to percutaneous cholecystostomy (P = 0.001)[24].

In another retrospective comparative study, technical and clinical successes in EUS guided gallbladder drainage (n = 45) and percutaneous cholecystostomy (n = 45) were similar. Technical success was achieved in 98% and 100% respectively (P = 0.88), whereas clinical success was 96% and 91% respectively (P = 0.20). Post-procedure pain score (2.5 *vs* 6.5; P < 0.05), hospital stay (three days *vs* nine days, P = 0.05) and repeat interventions (11 *vs* 12) were significantly low in EUS guided gallbladder drainage compared to percutaneous cholecystostomy. This study also demonstrated a non-significant trend towards lower adverse events (11% *vs* 32%; P = 0.27) in EUS guided gallbladder drainage compared to percutaneous cholecystostomy[26].

In a prospective cohort study of 118 patients technical success and clinical success for EUS guided gallbladder drainage (n = 59) and percutaneous cholecystostomy (n = 59) were comparable. The rate of overall adverse events (32.2% *vs* 74.6%; P < 0.001), serious adverse events (23.7% *vs* 74.6%; P < 0.001) and procedure related readmission rates (6.8% *vs* 71.2%; P < 0.001), were significantly lower in EUS guided gallbladder drainage compared to percutaneous cholecystostomy. Recurrent acute cholecystitis was also lower in the EUS group (0% *vs* 6.8%) compared to percutaneous cholecystostomy[27].

In a multicenter retrospective study, technical success of EUS guided drainage (n = 42) and percutaneous cholecystostomy (n = 113) drainage (95% *vs* 99%; P = 0.179) as well as clinical success (95% *vs* 86%; P = 0.157). EUS guided drainage required a lower number of repeat procedures compared to percutaneous drainage (10% *vs* 24%; P = 0.037). There was no significant difference in readmission rate or adverse events between the two[28].

A retrospective study evaluated the role of EUS guided gallbladder drainage (n = 14) and percutaneous cholecystostomy (n = 19) in patients with malignant cystic duct obstruction. The technical success (85.7% *vs* 100%) and clinical successes (91.7% *vs* 86.4%) were comparable. Adverse events were similar in both the groups (28.5% *vs* 21.1%). In this study, none of the patients who had clinically successful EUS guided gallbladder drainage required stent removal until endo of life. The mean duration of stent patency was 130.3+/-

35.3 d. However, only in 35.5% of the patients, the cholecystostomy tube was kept until the end of life[29].

The above studies have clearly shown that in appropriately selected patients EUS guided gallbladder drainage is an efficient and safe alternative to percutaneous cholecystostomy for acute cholecystitis among non-surgical patients. EUS guided gallbladder drainage is associated with a reduced hospital stay, adverse events and requires fewer repeat interventions, and is associated with less severe procedure-related pain. The rate of adverse events is either similar or trend lower than percutaneous cholecystostomy. In a retrospective study, the rate of recurrent cholecystitis (17.2% *vs* 0%; $P = 0.043$) was also noted to be significantly low in patients who had EUS guided gallbladder drainage when compared to percutaneous cholecystostomy[30].

EUS guided gallbladder drainage unlike percutaneous cholecystostomy obviates the need for external drainage tube, discomfort, and pain caused by percutaneous cholecystostomy. EUS procedures may require general anesthesia and can take a longer time to complete the procedure compared to percutaneous cholecystostomy. Since patients who are not suitable for surgery also tend to be high-risk for general anesthesia[31]. LAMS allows extraction of gallstones and provides better tissue apposition. They reduce the risk of biliary leak and peritonitis but do not completely mitigate the risk and therefore the caution has to be exercised when using it in patients with coagulopathy and ascites[32-34]. Even though lumen-apposing metal stents can be left in situ, permanently stent migration, occlusion and dislodgement have occurred. The reported adverse events after EUS guided gallbladder drainage by LAMS are recurrent cholecystitis (5.1%), gastrointestinal bleeding (2.6%) and stent migration (1.1%)[35].

Internalization of biliary drainage after placement of a percutaneous cholecystostomy

A percutaneous cholecystostomy tube can be replaced with EUS guided gallbladder drainage through LAMS. It can be considered when percutaneous cholecystostomy tube is used as a bridge therapy for surgery, but the disease course of the patient makes them unsuitable for surgery. This will prevent unwanted discomfort the external drain that comes with percutaneous cholecystostomy.

The gallbladder is usually shrunken after the placement of a percutaneous cholecystostomy. Saline with some contrast can be injected through the tube to enlarge the shrunken gallbladder, and subsequently, it can be punctured under direct visualization by EUS and placement of LAMS. A retrospective study of 7 patients demonstrated 100% technical and clinical success with successful removal of the cholecystostomy tube[36].

In another retrospective study, 21 patients had a replacement of percutaneous cholecystostomy tube with EUS guided LAMS gallbladder drainage with 90.5% technical success. There were no early adverse events. However, two patients required repeat interventions[37]. Larger studies are lacking at this time to accurately predict the risks and benefits of replacing percutaneous cholecystostomy with EUS guided LAMS drainage.

EUS guided gallbladder drainage vs Endoscopic trans-papillary gallbladder drainage

A recent retrospective study compared EUS guided gallbladder drainage to endoscopic trans-papillary drainage. EUS guided gallbladder drainage had significantly better technical success (100% *vs* 77.3%; $P = 0.028$). Clinical success (88.9% *vs* 72.4%; $P = 0.076$) and adverse events (19.1% *vs* 16.3%; $P = 0.76$) were comparable[38].

In a multicenter comparative study, 372 patients were included in the study, 102 patients underwent EUS guided gallbladder drainage, 124 by endoscopic trans-papillary drainage and 146 by percutaneous cholecystostomy. The mean follow up period was 5.2 mo (range 1-34). The technical success for EUS guided gallbladder (94%) and percutaneous cholecystostomy (98%) were significantly higher than trans-papillary drainage (88%) ($P = 0.004$). The clinical success rate for EUS guided drainage (90%) and percutaneous cholecystostomy was also significantly higher ($P = 0.001$) compared to trans-papillary drainage (80%). Mean number of procedures required for clinical success was significantly lower for EUS guided drainage compared to trans-papillary and percutaneous cholecystostomy drainage (1 *vs* 1.7 *vs* 2.2; $P < 0.001$). EUS guided drainage and trans-papillary drainage had significantly lower adverse events (13% *vs* 7% *vs* 20%; $P = 0.01$) and unplanned hospital admissions (4% *vs* 3.2% *vs* 19.8%; $P < 0.001$) compared to percutaneous cholecystostomy. Mean hospital stay for EUS drainage was significantly lower compared to both trans-papillary drainage and percutaneous cholecystostomy (16 *vs* 18 *vs* 19 d; $P = 0.01$)[39].

A retrospective study compared EUS guided gallbladder drainage ($n = 76$) to trans-papillary gallbladder drainage ($n = 96$). Technical success (98.8%, 82/83 *vs* 83.3%, 80/96, $P < 0.01$) and clinical success (98.8%, 82/83 *vs* ETC: 82.3%, 79/96, $P < 0.01$) of EUS guided gallbladder drainage was significantly better compared to trans-papillary drainage. Post-procedure adverse events were significantly lower in EUS guided gallbladder drainage compared to trans-papillary gallbladder drainage[22].

Above studies and previously published data has shown a clear advantage of EUS guided gallbladder drainage to be a safe and efficient procedure compared to trans-papillary drainage with significantly better technical and clinical success with lower adverse events and lesser hospital stay and fewer repeat procedures.

CONCLUSION

Cholecystectomy is the gold standard for treatment of acute cholecystitis, and early cholecystectomy is

preferred over delayed or interval cholecystectomy. Elderly patients with significant comorbidities and not candidates for surgery are usually managed with non-surgical interventions like percutaneous cholecystostomy or ERCP. Recent advances in endoscopic methods and utilization of EUS guided LAMS has led to the development of EUS guided gallbladder drainage. Over last decade EUS guided gallbladder drainage has gained significant popularity with high technical and clinical success comparable to that of percutaneous cholecystostomy or trans-papillary drainage. It has lower adverse events, hospital stay and requires fewer repeat procedures[24,26-28,32].

EUS guided gallbladder drainage is a safe, effective and viable non-surgical method of gallbladder drainage for acute cholecystitis, in patients who are deemed to never undergo cholecystostomy as they are not fit for surgery. Although the limited available evidence is promising, prospective large multicenter studies are needed before EUS guided gallbladder drainage can be used as a first-line treatment instead of percutaneous cholecystostomy as a bridge therapy for all patients who are non-surgical candidates initially and require definitive surgical intervention later for acute cholecystitis.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Coeliac disease in the modern era: Severity of small bowel mucosal injury at diagnosis with analysis of clinical correlates and rate of improvement on a gluten free diet

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Abstract

AIM

To analyze the relationships between pre-diagnosis coeliac serology, duodenal histopathology, primary presenting symptoms, coeliac-related comorbidity and response to treatment in a modern cohort with new diagnosis of coeliac disease (CD).

METHODS

A retrospective cohort study including 99 participants diagnosed with CD between 1999 and 2013. All patients had the following data recorded: baseline characteristics, coeliac serology, small bowel histopathology. A subset of this cohort underwent a repeat small bowel biopsy. Independent associations were assessed with logistic regression.

RESULTS

The mean age at diagnosis was 43 years (Interquartile range 30-53 years) and 68% of the cohort was female. At diagnosis 49 (49%) patients had total villous blunting (MS 3c), 12 (12%) had subtotal villous blunting (MS 3b), and 29 (29%) had partial villous blunting (MS 3a). The prevalence of symptoms pre diagnosis was not related to the severity of villous blunting (P = 0.490). 87 (88%) of the cohort underwent repeat small bowel biopsy after a median of 7 mo (IQR 6-11 mo). 34 (39%) patients had biopsy results $\geqslant$ MS 3a which

compared to 90 (90%) at the initial biopsy. 24 (71%) of this group reported adherence to a gluten free diet (GFD). Persistent MS ⩾ 3a at repeat biopsy was not associated with symptoms (P = 0.358) or persistent positive coeliac serology (P = 0.485).

CONCLUSION

Neither symptoms nor serology predict the severity of the small bowel mucosal lesion at CD diagnosis. Whilst a GFD was associated with histological improvement many patients with newly diagnosed CD had persistent mucosal damage despite many months of gluten restriction. Negative CD serology did not exclude ongoing mucosal injury.

Key words: Coeliac disease; Gluten-free diet

Core tip: Coeliac disease (CD) is a common, under-recognized gastrointestinal disorder. The findings in this study support other larger studies which have reported a trend toward an asymptomatic or silent presentation of CD. Thyroid related autoimmune co-morbidities were common (n = 17, 17%). Symptoms at presentation were not associated with the degree of villous blunting on biopsy. Similarly, persistent villous blunting at repeat biopsy was not associated with symptoms or positive coeliac serology. Negative coeliac serology did not exclude ongoing mucosal injury.

Cronin O, Flanagan E, Dowling D. Coeliac disease in the modern era: Severity of small bowel mucosal injury at diagnosis with analysis of clinical correlates and rate of improvement on a gluten free diet. *World J Gastrointest Pharmacol Ther* 2018; 9(6): 55-62 Available from: URL: http://www.wjgnet.com/2150-5349/full/v9/i6/55.htm DOI: http://dx.doi.org/10.4292/wjgpt.v9.i6.55

INTRODUCTION

Coeliac disease (CD) is estimated to affect 1.2% of Australians[1]. It is a gastrointestinal disorder that involves an immune response to dietary gluten, resulting in small bowel mucosal damage[2]. Most common presentation of CD in adults is diarrhea although this presentation occurs in less than 50% of cases. Silent or atypical presentations of CD are becoming more common[3,4]. The diagnosis of CD is dependent on correlation between history, serological markers and characteristic histological features on duodenal biopsy[1]. It is currently unclear whether the presenting symptoms of CD have any relationship to the severity of small bowel injury at diagnosis. It also remains unclear whether the severity of small bowel mucosal injury is related to complications of CD such as osteoporosis.

The only known treatment for CD is adherence to a gluten free diet (GFD) which may reduce the risk of long-term complications such as osteoporosis and malignancy[5]. Whilst small bowel mucosal injury is known to improve on a GFD, the rate and completeness of such improvement has been a subject of limited study.

In the current study we analysed the relationship between both pre-diagnosis coeliac serology and initial duodenal histopathology, and primary presenting symptoms, coeliac related comorbidity and response to a GFD.

MATERIALS AND METHODS

This retrospective cohort study included 99 participants who presented to a single Gastroenterology practice in Victoria (Australia) from 1999-2013. Patients were referred to this practice either by General Practitioners or other specialists. All patients were assessed by a Gastroenterologist. Data collected at baseline included: Gender, age at diagnosis, primary presenting symptom as assessed by a Gastroenterologist, duration of symptoms prior to diagnosis, family history of CD, complications of CD, associated autoimmune condition. Serological and histology data included the presence of anti- tissue transglutaminase (tTG) antibodies or endomysial (EM) antibodies; small bowel histopathology at the time of diagnosis and at least six months after commencing a GFD, quantified by Marsh-Oberhuber Score (MS). Data were recorded in a Microsoft Excel (2011) spreadsheet and then transferred to SPSS Version 25.0 (IBM SPSS Inc., Chicago, IL, United States) for statistical analysis. Numerical data were presented as median and inter-quartile range (IQR). The association of severity of duodenal blunting to symptoms and serology were examined using logistic regression.

RESULTS

Presentation

Among the cohort of 99 patients the mean age at diagnosis was 43 years (IQR 30-53 years) and 68% of the cohort was female (Table 1). Over half of the patients (n = 51, 52%) were asymptomatic at presentation, some of whom for example had been referred by their General Practitioner after having positive CD serology as part of a work-up to investigate iron deficiency. The most common presenting symptom was diarrhoea (n = 31, 31%). Of symptomatic patients, the majority (n = 34, 71%) described symptoms for over 1 year prior to diagnosis (Table 2).

At diagnosis, 17 (17%) patients had an associated autoimmune condition including thyroid pathology (n = 10), Type 1 Diabetes (n = 8), Rheumatoid Arthritis (n = 1) and Pernicious anaemia (n = 1) (Table 3).

Diagnosis

88 (89%) patients had positive CD serology at the time of diagnosis. Small bowel histopathology at diagnosis revealed total villous blunting (MS 3c) in 49 (49%), subtotal villous blunting (MS 3b) in 12 (12%) and partial

Table 1 Comparison of 99 patients with coeliac disease n (%)

	n (%)
Age, yr	43 (30-53)
Male gender	32 (32)
Family history	24 (24)
Main symptom at presentation	
Abdominal pain	5 (5)
Bloating	6 (6)
Bone disease	6 (6)
Diarrhoea	31 (31)
Fatigue	6 (6)
Iron deficiency	21 (21)
Incidental[1]	6 (6)
Screening	14 (14)
Other[2]	4 (4)

[1]Gastroscopy performed to investigate dyspepsia; [2]Vitamin B12 deficiency (n = 3), hypoalbuminaemia (n = 1). Continuous variables are presented as median (inter-quartile range).

Table 2 Comparison of duration of 48 patients with symptoms at diagnosis

Duration of symptoms prior to diagnosis	*n* (%)
< 1 yr	14 (29)
1-3 h	12 (25)
> 3 yr	22 (46)

villous blunting (MS 3a) in 29 (29%) patients, while 9 (9%) patients had lesser degrees of injury with crypt hyperplasia or only intra-epithelial lymphocytosis (Table 4). Of the patients with MS 3b or 3c, 10 (83%) and 44 (90%) had positive serology respectively (Table 4). The majority of patients with MS ⩾ 3a were symptomatic at diagnosis. There was no difference in symptoms between patients in a combined group of MS 3a/b compared to MS 3c (P = 0.490) (Table 5). Of the 9 patients who had lesser degrees of injury with crypt hyperplasia or only intra-epithelial lymphocytosis, 2 (22%) patients had presented with fatigue, 4 (44%) patients had been detected on screening by a General Practiotioner, 2 (22%) had been investigated for iron deficiency and 1 (11%) patient had been investigated for dyspepsia. Concomitant autoimmune conditions were present in 4 (10%) patients with MS 3a/b and 9 (18%) patients with MS 3c (P = 0.298). 2 (5%) of patients with Marsh 3a/b had osteoporosis or osteopenia at diagnosis compared to 4 (8%) of patients with Marsh 3c (P = 0.534).

Follow-up

87 (88%) of the cohort underwent repeat small bowel biopsy after a minimum of six months (Table 6). Of this group 76 (87%) reported adherence to a GFD at the time of repeat biopsy.

Of the 76 patients reporting adherence to a GFD at the time of the second biopsy 48 (63%) had negative serology, 14 (18%) had positive serology and 14 (18%) did not have serology results available. 37 (49%) were asymptomatic, 7 (9%) reported symptoms and 32 (42%) did not have data recorded. All 7 patients with a concomitant autoimmune disorder who reported compliance with a GFD and had negative serology had persistent MS ⩾ 3a.

Table 3 Comparison of 17 patients with an associated autoimmune condition at diagnosis

Thyroid pathology	
Graves' disease	4
Autoimmune thyroiditis	1
Hypothyroidism[1]	5
Type 1 diabetes	5
Rheumatoid arthritis	1
Pernicious anaemia	1

[1]Includes 1 patient with Hashimoto's thyroiditis.

30 (34%) patients had biopsy results revealing a normalization of histology (MS0), 18 (60%) of whom had negative repeat serology, 6 (20%) had positive serology and 6 (20%) did not have serology results available. All 30 patients with MS0 reported adherence to a GFD.

34 (39%) patients had biopsy results ⩾ MS 3a which compared to 90 (90%) at the initial biopsy. Of the 34 patients with persistent ⩾ MS 3a, 18 (53%) had negative repeat serology, 8 (24%) had positive serology and 8 (24%) did not have serology results available. 24 (71%) of this group reported adherence to a GFD.

47 patients reported compliance with a GFD and had negative serology consistent with absent dietary gluten exposure. Among this cohort the repeat biopsy was undertaken at a median of 7 mo (IQR 6-11 mo) and the incidence of persistent villous blunting was 62%. Among the 29 patients with persistent villous blunting, in 16 (55%) the change was ⩾ MS 3a.

Multivariate analysis did not reveal an association between MS ⩾ 3a at diagnosis of CD and positive serology or symptoms at diagnosis (Table 7). Lack of improvement in small bowel histology was not associated with persistently positive coeliac serology or ongoing symptoms at the time of repeat biopsy (Tables 8 and 9).

DISCUSSION

The findings in this study support other larger studies which have reported a trend toward an asymptomatic or silent presentation of CD rather than the traditional presentation of diarrhea[4,6-8]. The "coeliac iceberg" is often used to describe the large proportion of undiagnosed asymptomatic or subclinical coeliac disease[9,10]. Nenna *et al*[10] reported that the traditional presentation of CD accounted for 28% of cases, whereas the majority of cases presented as silent forms or non-classical presentations of CD. A third group termed latent CD is also described comprising individuals who are considered at risk due to having a coeliac related HLA type and positive coeliac serology in the absence of current villous blunting. Genetic composition plays a pivotal role in determining the predisposition to CD, with

Table 4 Symptoms, serology and histology results for 99 patients divided by severity of duodenal histology at initial biopsy

Biopsy score[1]	*n* (%)	Positive serology[2]	Symptoms at diagnosis (%)
0	0 (0)	-	-
1	7 (7)	Positive = 7 (100) Negative = 0 (0) Unknown = 0 (0)	0 (0)
2	2 (2)	Positive = 2 (100) Negative = 0 (0) Unknown = 0 (0)	2 (100)
3a	29 (29)	Positive = 25 (86) Negative = 4 (14) Unknown = 0 (0)	14 (48)
3b	12 (12)	Positive = 10 (83) Negative = 1 (8) Unknown = 1 (8)	7 (58)
3c	49 (49)	Positive = 44 (90) Negative = 2 (4) Unknown = 3 (6)	25 (51)

[1]Marsh-Oberhuber score at diagnosis; [2]tissue Transglutaminase antibodies or endomysial antibodies.

Table 5 Presenting symptom of Marsh-Oberhuber score 3c compared to Marsh-Oberhuber score 3a/b *n* (%)

Presentation	Marsh-Oberhuber score 3a/b[1]	Marsh-Oberhuber score 3c[2]	Odds ratio	95%CI	*P* value
Diarrhoea	13 (32)	18 (37)	1.39	0.33-5.79	0.66
Iron deficiency	8 (20)	11 (22)	1.38	0.30-6.40	0.69
Bone disease	2 (5)	4 (8)	2.00	0.24-16.36	0.52
Bloating	4 (10)	2 (4)	0.50	0.06-4.09	0.52
Fatigue	1 (2)	3 (6)	3.00	0.23-39.60	0.40
Abdominal pain	3 (7)	2 (4)	0.67	0.76-5.88	0.72
Incidental	2 (5)	3 (6)	1.50	0.17-13.23	0.72
Screening	5 (12)	5 (10)	0.33	0.25-4.40	0.40
Other	3 (7)	1 (2)	1.38		0.89

[1]n = 41; [2]n = 49. CI: Confidence interval.

HLA-DQ2 and DQ8 haplotypes expressed in 90% and 5% of affected patients respectively[11]. Gluten is required to trigger the disease but the transition from tolerance to a gluten related immune response is poorly understood[11]. Possible triggers for this immune transition include intestinal infections, the amount and quality of gluten and the composition of the intestinal microbiota[11]. A gluten related immune response may develop early in life and many silent cases are unrecognized for many years, if ever[12]. It has been suggested that although the majority of CD cases have not been diagnosed, population screening may not be appropriate as evidence is lacking as to whether the majority of silent CD cases actually translate into any significant morbidity. It also remains unclear whether these clinically silent cases would benefit from a GFD[13,14].

Microscopic enteritis is a histopathological inflammatory condition (Marsh 0-Ⅱ) which clinically may present as malabsorption or more subtle micronutrient deficiencies but with a relatively intact villous structure[15]. 9 (9%) patients in this cohort could be classified at initial biopsy with microscopic enteritis secondary to CD. Microscopic enteritis is an important, novel diagnostic category of patients whom were previously diagnosed with a functional enteropathy[15].

The contrary view has also been argued, that population screening may be beneficial given there is a high prevalence of associated autoimmune conditions and nutritional deficiencies could contribute greatly to population morbidity[16]. Owing to the absence of identifiable features predicting risk, targeted screening of at risk populations would be difficult. Whilst most seropositive patients will have villous blunting[17], among those seropositive patients with normal small bowel mucosa there is no reliable means of identifying which subsets will go on to develop villous blunting and potentially long term complications of CD. Further clarification *via* large population studies is needed to resolve issues around cost-benefits of screening, which populations and age groups to screen as well as laboratory reference range cut-offs for screening tests[9].

This study found the majority of patients to be female, most patients to be asymptomatic and a minority to present with diarrhea. The widely reported trend toward silent CD could possibly be partly explained by the increased access to serology and upper gastrointestinal endoscopy which have enabled for easier diagnosis of CD[18]. However the reported decrease in the proportion of patients presenting with symptoms such as diarrhea started before the advent widespread availability of

Table 6 Symptoms, serology and histology results for 87 patients with repeat biopsy

Biopsy score[1]	Repeat biopsy score	Positive serology[2]	Reported gluten free diet adherence	Symptoms at repeat biopsy
0	31 (36)	Positive = 6	Yes = 31	Yes = 4
		Negative = 19	No = 0	No = 14
		Unknown = 6		Unknown = 13
1	17 (20)	Positive = 4	Yes = 16	Yes = 2
		Negative = 9	No = 1	No = 10
		Unknown = 4		Unknown = 5
2	5 (6)	Positive = 1	Yes = 5	Yes = 1
		Negative = 4	No = 0	No = 2
		Unknown = 0		Unknown = 2
3a	26 (30)	Positive = 4	Yes = 20	Yes = 3
		Negative = 17	No = 6	No = 12
		Unknown = 5		Unknown = 11
3b	1 (1)	Positive = 0	Yes = 1	Yes = 0
		Negative = 0	No = 0	No = 0
		Unknown = 1		Unknown = 1
3c	7 (8)	Positive = 4	Yes = 3	Yes = 1
		Negative = 1	No = 4	No = 4
		Unknown = 2		Unknown = 2

[1]Marsh-Oberhuber score at diagnosis; [2]Anti-transglutaminase antibodies or endomysial antibodies.

Table 7 Independent predictors of a Marsh-Oberhuber score ⩾ 3a at diagnosis of coeliac disease for 99 patients

Characteristic	Odds ratio	95%CI	*P* value
Age below 40 yr	0.38	0.08-1.85	0.231
Female gender	3.20	0.35-29.10	0.301
Positive serology	2.06	0.17-25.52	0.573
Symptoms for over 3 yr	0.70	0.04-11.37	0.804
Symptoms at diagnosis	4.54	0.51-40.60	0.176

CI: Confidence interval.

Table 8 Independent predictors of a Marsh-Oberhuber score ⩾ 3a after repeat duodenal biopsy, at least 6 mo after diagnosis of coeliac disease for 87 patients

Characteristic	Odds ratio	95%CI	*P* value
Age below 40 yr	0.59	0.23-1.57	0.292
Female gender	1.13	0.40-3.20	0.824
Gluten free diet	0.03	0.00-0.34	0.004
Symptoms at second biopsy[1]	0.45	0.81-2.48	0.358
Positive serology at second biopsy	0.64	0.18-2.27	0.485

[1]*n* = 51 patients. CI: Confidence interval.

serologic testing[4]. The proportion of atypical or silent presentations of CD is increasing, most often manifesting as bone disease, anaemia or an incidental finding at the time of investigation of dyspepsia *via* endoscopy[8,19]. There is also an increased proportion of diagnoses through screening of first degree relatives[20]. Age at diagnosis has slightly increased since the 1960s, which it is suggested is at least partly related to the later administration of dietary gluten to infants[21].

17 (17%) of cases in this study had autoimmune co-morbidities, mainly thyroid-related. Other studies have reported increased rates of autoimmunity, predominantly thyroid-related although at rates are slightly lower than reported in this study[3,16,22,23]. Ventura *et al*[11] reported a higher prevalence of autoimmune disorders in a CD population relative to healthy controls. While the higher prevalence of autoimmune conditions in CD is often explained by shared HLA antigens, Ventura *et al*[24] reported that the prevalence of autoimmune disorders in CD was associated with the duration of exposure to gluten. They found that the age at diagnosis of CD was the single best predictor of the prevalence of autoimmune disease when corrected for gender and actual age of the patients[24]. It is possible that the increased prevalence of autoimmune comorbidity in the current cohort compared with other cohorts reported in the literature[3,16,22,23], reflect the relatively advanced age at diagnosis which correlated with many years of gluten exposure prior to diagnosis.

We identified 6 (6%) of patients in this study to have osteoporosis or osteopenia. Low BMD is more common in patients with CD[25]. Compared with the current cohort, Kemppainen *et al*[25] have previously reported higher rates bone disease at the time of CD diagnosis (*n* = 20, 26%) although this could perhaps be explained by the relatively older study population in that study (mean 46 years). Kemppainen *et al*[25] has previously reported that low BMD was associated with a new diagnosis of CD, as well as patients not in disease remission. Kemppainen *et al*[25] did not find that mean BMD differed between patients classified by disease severity. Patients with newly diagnosed osteoporosis have higher rates of CD relative to the general population with one study reporting the prevalence of CD in an osteoporotic population to be 3.4%[26]. Patients with CD have significantly decreased bone mineral density (BMD) in the femoral neck and lumbar spine. The pathogenesis of bone mineral loss associated with CD is not well understood. Chronic inflammation of the damaged intestinal mucosa results in release pro-inflammatory cytokines such as tumour

Table 9 Independent predictors of a Marsh-Oberhuber score < 3 on repeat duodenal biopsy, at least 6 mo after diagnosis of coeliac disease for 87 patients

Characteristic	Odds ratio	95%CI	*P* value
Age below 40 yr	1.16	0.63-4.31	0.313
Female gender	0.90	0.32-2.52	0.834
Negative serology at time of repeat biopsy	0.72	0.26-1.99	0.524
Asymptomatic at repeat biopsy	1.07	0.41-2.80	0.899
Gluten-free diet	23.57	2.61-212.99	0.005

CI: Confidence interval.

necrosis factor α and Interleukin (IL)-6. Higher levels of these cytokines, which directly trigger osteoclasts, have been found in untreated CD patients[27,28]. At the same time lower levels of IL-18 and IL-12, which play an inhibitory role, have been observed in CD patients[27,28]. Other important contributors of decreased BMD may differ between patients but include: malabsorption of calcium; secondary hyperparathyroidism driven by vitamin D deficiency; inadequate dietary intake; lapses from GFD[29,30]. Treatment of CD with a GFD has been shown to improve axial BMD however loss of peripheral skeletal BMD may persist[29]. While patients with CD have increased bone loss, the overall fracture rate is only slightly increased and therefore it is argued osteoporosis related morbidity does not justify population screening for coeliac disease[31]. It has been suggested that screening for CD should be performed in all patients with osteoporosis[26]. However other studies have not supported screening of this population citing that while the prevalence of CD may be increased in osteoporotic cohorts, it makes up only a small contribution relative to the overall post-menopausal osteoporotic population[32,33].

After diagnosis, the key endpoints for CD management are absence of symptoms and histologic evidence of mucosal healing[34]. As was found in this study, negative serological markers are not reliable surrogates for mucosal healing[17,19,35]. Serum EM antibodies and tTG antibodies are often used as surrogate measures of villous health. However these tests were designed for screening for CD among untreated persons consuming gluten. For monitoring known CD patients on a GFD, both EM and tTG antibodies have a high specificity but a low sensitivity resulting in the majority of patients on a GFD with villous blunting having normal serological levels. This is contrasted with a high specificity and sensitivity in patients with untreated CD. False positive tests for patients on a GFD are less common[36].

39% of patients in the current study had persistent villous blunting at repeat biopsy which is higher than similar studies[37,38]. Hutchinson *et al*[37] reported 80% of cases demonstrated histological improvement while Ciacci *et al*[38] reported severe intestinal damage persisted in only 23.8% of patients. An explanation for the difference could be the longer time to follow-up relative to our study of 1.0 year[37] and 6.9 years[38]. There is no consensus on timing of repeat biopsy; some experts favour repeat biopsy in 1 year and others do not recommend a repeat biopsy in the management of uncomplicated CD cases[39]. Serology often does not reflect the mucosal health in patients on a GFD however there is a paucity of evidence to address whether a repeat biopsy changes clinical outcomes and the cost-benefit analysis is yet to be established. A repeat biopsy may be needed, especially in patients with ongoing symptoms. The optimal timing of any such biopsy is unclear[39]. In a cohort of 39 patients with CD reporting GFD adherence all of whom had responded clinically, 77% had abnormal endoscopic and histopathologic appearances on repeat biopsy performed after a mean of 8.5 years[40]. A strict GFD is associated with improvement of histology which has been supported by previous studies, re-enforcing that diet modification is the only known effective management option for these patients[41,42]. The cause of persistent villous blunting is thought to often be caused by trace amounts of gluten consumed inadvertently by the patient. GFD adherence as assessed by interview has been demonstrated as an effective low-cost, non-invasive surrogate for villous damage[38].

This study has a number of limitations. Firstly, this is a relatively small study from a single specialist centre, thus may not reflect results in the greater community. However, a strength is that all patients were assessed by the same local protocol by a single Gastroenterologist which avoided heterogeneity between observers. Secondly, data were collected retrospectively. A number of patients did not have a repeat biopsy nor had missing data at the time of the repeat biopsy. A strength of this study is that it is the first study to look at the presentation of CD in an Australian population in the modern era. There are no published Australian studies which have recognized the changing nature of CD presentations and a prospective study would further add to this field.

In this study, the majority of patients were asymptomatic at the time of CD diagnosis. Neither symptoms nor serology predicted the severity of the small bowel mucosal lesion. The majority of patients had histological improvement on repeat biopsy. Whilst a GFD was associated with histological improvement many patients had persistent mucosal damage despite a GFD. Early repeat duodenal biopsy may have limited diagnostic and prognostic value due to delayed mucosal healing. Biopsy after at least 1 year may provide more valuable results rather than an earlier biopsy as was done in this cohort. Negative CD serology did not exclude ongoing mucosal

injury.

ARTICLE HIGHLIGHTS

Research background

Coeliac disease (CD) is a common gastrointestinal disorder that involves an immune response to dietary gluten. The condition is under recognised, particularly because silent or atypical presentations are becoming more common. Diagnosis is made with the combination of symptoms, serology and characteristic features seen on duodenal biopsy. It remains unclear whether there is an association between symptoms at diagnosis and the degree of small bowel injury. In addition, it is unclear whether symptoms and serology at the time of repeat duodenal biopsy are associated with the degree of mucosal healing.

Research objectives

The aim of this study was to analyze the association between both pre-diagnosis coeliac serology and initial duodenal histopathology, and primary presenting symptoms, coeliac related comorbidity and response to a gluten-free diet (GFD). Most patients in this study were asymptomatic at diagnosis. Neither symptoms nor serology were associated with the severity of small bowel injury. Many patients had persistent mucosal damage at the time of repeat duodenal biopsy despite reported adherence to a GFD suggesting that mucosal healing may take longer than previously reported. These findings have revealed the increasing difficulty in recognizing the symptoms of CD. Further research is needed to develop more reliable non-invasive biomarkers to be used as surrogates to assess mucosal healing.

Research methods

This was a retrospective cohort study which included 99 participants who presented to a single Gastroenterology practice in Victoria, Australia from 1999-2013. Patients were referred from General Practitioners or other specialists. All patients were assessed by a Gastroenterologist. Data recorded included: baseline demographics, co-morbidities, family history, duration of symptoms, complications of CD. Serology and histology results were recorded for each patient. The majority of these patients underwent repeat duodenal biopsy after a period on a GFD to check for mucosal healing. Results were compared to repeat serology and symptoms. Numerical data were presented as median and inter-quartile range (IQR). The association of severity of duodenal blunting to symptoms and serology were examined using logistic regression.

Research results

The mean age at diagnosis was 43 years (IQR 30-53 years) and the majority was female. Most patients (n = 51, 52%) were asymptomatic at diagnosis. 17 (17%) patients had an associated autoimmune condition, the majority of whom had thyroid pathology (n = 10, 59%). The majority of patients with Marsh-Oberhuber Score (MS) $\geqslant$ 3a were symptomatic at diagnosis. There was no difference in symptoms between patients in a combined group of MS 3a/b compared to MS 3c. There was no difference of concomitant autoimmune conditions between patients with MS 3a/b (n = 4, 10%) and MS 3c (n = 9, 18%). Multivariate analysis did not reveal an association between MS $\geqslant$ 3a at diagnosis of CD and positive serology or symptoms at diagnosis. 87 (88%) patients had repeat biopsy. Lack of improvement in small bowel histology was not associated with persistently positive coeliac serology or ongoing symptoms at the time of repeat biopsy.

Research conclusions

This study supports larger studies that have reported an increase in asymptomatic presentations of CD. Severity of villous blunting at diagnosis was not associated with symptoms. This study did not find an association between symptoms and serology at the time of repeat duodenal biopsy with persistent villous blunting. Duodenal healing whilst on a GFD may persist for longer than previously reported. Discovery of new non-invasive biomarkers is needed to better predict the degree of villous blunting.

Research perspectives

Duodenal healing whilst on a GFD may persist for longer than previously reported. Discovery of new non-invasive biomarkers is needed to better predict the degree of villous blunting.

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MINIREVIEWS

Potassium-competitive acid blockers - are they the next generation of proton pump inhibitors?

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Abstract

The modern lifestyle caters to an increase in the incidence of peptic ulcer disease, gastroesophageal reflux disease and several other acid-related conditions of the gut. The drugs to prevent these conditions work either through H2 receptor blockade or inhibition of the H^+, K^+ ATPase enzyme. Although proton pump inhibitors have been proven to be efficacious, they have a slow onset of action with limited resolution of symptoms in most patients. Potassium-competitive acid blockers (P-CABs) are novel drugs that bind reversibly to K^+ ions and block the H^+, K^+ ATPase enzyme, thus preventing acid production. P-CABs have a fast onset of action and have dose-dependent effects on acid production. Animal studies exist that differentiate the better results of P-CABs from proton pump inhibitors; further human trials will give a comprehensive picture of the results and will help to elucidate the therapeutic benefits of this new group of drugs.

Key words: Potassium-competitive acid blockers; Gastroesophageal reflux disease; Proton pump inhibitors; Peptic ulcer disease; Vonoprazan

Core tip: There have been tremendous changes in the treatment of acid-related diseases. In this rapidly evolving field, novel drugs such as potassium-competitive acid blockers (P-CABs) show promising potential. This review aims to provide a perspective on this new class of drugs by summarizing the mechanism of action, therapeutic benefits, adverse effects and approval status of various P-CABs in the market.

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INTRODUCTION

A principal and vital component aiding in digestion is gastric acid. Gastric acid is secreted by the parietal cells into the lumen of the stomach. However, gastric acid is also responsible for the pathogenesis of gastric ulcers, gastroesophageal reflux disease (GERD), nonsteroidal anti-inflammatory drug-induced gastrointestinal damage and ulcers in Zollinger Ellison Syndrome. The identification of the bacterium *Helicobacter pylori* (*H. pylori*) as the cause for peptic ulcer was a breakthrough approximately 30 years ago, and *H. pylori* eradication could prevent or cure these conditions. The cure is directly related to the decrease in acid secretion by parietal cells[1].

Gastric acid is secreted by the parietal cells of the gastric glands. This secretion is related to food intake, although it can also occur due to the taste, smell or thought of food. The stimulation of the parietal cell occurs through 3 kinds of receptors namely, H2 (histamine) receptors, M3 (cholinergic muscarinic) receptors and CCK2R (gastrin receptors)[1,2].

HISTORY OF POTASSIUM-COMPETITIVE ACID BLOCKERS - VARIOUS DRUG TYPES

Potassium-competitive acid blockers (P-CABs) are a group of drugs developed in the early 1980s. The first drug developed was SCH28080, an antisecretory drug that inhibited H^+, K^+ ATPase via a competitive interaction with K^+ site of the enzyme. However, further development of the drug was stopped due to its toxic effects on the liver[2]. Another drug was developed, AZD0865, which was potent but a reversible inhibitor of H^+, K^+ ATPase with a rapid onset of action. In phase II and III trials, this drug displayed similar efficacy to esomeprazole for treating esophagitis and for symptomatic relief of nonerosive reflux disease (NERD); however further trials could not be conducted on this drug, as it was not superior to esomeprazole, and there was an adverse drug reaction: hepatotoxicity with reversible elevation of hepatic transaminases[3]. The first P-CAB used in clinical practice was revaprazan (YH-1885, Revanex), marketed in South Korea. Like other P-CABs, it had a quick action onset, however, was not superior to the existing proton pump inhibitors (PPIs)[4]. The second P-CAB introduced in clinical practice was vonoprazan fumarate (TAK-438), marketed in Japan in early 2015; it became popular because of its superior properties such as rapid onset of action, long duration of action, and consistent and potent acid suppression compared to the traditional PPIs[4].

Phase III trials were conducted in South Korea for reflux esophagitis for comparing the safety and efficacy of a new P-CAB, tegoprazan (RQ-00000004/CJ-12420) 50 mg and 100 mg along with esomeprazole. The complete and final results of this study are not yet published[4]. Tegoprazan was approved for the treatment of erosive esophagitis (EE) and NERD in South Korea in July 2018.

MECHANISM OF ACTION/PHARMACOKINETICS

The P-CABs are weak bases, and the protonated form of these drugs inhibits the H^+ K^+ ATPase enzyme. It is found that linaprazan's potency was high when it was exposed to vesicles that are ion-tight rather than to ion-leaky vesicles. This suggests that the drug gets concentrated under low pH and acts in the gastric lumen. The pKa of these drugs varies: 5.6 (SCH28080), 6.1 (linaprazan) and 9.3 (vonoprazan). Since the pKa of vonoprazan is high at 9.3, most of it gets protonated easily and exerts its inhibitory action. Additionally, since the protonated forms are less prone to cross membranes than the nonionic molecules, these protonated forms of P-CABs concentrate in the acid-secreting canaliculi of parietal calls where they exert the effect of H^+ K^+ ATPase enzyme inhibition[5].

THERAPEUTIC BENEFITS OF P-CABs

GERD is a common condition where reflux of the gastric contents leads to various gastrointestinal symptoms and complications. Most patients have one of 3 types, namely, NERD, EE and Barrett's esophagus.

PPIs and H2 receptor antagonists are the current treatment of choice of this condition, which causes gastric acid suppression. The main goals of the treatment are to give symptomatic relief, heal and maintain remission of EE, prevent complications and improve the quality of life. Presently, there are several unmet needs in this therapy[6].

P-CABs represent a heterogeneous group of drugs which inhibit H^+, K^+ ATPase in a potassium-competitive reversible mechanism. They do not require proton pump activation to achieve their action; further, they have rapid action onset and reduce acid secretion due to a steady rise in their plasma concentration.

Vonoprazan is an acid-stable and fast absorbing drug approved for the treatment of reflux esophagitis for prevention of relapse[7]. In GERD, vonoprazan improves epigastric pain, postprandial distress, constipation, and diarrhea[8]. Linaprazan (AZD8065) has shown similar efficacy as esomeprazole in healing and preventing symptoms of GERD with EE; however, it has not shown any benefit in patients with NERD. Soraprazan showed immediate acid suppression in *in vitro* studies. It was also found to be superior to esomeprazole in rapid action onset and the duration of maintaining gastric pH > 4 in animal models. However, no clinical studies are available for this drug. Revaprazan was found to be similar to PPIs in acid suppression[6].

Peptic ulcer disease

Vonoprazan has been approved in Japan for the treatment of gastric and duodenal ulcers[7]. Two randomized controlled trials were conducted to evaluate the drugs vonoprazan and lansoprazole for the treatment of gastric ulcer (GU) and duodenal ulcer (DU). For GU, approximately 93.5% of patients treated with vonoprazan and 93.8% of patients treated with lansoprazole achieved a cure. It was then confirmed that vonoprazan is equally effective as lansoprazole with only a difference of 0.3% in cure rate. In the case of DU, 95.5% of patients on vonoprazan and 98.3% on lansoprazole achieved a cure. Here, the difference is 2.8%, and hence, vonoprazan was not confirmed to be superior or equally potent as lansoprazole. However, it was found that the treatment-emergent adverse events were slightly lower in GU than DU with vonoprazan. There was a single death case reported due to subarachnoid hemorrhage in the vonoprazan-treated DU group; the possibility of a causal association between the study drug and the unexpected death could not be ruled out. The study concluded that vonoprazan 20 mg has a tolerability profile similar to that of lansoprazole 30 mg with similar efficacy in DU healing and noninferior with respect to GU healing[9].

H. pylori eradication

A multicenter study was done to assess the safety and efficacy of vonoprazan-based triple treatment. The triple therapy included treatment with vonoprazan and two antibiotics (amoxicillin and clarithromycin or metronidazole). The eradication among 799 patients in the study was 94.4% in the per-protocol analysis for the first-line therapy and 97.1% for the second-line therapy. The first line included vonoprazan 20 mg, amoxicillin 750 mg and clarithromycin 200 or 400 mg, twice a day for one week and the second line included vonoprazan 20 mg, amoxicillin 750 mg, and metronidazole 250 mg, twice a day for one week. The incidence of adverse events was 4.4% with no patients hospitalized. It was thus concluded that vonoprazan-based triple therapy was safe and effective for *H. pylori* eradication[10].

Clinical studies were done in Japan to determine if P-CABs specifically showed superiority to PPIs for the eradication of *H. pylori*[11]. Approximately 573 patients who underwent *H. pylori* eradication therapy were reviewed retrospectively. The therapy included treatment with clarithromycin 200 mg, amoxicillin 750 mg and an acid-suppressing drug -lansoprazole 30 mg, rabeprazole 10 mg, esomeprazole 20 mg or vonoprazan 20 mg - taken twice daily for 1 wk. The *H. pylori* eradication was successful in approximately 73% of patients using intention-to-treat (ITT) analysis and 76% of patients in per protocol (PP) analysis. The vonoprazan-treated group had a significant and superior eradication rate of 83% in ITT and 85% in PP compared to the results for lansoprazole (66% ITT and 69% PP) and rabeprazole (67% ITT and 70% PP); however, the eradication rate of esomeprazole was similar - 83% ITT and 87% PP. Although the eradication rates with vonoprazan and esomeprazole were not significantly higher than that of the lansoprazole and rabeprazole groups with both ITT and PP analysis in mild gastric atrophy patients, the effects were significantly higher in severe gastric atrophy patients[11]. Further, the group treated with vonoprazan had a significantly higher eradication rate of *H. pylori* than the other

groups with a > 80% eradication rate irrespective of the degree of atrophy[11].

Endoscopic submucosal dissection induced artificial ulcers

Although vonoprazan is found to be superior to PPIs in inhibiting acid secretion, its efficacy in endoscopic submucosal dissection (ESD)-induced artificial ulcers was not found to be superior to any PPIs. A randomized prospective study was done to compare and assess the effects of vonoprazan and lansoprazole for ESD-induced artificial ulcers. This prospective study included 149 patients who had ESD for treatment of early gastric cancers for the period Apr 2015 to May 2017. Treatment was randomly provided with oral vonoprazan 20 mg/d or oral lansoprazole 30 mg/d. The primary endpoint was area and shrinkage ratio of the ulcers at 4 and 8 wk after ESD. Data were analyzed from 129 patients, and it was found that there was no significant difference between the vonoprazan and lansoprazole groups in the area and the shrinkage ratio of the ulcers at 4 and 8 wk respectively. Hence, it was concluded that vonoprazan and lansoprazole are equally effective in the treatment of ESD-induced artificial ulcers[12].

Secondary prevention of low dose aspirin or nonsteroidal anti-inflammatory drug induced gastric mucosal damage

Vonoprazan 10 mg and 20 mg were found to be very well tolerated and effective for the prevention of nonsteroidal anti-inflammatory drug (NSAID) related recurrence of peptic ulcer in Japanese patients, and this preventive action could be maintained with long-term use. A daily dose of vonoprazan 10 mg has been approved in Japan as the recommended clinical dose for the prevention of NSAID induced ulcers. It is foreseen that vonoprazan could become the primary treatment option for NSAID related adverse events in high-risk patients[13].

ADVERSE EVENTS OF P-CABs

Liver toxicity: The earlier P-CABs are not being used clinically worldwide due to their short duration of action and hepatotoxicity. These earlier P-CABs included SCH28080 (imidazopyridine), AZD0865, pyrimidines, imidazonaphthyridines and pyrrolopyridazines[14].

A phase III double-blinded, placebo-controlled, parallel group, multicenter study was conducted in Japan in patients aged ≥ 20 years with Grade N or M NERD and recurrent acid reflux symptoms. The incidence of the treatment-emergent adverse event (TEAE) was 32.7% with placebo, 27.7% with vonoprazan 10 mg and 28% with vonoprazan 20 mg. The most common TEAE with vonoprazan 10 mg and 20 mg in clinical studies was nasopharyngitis. Most of the TEAEs were mild, and no deaths were reported. One serious adverse event, diverticulitis, was reported in the vonoprazan 10 mg group and was considered to be likely due to the drug. Additionally, the mean levels of gastrin, pepsinogen I and pepsinogen II increased after administration of vonoprazan 10 mg and 20 mg[15]. Mild to moderate constipation or diarrhea was reported in certain preapproved clinical studies where vonoprazan was used for treating acid-related disorders[16].

OTHER P-CABs ON THE MARKET

Tegoprazan (CJ-12420) is a newer P-CAB with a potential to treat GERD. A phase I, randomized, double-blinded, placebo-controlled clinical study was conducted in 56 healthy Korean male volunteers. CJ-12420 was administered to 32 subjects in the doses of 50, 100, 200 and 400 mg in the single ascending dose (SAD) study. Either 100 or 200 mg of the drug was administered every 24 h to 8 subjects for 7 d in a multiple ascending dose (MAD) study. The plasma concentration of CJ-12420 and its metabolite M1 were measured by liquid chromatography-mass spectrometry. There were few adverse events reported in this study, and all were mild in nature. It was concluded that the drug tegoprazan is well tolerated in healthy subjects in the SAD and MAD studies. The study could also successfully elucidate the pharmacokinetics of the drug and its metabolite as well as the pharmacodynamics of gastric pH, thus providing clinical evidence that the drug can be used to treat acid-related disorders[17].

APPROVAL STATUS

Revaprazan was developed in Korea and was the first P-CAB approved. It is also

available in India. Vonoprazan was developed by Takeda; it was approved in Japan in February 2015 for the treatment of acid-related diseases which include reflux esophagitis, GERD, *H. pylori* eradication, EE and peptic ulcer disease (PUD). In the United Kingdom, phase I studies were conducted for GERD, however, no further update was reported[18]. Tegoprazan was approved for the treatment of erosive esophagitis (EE) and NERD in Korea in July 2018. The drugs vonoprazan and revaprazan are currently not available outside Asia, Europe and the United States[19].

CONCLUSION

Over the past 40 years, there have been tremendous changes in the treatment of acid-related diseases from diet and surgery to H2 receptor antagonists and then PPIs. Acid-related disorders are the result of excessive production of acid or decreased mucosal defense. The diseases such as GERD and PUD are important health care problems because of chronicity and high prevalence. Drug-induced gastric acid suppression is the principal component in the treatment of these conditions[20,21]. There has been observed variability in the management of various acid-related disorders, partly due to regional variations in the disease severity and prevalence and partly due to variations in the clinician assessment and application of various published evidence[22]. The first group of drugs identified for inhibition of acid secretion was H2 receptor antagonists in the 1970s. These drugs were not very effective due to a short duration of action, development of drug tolerance after several days of treatment, and finally, it was also found that their effect on meal-stimulated acid secretion was limited compared to their effect on acid secretion in the night. These drugs were then followed by irreversible inhibitors of H^+, K^+ ATPase enzyme - the PPIs, which were more effective in acid suppression[23]. The majority of patients were treated with a once-daily regimen of PPIs. However, there was a subgroup of patients who developed refractoriness to PPI therapy, most likely due to lack of drug effect, reflux patterns, reduced bioavailability of the PPIs, and increased metabolism of the drug and rarely due to mutations in cytochrome P450[24]. Another disadvantage of PPIs was a requirement of acidic parietal cell pH to facilitate the conversion of the prodrug to active form for the pharmacological effect. Considering the various limitations in PPIs, further research was done, and a considerable effort was put in to develop a different kind of inhibitor of H^+, K^+ ATPase without any of the limitations of PPIs. These K^+ competitive acid antagonists or blockers do not depend on acid activation and bind to the enzyme directly with a rapid action onset and better control of acid secretion. However, since they bind reversibly and not covalently, a constant plasma concentration of the drug has to be maintained for the sustained effect. They have a shorter duration of action than the PPIs, but then they are acid stable and are readily formulated into an extended-release tablet for a long duration of action, or they can be given twice daily to inhibit acid secretion during the day and night time[25]. The earlier drugs in this category were discontinued due to liver toxicity and then came TAK-438 (vonoprazan), a novel P-CAB antisecretory agent which had superior efficacy compared to PPIs and less incidence of adverse drug reactions[26]. Various studies were conducted on vonoprazan individually and in comparison with PPIs, and it was found that the drug was well tolerated and produced a rapid, profound and sustained suppression of gastric acid secretion. Because of the tolerability and enhanced effectiveness of P-CABs, it is very likely that they will change the future of treatment of acid-related disorders.

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