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Review Article

# Pregnancy and Inflammatory Bowel Disease: A Special Combination

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**Abstract**

Inflammatory bowel disease (IBD) comprises a spectrum of chronic immune-mediated diseases that affect the gastrointestinal tract. Onset typically occurs in early adulthood. The incidence of this disease has increased worldwide. Its prevalence has increased in Colombia and occurs predominantly in women. Considering that this disease is not curable, the main objective of management is to achieve remission. Many women are affected by IBD during different stages of their lives, including their reproductive life, pregnancy, and menopause. Because of this, the way the disease is managed in women of reproductive age can affect the course of IBD. Treatment and health maintenance strategies are very relevant; for patients with a desire to conceive, remission of the disease is very important at the time of conception and throughout the pregnancy to ensure adequate outcomes for both mother and fetus. Also, remission is necessary at least 3 months prior to conception. It is well known that active disease during conception and pregnancy is associated with adverse outcomes. In addition, active perianal disease is an indication of cesarean delivery, resulting in an increased risk of intestinal surgery and post-operative complications.

**Keywords:** Inflammatory bowel disease, Pregnancy, Colitis, Ulcerative, Crohn disease, Fertility, Women

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## Introduction

Inflammatory bowel disease (IBD) comprises a spectrum of chronic immune-mediated diseases that affect the gastrointestinal tract, with a peak incidence between the second and fourth decades of life.[1] The incidence of this disease has increased worldwide. In North America, it affects 2 million people, and 3.2 million in Europe. Western countries began to report stabilization of incidence and even sporadic decreases in some regions. Perhaps elevations in incidence are still being reported, and overall, it is ranging from 5 to 15 per 100 000 person-years for both Crohn's disease (CD) and ulcerative colitis (UC). Furthermore, the limit on the incidence of IBD seems to be 40 and 50 per 100 000 person-years. Considering that the disease is not curable, the main objective of management is to achieve remission.[2] In Colombia, there are two prevalence studies. In 2017, a prevalence of UC of 58.1/100 000 inhabitants per year, and of 8.9/100 000 for CD were reported, and an incidence of UC of 6.3/100 000 inhabitants per year, and of 0.74/100 000 for CD.[3] In 2020, another article on prevalence in Colombia was published, and 42 647 individuals were documented with a diagnosis of IBD, with an estimated prevalence of 87 cases per 100 000 inhabitants, most frequently in women (58% of cases), with a female/male ratio of 1.39:1. The prevalence of CD was 17 per 100 000 inhabitants, and of UC was 113 per 100 000 inhabitants.[4] However, it is a population in which information about clinical and therapeutic phenotypes is still not well known, and data about women are even scarcer.[5]

Women are affected by IBD during different stages of their lives, including reproductive life, pregnancy, and menopause, so the way the disease is managed in women of reproductive age can affect its course.[6] At least 50% of patients with IBD are diagnosed at age 35, and the disease most often affects women during their peak reproductive years.[7] Treatment and health maintenance strategies are very relevant. IBD poses a particular challenge during pregnancy because the health of the mother and fetus must be considered. For this reason, it is of utmost importance that the gastroenterologist and patients with IBD are aware of the effect of IBD on pregnancy, the effect of pregnancy on IBD, and the effect of IBD medications on the fetus and on pregnancy outcomes.[8] Taking into account the importance of the subject in daily clinical practice, it was decided to conduct the following review

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to demonstrate different aspects from preconception to postpartum in women with IBD.

## Inflammatory Bowel Disease and Women's Reproductive Health

### *What Is the Effect of Inflammatory Bowel Disease on Fertility?*

IBD occurs between 33.4 and 45 years of age, and it is vitally important to understand that infertility rates in women with non-active IBD are similar to those in the general population (8% to 10%).[9] Remission of the disease not only improves fertility rates but also, as most studies have shown, leads to more favorable pregnancy outcomes. Consequently, disease activity favors reduced fertility, probably in response to an inflammatory process and adhesions in the fallopian tubes or ovaries. Fear of infertility is common among patients with IBD and can negatively affect family planning decisions. Actually, women with inactive IBD and no previous pelvic surgery have similar infertility rates (5%–14%) to the general population. The active disease affects fertility, probably through multifactorial mechanisms, such as pelvic inflammation, malnutrition, decreased libido, dyspareunia, and depression. One small study showed decreased ovarian reserve in women with CD, especially those with active disease. Pelvic surgery significantly increases female infertility due to scars and adhesions.[10]

Surgery to control active IBD has a greater beneficial effect on fertility than uncontrolled disease. For the minority of women who require colectomy for UC and open ileal pouch, anal anastomosis surgery is associated with a two to three-fold increase in the rate of infertility. This is believed to be related to the pelvic adhesions; as described above, the open pouch surgery causes reduced motility and patency of the fallopian tubes. However, the new approach of laparoscopic pouch surgery is associated with lower infertility rates. Therefore, a minimally invasive approach to pouch surgery is preferable. In vitro fertilization success rates are similar for women after pouch surgery than for women without a history of IBD and surgery. Early referral to a fertility specialist should be considered for patients with ileal pouch-anal anastomosis surgery.[11-13]

It is clear that women who are affected by IBD and who are considering pregnancy often discontinue their treatment without informing their doctors. Studies in the Netherlands have shown that a systematic program of prior information with counseling prior to pregnancy improves the birth rate and reduces the risk of relapse of IBD during pregnancy.[12] Most medical treatments for IBD have no effect on the patient's ability to conceive. However, sulfasalazine is an exception, as it increases the risk of infertility in men by altering sperm counts, reducing sperm motility, and increasing the proportion of abnormal forms. A switch to 5-aminosalicylic acid (mesalazine) generally restores fertility and spermogram abnormalities. There is still some debate about the effects of thiopurines on fertility, but it is sometimes associated with impaired sperm motility.[14] Methotrexate may be responsible for oligospermia and is reversible when it is discontinued. This drug is contraindicated for both women and men because it is teratogenic. It appears that corticosteroids and cyclosporine have no effect on fertility. However, there is some debate about the effect of infliximab on fertility. In a small series of 10 patients with IBD, a trend toward decreased sperm motility with infliximab therapy was reported.[15] Data on the impact of adalimumab, vedolizumab, and ustekinumab on human fertility are insufficient.

The first step to treating infertility is to provide accurate counseling to positively impact preconception care. The optimization of nutritional status, vitamin supplementation (vitamin D and zinc), and the cessation of tobacco and alcohol are necessary. Overall, control of disease activity should be obtained and maintained. IBD couples facing infertility should be referred to specialized gynecology centers. However, the medical literature is scarce on infertility treatment in patients with IBD.[16,17]

### *What Is the Effect of Inflammatory Bowel Disease on Pregnancy?*

Patients with active IBD, either CD or UC, have worse pregnancy outcomes compared with healthy women.[18] Studies have also shown that there is a greater chance of worse pregnancy outcomes in patients with CD than in patients with UC.

According to a review conducted by Subhani and Hamilton in 1998,[19] CD, especially when it is active, is associated with low birth weight (LBW), preterm birth, and cesarean section. Furthermore, it is evident that in patients with IBD, induction of labor (32% vs. 24%, $P=0.002$), chorioamnionitis (7% vs. 3%, $P=0.04$) and cesarean section (32% vs. 22%) are more frequent than in the general population. Neonatal complications include low birth weight, intrauterine growth restriction, low Apgar scores, and congenital anomalies, which are similarly found between populations with and without IBD.[20] There are no studies reporting a higher probability of fetal malformation in these patients. Although there may be multiple factors associated with fetal malformation, it should be noted that the product of the first gestation (fetal death) was related to the debut of inflammatory disease with the morphological alterations described. This invites us to reflect on this issue, and although there is no clear evidence in this regard, it does mean that prenatal follow-up of these patients should be much closer.

Another study of 461 pregnant patients with IBD showed that these patients were at increased risk of spontaneous abortion, eclampsia, pre-eclampsia, placenta previa, abruptio placentae, and premature rupture of membranes. In this study, disease activity was not associated with a worse outcome. However, a diagnosis of IBD, a history of intestinal surgery for IBD, and not being white were found to be independent predictors of worse

outcomes.[21]

These results support current treatment guidelines, which indicate that maintaining remission during pregnancy is vital. It is important to know that the risk in this type of patient could be similar to that of the general population if their disease is controlled at the beginning of pregnancy.

### *What Is the Effect of Pregnancy on Inflammatory Bowel Disease?*

As stated earlier, many known chronic diseases can have active bouts during pregnancy. Moreover, about 30%-40% of women have active IBD during conception with an intense flare-up and adverse outcomes like spontaneous abortions, preterm and LBW (<2500 g regardless of gestational age), ischemic placental disease, stillbirth, and cesarean delivery. There is evidence that the disease activity is more detrimental to gestation and, consequently, to the fetus than medical therapy itself. Hence, as a first recommendation, the patient must be in disease remission at conception, favoring a pregnancy with lower risks of gestational adversities (Figure 1). Most of the conditions are associated with the maternal milieu and depressed nutrient delivery to the growing fetus.[22]

About 80% of women with IBD who become pregnant when the disease is in remission tend to be in remission in the intrapartum and postpartum periods.[23] It is reported that about 66% of patients who become pregnant when the disease is active continue to have disease activity or worsening of their symptoms.

Comparatively, it is described that in up to 45% of patients diagnosed with UC who conceive while their disease is active, the disease worsens during pregnancy, and in about 30% of patients with CD who conceive while their disease is active, the disease worsens during pregnancy.[22]

A prospective study found that the rates of disease exacerbation were similar in pregnant patients with CD while their disease was in remission and in non-pregnant patients with CD. On the other hand, relapse rates were higher in pregnant women with CD who conceived while their disease was active than in non-pregnant patients with CD (50% vs. 33%, respectively). Patients with UC who were pregnant had a higher risk of disease exacerbation in the intrapartum and postpartum period compared with controls, and exacerbations of disease were found to be more frequent in the first 6 months of pregnancy and in the first 3 months of the postpartum period.[24]

It should, therefore, be clear that disease activity at the time of conception helps to predict the course of the disease during pregnancy. Ideally, women should be in remission at the time of conception (Figure 1).

### *How Do the Drugs Used to Manage Inflammatory Bowel Disease Affect Fertility?*

There are no data on the effect of drugs on female fertility. However, it is worth mentioning that the use of immunosuppressants such as methotrexate has a clear association with teratogenicity, and they are totally contraindicated in patients who wish to conceive.

The use of sulfasalazine has been described to cause a reversible reduction in sperm motility, an effect related to the dose of the drug.[25] Methotrexate promotes the presence of oligospermia, which may improve over time when the drug is discontinued.[26] Infliximab appears to affect semen quality by reducing sperm motility.[15] There

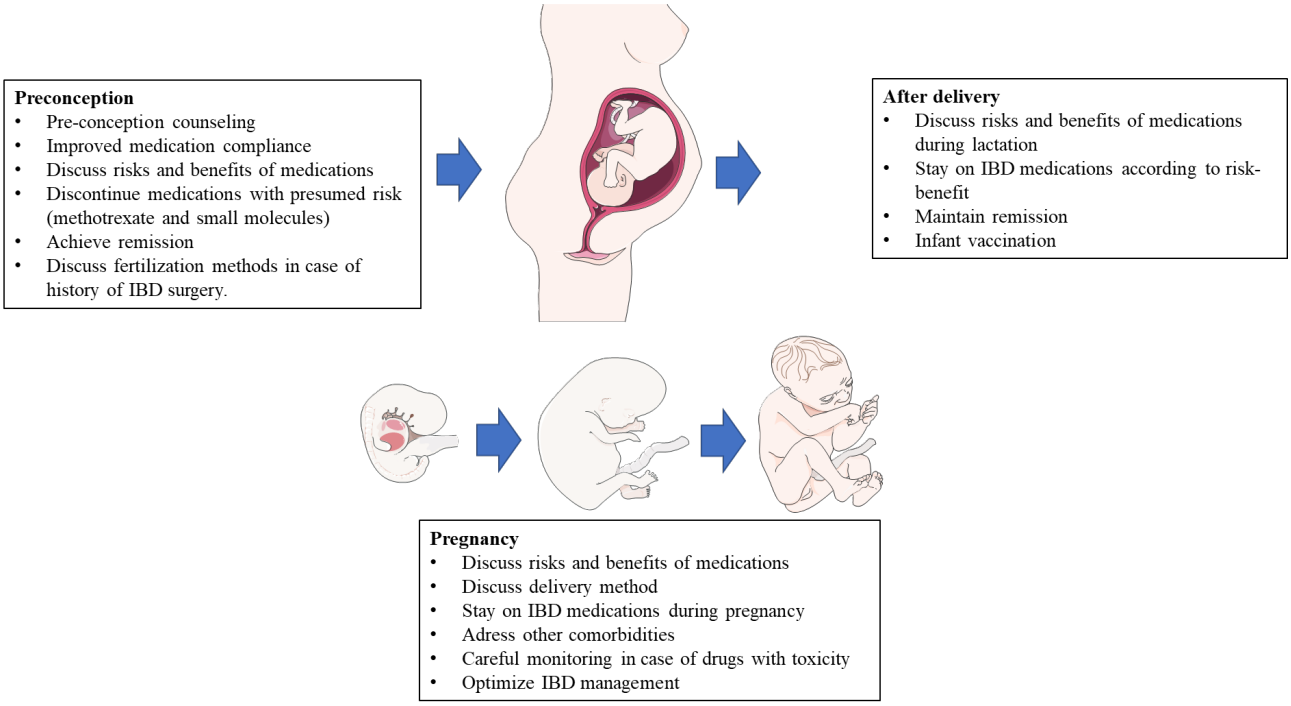


**Figure 1.** Preconception counseling and care during the different stages of gestation in women with inflammatory bowel disease. Source: Scheme made using images from Servier Medical Art, under their own conditions of use

are no conclusive results with regard to the possible effects of thiopurines on sperm quality.[14,27]

IBD is often diagnosed in the reproductive years and is most often diagnosed before the first pregnancy. Relapse of IBD during conception and pregnancy has been associated with a negative pregnancy outcome. Therefore, intensive preconception and pregnancy care is of utmost importance (Figure 1), and current guidelines advise maintaining medications such as tumor necrosis factor-alpha (anti-TNFα) to prevent relapses (Table 1). Most IBD medications are considered to be low risk during pregnancy, as no increase in congenital malformations has been reported (Table 1). However, the effects on the developing immune system, especially of drugs transferred through the placenta, are unknown, as most published cohorts are small and retrospective.[28]

Preconception counseling has been associated with improved medication compliance and reduced relapses during pregnancy, and it is important in optimizing disease management. The authors of this article recommend that all gastroenterologists discuss with their patients of reproductive age the risks and benefits of medications before conception, during pregnancy, and during lactation (Figure 1). The goal of treatment in patients with IBD is remission. If clinical remission is achieved during pregnancy, it is likely to be maintained throughout the rest of the pregnancy, thus reducing risks to the fetus.[29]

According to the recommendations of the management guidelines for IBD and pregnancy, women who need drug treatment to maintain remission should continue treatment during pregnancy, considering that methotrexate should be discontinued before conception and during pregnancy (Table 1). Also, if during the pregnancy, there is an exacerbation of the disease, the treatment must be aggressive. Regarding the drugs to be used, we will describe the following:

Aminosalicylates and sulfasalazine. They are generally considered safe. A cohort study conducted in Denmark found an increased risk of premature birth and fetal death in women who received aminosalicylates during pregnancy. However, that study did not distinguish between the effects of disease activity and the use of aminosalicylates.[30] In other studies, no significant association was found between aminosalicylates and adverse effects during pregnancy.[31] Sulfasalazine is known to inhibit folate synthesis, so women using this drug should be supplemented with folic acid to reduce adverse effects on the neural tube.[32]

In summary, aminosalicylates and sulfasalazine can be used without limitation during pregnancy. They are not associated with significant adverse outcomes during pregnancy.

*Thiopurines (azathioprine):* This drug has been shown to reach fetal serum levels as high as 5% of the maternal drug level. The results of human studies on the safety of using azathioprine during pregnancy have been discordant. However, it is recommended to continue this medication in order to keep the disease in remission during pregnancy. Recent studies have shown that the use of azathioprine does not increase the risk to the fetus, and in turn, it is safe to continue the medication during pregnancy.[33] It is considered that the activity of the disease in exchange for the use of the medicine may favor greater effects on the fetus. Therefore, in view of the current information, its continuation is safe; also, it

**Table 1.** Recommendations on medications to be used during pregnancy and lactation

| Medication | Recommendation in pregnancy | Recommendation in lactation |
|---|---|---|
| Corticosteroids | Potentially toxic Use with caution throughout pregnancy. Increased risk of preterm birth, low birth weight, and neonatal intensive care unit admission. | Potentially toxic Use with caution throughout lactation. Pass into breast milk. |
| Aminosalicylates | Low risk Safe to continue Increase folate supplementation with sulfasalazine use. | Mesalazine is preferred Avoid sulfasalazine |
| Antibiotics | | |
| Metronidazole | Low risk Not recommended during the first trimester | Low risk Low levels are detected in breast milk. |
| Ciprofloxacin | Potentially toxic Crosses the placenta | Low risk Low levels are detected in breast milk. |
| Penicillins | Low risk First line therapy | Low risk First line therapy |
| Immunomodulators | | |
| Cyclosporine | Potentially toxic Consider risk-benefit Crosses de the placenta Use with caution | Avoid during lactation Present in breast milk. |
| Methotrexate | High risk Contraindicated Discontinue 3-6 months before attempting pregnancy. | High risk Avoid during lactation |
| Thiopurines | Low risk Safe to continue Avoid new starts | Low risk Safe to continue |
| Biologics | | |
| Adalimumab | Low risk Safe to continue | Low risk Safe to continue |
| Certolizumab | Low risk Safe to continue | Low risk Safe to continue |
| Golimumab | Low risk Safe to continue | Low risk Safe to continue |
| Infliximab | Low risk Safe to continue | Low risk Safe to continue |
| Natalizumab | Low risk Safe to continue | Low risk Safe to continue |
| Ustekinumab | Low risk Safe to continue | Low risk Safe to continue |
| Vedolizumab | Low risk Safe to continue | Low risk Safe to continue |
| Small molecules | | |
| Tofacitinib | Presumably crosses the placental barrier. Discontinue 1 month before attempting pregnancy. | Avoid (limited data) |

is recommended to avoid starting this medication during pregnancy.

*Methotrexate:* It is well known that methotrexate is teratogenic and abortive, so it is contraindicated during conception and pregnancy. The use of methotrexate between weeks 6-8 of pregnancy may lead to congenital anomalies, and its use in the second and third trimesters may lead to abortions. In addition, it is considered that methotrexate should be discontinued 3-6 months before attempting pregnancy since the drug remains active for some time in the tissues.[32]

*Corticosteroids:* Glucocorticoids are known to cross the placenta and may reach the fetus, but it should be noted that placental enzymes convert corticosteroids to fewer active metabolites. This type of medication is often used to treat episodes of IBD activity, and conflicting results have been found in pregnancy. Recently, in a prospective registry, a statistically significant association was found for increased risk of preterm birth ( < 37 weeks) (OR: 1.79, 95% CI: 1.18-2.73), LBW (OR: 1.76, 95% CI: 1.07-2.88) and neonatal intensive care unit admission (OR: 1.54, 95% CI: 1.03-2.30).[34] Also, there is an increase in reports of association between orofacial cleft in newborns and the use of these drugs in the first trimester of pregnancy.[35]

There is little data on the exact dose of corticosteroids that induce toxicity to the mother and fetus. Therefore, these should be administered with caution, following the criteria of the treating physician. Extrapolated studies on other autoimmune diseases have documented that the use of corticosteroids can promote preterm birth and LBW.

*Antibiotics:* Metronidazole and ciprofloxacin are used with some frequency in IBD to treat abscesses and fistulas. Low levels of both drugs are detected in breast milk. A study of women with IBD who required the use of metronidazole during pregnancy found that it was safe in all trimesters. However, it is recommended not to use it during the first trimester.[36] As for ciprofloxacin, studies have not reported a significant increase in major congenital anomalies, including musculoskeletal problems, but, in view of the risk of congenital arthropathy, it is recommended not to use it during pregnancy.[37] As for penicillins, they have not been shown to cause fetal malformations or adverse pregnancy outcomes, and are considered the first line therapy in pregnancy.

*Cyclosporine:* This drug crosses the placenta, but no teratogenicity has been found in animal models. Studies with this drug have been conducted in connection with kidney transplantation, and a relationship with LBW and preterm delivery is suggested. Similarly, cyclosporine has been used in severe relapses of UC during pregnancy, with favorable responses. It has reduced the need for colectomy and has had no significant adverse effects. The most frequently reported side effect is hypertrichosis in the mother. Other adverse effects, such as nephrotoxicity and hepatotoxicity, have also been described.[38] Therefore, the use of cyclosporine may be considered in patients with fulminant UC during pregnancy.

*Biological agents and small molecules:* These drugs include anti-TNFs such as infliximab, adalimumab, certolizumab, golimumab, anti-integrin such as vedolizumab, anti-IL-12/23 such as ustekinumab, and small molecules such as tofacitinib.[39] These are used for the management of moderate to severe IBD and fistulizing-stenosing CD.[40] TNF levels increase during pregnancy as it is produced mainly by the placenta. It is important in the early stages of pregnancy and also for the development of the fetal immune system.

Observational studies and systematic reviews have demonstrated its safety during pregnancy.[41] In relation to infliximab and adalimumab it should be noted that they are monoclonal IgG1 antibodies and cross the placenta, while certolizumab is a Fab fragment of IgG1 that has no transplacental transport.[42] Because of this, it has been recommended not to use infliximab and adalimumab from the second trimester of pregnancy. Other groups recommend continuing biological therapy throughout pregnancy, especially in high-risk patients and patients with disease activity, and only recommend stopping it if the mother wishes to do so.[43] In case of considering suspending biological therapy to decrease fetal exposure, it is recommended to suspend administration between the 22nd and 26th week of gestation.

No increase in the rates of spontaneous abortion, fetal death, congenital malformations, or preterm delivery has been observed among pregnant women exposed to adalimumab or golimumab.[44] In turn, anti-TNFs do not increase the risk of complications during pregnancy compared to thiopurines and the non-use of medications.

Infliximab and adalimumab levels have been detected in infants up to 12 months postpartum.[45] Infections and allergic reactions have not increased, nor has the response to vaccinations decreased, but an increase in infections has been observed among infants between 9 and 12 months of age exposed to the combination of immunomodulators and biological agents.[46]

*Anti-integrin:* The first one to be used was a humanized monoclonal IgG4 antibody that acts against the adhesion molecule α4-integrin, but there is little data on the use of this drug during pregnancy. The review of natalizumab's overall safety database showed no increase in birth defects in children whose mothers were exposed to natalizumab during pregnancy. In its extrapolation to other diseases, multiple sclerosis is described in the pregnancy outcomes of 35 patients who accidentally became pregnant while being treated with natalizumab. Of these patients, 29 had viable pregnancies, 28 had children without alterations, and one child was born with hexadactyly. Of the remaining six patients, one decided to have an abortion, and the other 5 had early abortions.[46]

Vedolizumab (VDZ) is an IgG1 monoclonal antibody approved for the treatment of UC and CD. VDZ acts on α4β7 integrin, which is selective in blocking intestinal lymphocyte transport and thus avoids many undesirable systemic effects. Mahadevan and colleagues analyzed

data from six initial VDZ clinical trials involving 27 pregnancies with exposure during pregnancy, showing no adverse effect on pregnancy outcomes.[47] In a more recent retrospective observational study, Moens and others identified 23 pregnancies in patients exposed to VDZ, including three patients who continued on VDZ throughout the pregnancy. This study described 18 live births, including two congenital abnormalities, as well as one case of intrauterine growth retardation and two cases of premature rupture of membranes and five pregnancies still in progress at the time of the study.[48] Given the number of congenital abnormalities and complications among the small number of identified pregnancies, further research is needed to determine the safety of VDZ during pregnancy and for the strict monitoring of any pregnant woman receiving VDZ. The conclusion of the study by Moen and colleagues shows that this is the largest cohort study reporting on pregnancy outcomes in patients treated with VDZ.[48] Although the number of pregnancies remains low and no guidelines are available, these results support the fact that VDZ should only be used in pregnancy if the benefits to the mother outweigh the potential risks to the mother and fetus. Meanwhile, strict surveillance and monitoring of pregnant patients with IBD treated with VDZ are guaranteed. Prospective studies are needed, not only on the outcomes of pregnancy with VDZ, but also on the minimum levels of VDZ in the mother and the newborn. Therefore, although there is less evidence on the use of anti-integrins in pregnancy, it can be suggested that they may be safe.[6]

*Anti-IL12/23 (Ustekinumab):* An all-human type IgG1 monoclonal antibody. It binds to the IL-12 and IL-23 via the p40 subunit in both cytokines, thus blocking the inflammatory cascade these cytokines trigger. It is used for the treatment of CD and UC. The safety of continuous ustekinumab (UST) treatment in patients with IBD during pregnancy is unclear. No reports of meta-analyses of UST exposure during pregnancy is available. One study described a case report of a pregnant patient with CD who was successfully treated with UST maintenance therapy throughout pregnancy and delivered a baby without congenital malformations, neurological abnormalities, or birth defects and with the maintenance of clinical, biological, and endoscopic remission of CD during and after pregnancy.[49] Mahadevan and colleagues suggest that in pregnant patients with IBD it is recommended to adjust the dose weeks before pregnancy according to the estimated date of delivery.[50] However, it is important to note that IL-12 is an important cytokine in uterine angiogenesis and vascular remodeling. IL-12 depletion has a potential role in implantation failure after in vitro fertilization.[3] There is even a report of an abortion using this molecule.[51,52] The literature on rheumatology reports the use of ustekinumab during pregnancy in a total of 176 patients, mainly in psoriasis and psoriatic arthritis.[53] However, more studies are needed to assess the safety and vulnerability of the fetus during pregnancy and lactation.

*Small molecules (Tofacitinib):* This is an oral Janus kinase inhibitor used for the treatment of UC. Since it is a small molecule, tofacitinib is likely to cross the placental barrier. However, information on the effects of tofacitinib on pregnancy outcomes is limited. There is a study that reported pregnancy and newborn outcomes among patients in UC clinical trials with prenatal (maternal/paternal) exposure to tofacitinib. Of 1157 patients enrolled in the UC interventional studies, 301 were women of childbearing age. Eleven cases of maternal exposure and 14 cases of paternal exposure to tofacitinib (doses of 5 mg or 10 mg twice daily) before/at the time of conception or during pregnancy were identified. Outcomes included 15 healthy newborns, no fetal deaths, no neonatal deaths, no congenital malformations, two spontaneous abortions, and two medical terminations. Outcomes across other tofacitinib studies and post-marketing cases were consistent, with a healthy newborn being the most common outcome and no fetal deaths. However, the results are limited, and more studies are needed to evaluate the safety of this molecule during pregnancy and lactation.[54]

### What Should Be the Type of delivery in Pregnant Women with Inflammatory Bowel Disease?

In the context of pregnancy and IBD, it should be borne in mind that delivery should be managed in a multidisciplinary manner by the obstetrician, the gastroenterologist, and the coloproctologist.

In the presence of active perianal disease, rectovaginal involvement, or surgical history of ileoanal reservoir or ileorectal anastomosis secondary to IBD, cesarean delivery is indicated. It has been shown that vaginal delivery with episiotomy may be associated with increased risk of perianal involvement.[55] Another point to be highlighted is that patients with IBD without perianal involvement have vaginal delivery indicated, with all the benefits it brings to the newborn. Studies report and suggest that cesarean delivery is a risk factor for the development and exacerbation of IBD. Multidisciplinary management is essential for the comprehensive management of this difficult pathology.[56]

### What Should Be Considered During Lactation?

Lactation may be associated with increased inflammation, as prolactin is associated with increased TNF production. However, one study found no increase in the rate of disease relapse in the first year postpartum among women who breastfed (26%) and those who did not (29.4%).[57] Some studies have found that infants breastfed by mothers on biological drugs, immunomodulators, or combination therapies have similar risks of infection compared to non-breastfed infants or those not exposed to these drugs.[58]

Regarding the use of medication during breastfeeding (Table 1), it should be noted that:

1. Aminosalicylates and sulfasalazine can be continued during lactation, bearing in mind that

aminosalicylates can cause osmotic diarrhea and that sulfasalazine can cause jaundice. However, drug concentrations in breast milk are low.
2. Azathioprine can be continued during lactation. Low concentrations of azathioprine have been detected in breast milk; higher concentrations of the drug have been found during the first 4 hours after taking it, so it is recommended to discard the milk obtained in that period of time.
3. Given its teratogenic potential, methotrexate is contraindicated during lactation.
4. Corticosteroids are found in low concentrations in breast milk, with moderately high levels found in the first 4 hours after taking the drug. Because of this, it is recommended that milk obtained during this time interval be discarded to reduce the risk of transfer to the infant.
5. Biological agents can be continued during pregnancy. Minimal concentrations of infliximab and adalimumab have been found in breast milk, and no significant adverse events have been reported in infants. Detectable levels in the newborn after birth are considered to be related to placental transfer during pregnancy. Furthermore, no association has been found between breastfeeding and the risk of infection in newborns exposed to biological agents.[45]

### *How Should Babies Be Vaccinated?*

Vaccination with non-living virus vaccines in newborns exposed to anti-TNF in utero is not different from vaccination in unexposed infants, and they have an adequate response to vaccination. Regarding live virus vaccines, such as rotavirus, oral polio, and BCG, they should be given when anti-TNF levels are not detectable. For this reason, newborns should not receive live vaccines during the first 6 months of life, so it is recommended that anti-TNF be discontinued at the 33rd week of pregnancy; in this way it is possible to reach the time of delivery with undetectable levels of anti-TNF, which allows the newborn's vaccination schedule not to be affected.

### *And What About the Infants of Women Who Use Non-anti-TNF Biologicals or Small Molecule Agents?*

The vaccination in infants of women with the use of non-anti-TNF biologicals or small molecule agents is still a matter of uncertainty. In this specific setting, the evidence is much scarcer. However, the dearth of reported adverse events in exposed infants does not mean that there is no risk of harm, and each case must be individualized depending on the characteristics of the drug exposure, concomitant maternal immunosuppressive therapy, and potential postnatal exposures to infectious diseases. So, it is recommended that vaccination with non-living virus vaccines does not differ from unexposed infants, while live vaccines should not be given until they reach the age of 6 months.

## Conclusion

The medical team involved in the follow-up of patients with IBD must know how to deal with and be clear about the preconceptual, conceptual, and postpartum management of these patients since multiple factors must be considered, such as the control of the disease during the fertile period, in order to achieve a successful pregnancy. They must also be clear about the use of the medications during the different stages of childbearing age, which will create peace of mind for both the treating physician and the patient. Therefore, such awareness of appropriate education increases the likelihood that physicians will follow best practice guidelines in the management of pregnant patients with IBD.

### Authors' Contribution

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### Competing Interests

The authors declare no conflict of interest related to this work.

### Data Availability Statement

The data and material available for publication are in the manuscript, and no information is omitted.

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Not applicable.

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Original Article

# Opium Effects on Pancreatobiliary System in Opium Abusers Evaluated by Endoscopic Ultrasonography

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**Abstract**

**Background:** Opium use is a significant social and public health issue. There are numerous effects of opium documented as affecting the pancreatobiliary system. The aim of the study was to assess the pancreatobiliary changes in patients with opium addiction by endoscopic ultrasonography (EUS).

**Methods:** During the study period, consecutive patients who were referred for EUS of submucosal upper gastrointestinal lesions were included. The history of opium addiction and clinical symptoms were recorded prospectively. Diameters of the common bile duct (CBD), pancreatic duct (PD), size of the ampulla of Vater, and gallbladder abnormalities were evaluated using EUS.

**Results:** A total of 254 patients (53.1% male, mean age of 55.4 ± 14.2 years) were studied. A history of opium addiction was present in 56 patients (22.0%). Choledocholithiasis was found in two patients (3.6%) and one control (0.5%) patient ($P=0.06$). Gallbladder stones were found in 13 opium-addict (23.2%) and 16 control (8.1%) patients ($P=0.002$). The mean diameter of the CBD, size of the ampulla of Vater ($P<0.001$), and PD ($P=0.04$) were all significantly greater in patients with opium addiction.

**Conclusion:** Dilation of the biliary and PDs is seen more commonly in patients addicted to opium. However, the clinical implications of these findings need to be further evaluated in future studies.

**Keywords:** Opium, Endosonography, Biliary tract, Pancreatic duct, Sphincter of Oddi dysfunction

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## Introduction

Opium has several effects on the gastrointestinal tract. One of the most widely recognized aspects of the prolonged use of opium is its effects on the pancreatobiliary system. First and foremost, opium can cause biliary dilation. The mechanism responsible for this finding can be due to an increase in both basic pressure and frequency of phasic contractions of the sphincter of Oddi (SOD), leading to an increase in intraluminal pressure of the common bile duct (CBD).[1-3] These patients usually present with biliary pain as well as dilated bile ducts, even though asymptomatic bile duct dilation has been described in patients with opium addiction, too.[4,5]

The etiology of CBD dilation may be found via transabdominal ultrasonography (TUS) for cases in which the CBD enlargement is due to mechanical obstruction. The cause of extrahepatic bile duct dilation might be a CBD stone or periampullary lesions, including tumors of the distal CBD, pancreatic head, ampulla of Vater, and the second portion of the duodenum. Although TUS can detect large CBD stones and sometimes large pancreatic masses, it provides only modest diagnostic accuracy in diagnosing distal CBD stones and periampullary lesions because of overlying bowel gas. In addition, ultrasound quality is extremely operator-dependent.[6,7]

Although endoscopic ultrasonography (EUS) is operator-dependent as well, it is one of the best imaging modalities for evaluations of both the periampullary area and the diameters and wall thicknesses of biliary and pancreatic ducts (PDs). Furthermore, bowel gas does not affect its accuracy. In this study, we aimed to evaluate pancreatobiliary abnormalities found on EUS in opium-addict patients.

## Materials and Methods

In the current cross-sectional study conducted from January 2018 to June 2019, 254 consecutive adult patients were referred to our center for EUS and evaluation of sub-epithelial lesions in the upper gastrointestinal tract and were included in the study. Exclusion criteria were age younger than 20, anatomical alterations due to previous surgeries in the upper gastrointestinal tract, obstructive pancreatobiliary disorders, and lack of informed consent.

Cases were defined as patients questioned admitting to abusing opium (either in the past or currently). The control group was comprised of patients for whom no opium use was detected.

Patients were examined after an overnight fast with the patient in the left lateral decubitus position under deep sedation with propofol given by an anesthesiologist.

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EUS was performed using a linear echoendoscope (EG-3870UTK, Pentax Optical Co Ltd, Tokyo-Japan) having a frequency of 5 MHz. The periampullary area was examined as were proximal and distal CBD diameters, CBD and gall bladder (GB) wall thicknesses, ampullary dimensions, PD diameters in the head and body portions of the pancreas, the presence of gallstones or biliary sludge, and other abnormalities including causes of CBD or PD dilation. A CBD was considered dilated when measured at greater than 6 mm in patients with an intact GB or more than 9 mm in patients with a previous cholecystectomy. PD dilation was defined as a PD diameter greater than 3 and 2 mm in the head and body of the pancreas, respectively.

GB and CBD were considered thickened if wall thicknesses exceeded 3 and 1.5 mm, respectively. The size of the ampulla of Vater was measured based on the formula used in a study by Skalicky et al[8]:

$$Ampulla\ size = \frac{ampulla\ width \times ampulla\ length}{2.54}$$

Finally, the portal vein diameter was also measured.

We estimated that a sample size of 54 patients in each group would be required to show a significant difference for an alpha error of 0.05, and a statistical power of 0.8, assuming a standard deviation of 2.58 cm for a mean difference of 1.41 cm between two groups.

## Results

During the study period, 254 patients (53% male with a mean age of 55.4 ± 14.2) were referred for EUS for evaluation of sub-epithelial lesions in the upper gastrointestinal tract. A history of opium addiction was noted in 56 patients (22%). The route of opium use was through inhalation in 37 patients (66.1%) and orally in 19 (33.9%) patients. 28 patients had undergone a previous cholecystectomy (7 patients, 12.5% in cases versus 21 patients, 10.6% in the control group, $P = 0.69$). Table 1 illustrates the patients' presenting symptoms. No significant differences were noted regarding clinical manifestations, including abdominal pain, nausea, and vomiting, when comparing both groups. Seven (12.5%) opium-addicted patients and 35 (17.7%) controls provided a history of abdominal pain ($P = 0.36$).

Gallbladder stones were diagnosed in 13 cases and 16 controls (23.2% vs 8.1%, $P = 0.002$). Moreover, choledocholithiasis was detected in two opium-addicted patients and one patient in the control group ($P = 0.61$); the bile duct was dilated in all three of these patients. Juxta-ampullary diverticula were noted in two cases compared with none in the controls ($P = 0.008$). We found no peri-ampullary tumors in any of the patients.

Table 2 illustrates the measurements of the pancreatobiliary system. All mean diameter parameters were significantly different between the two groups. The mean portal vein diameter was greater in patients with a history of opium addiction. We did not find any evidence of liver disease in any of the patients.

**Table 1.** Clinical manifestation in candidates for endoscopic ultrasound

| Clinical manifestation | Number | Percent |
|---|---|---|
| Nausea, vomiting | 15 | 5.9 |
| Anorexia | 3 | 1.2 |
| Weight loss | 9 | 3.5 |
| Abdominal pain | 42 | 16.5 |
| Constipation | 2 | 0.8 |
| Fever and chills | 1 | 0.4 |
| Pruritus | 1 | 0.4 |

## Discussion

A few studies have reported pancreatobiliary changes amongst opium addicts. The current study demonstrates that in addition to larger diameters in both the main bile and PDs, the rates of GB, as well as biliary duct abnormalities, are greater in patients with opium addiction compared to controls.

A study of 12767 autopsies by Hwang reported a total GB stone incidence of 6.6%.[9] That study included 43 patients with opium addiction, and 18 (41.9%) of these exhibited GB stones. Sharma et al reported EUS findings in 15 patients with opium addiction who presented with abdominal pain.[10] None of those patients had GB stones. This discrepant finding might be due, at least in part, to the small number of patients in their sample. The frequency of GB stones in our population with opium addiction was greater than in the controls (23.2% vs 8.1%). Moreover, although the frequency of CBD stones was not significantly different, there were a trend towards a greater frequency of CBD stones in the patients with opium addiction ($P = 0.06$). Thus, further studies with larger sample sizes are needed to more confidently confirm this finding.

**Table 2.** Pancreatobiliary measurements in patients with opium addiction (OA) and control (C) patients

| Variable | Group | Mean (mm) | SD | *P* value |
|---|---|---|---|---|
| GB wall thickness | OA | 2.6 | 0.8 | 0.023 |
| | C | 2.4 | 0.7 | |
| Mid-CBD diameter | OA | 7.3 | 2.8 | <0001 |
| | C | 4.5 | 1.5 | |
| Distal CBD diameter | OA | 4.2 | 1.7 | <0.001 |
| | C | 3.0 | 1.0 | |
| PD diameter (head) | OA | 3.3 | 1.2 | <0.001 |
| | C | 2.2 | 0.7 | |
| PD diameter (body) | OA | 1.8 | 0.6 | 0.042 |
| | C | 1.6 | 0.6 | |
| Ampulla of Vater surface area | OA | 39.1 | 19.0 | <0.001 |
| | C | 28.2 | 13.5 | |
| Portal vein diameter | OA | 10.5 | 2.1 | <0.001 |
| | C | 8.9 | 2.1 | |

Abbreviations: GB, gallbladder; CBD, common bile duct; PD, pancreatic duct.

**Table 3.** Biliary findings in patients with opium addiction in different studies

| Author | Year of study | Study design | Country | Imaging | Sample size (addicts/control) | Main finding |
|---|---|---|---|---|---|---|
| Chuah et al[5] | 2003 | Case-Control | Singapore | TUS | 7 / 7 | Dilated CBD in OA |
| Farahmand et al[4] | 2007 | Cross-sectional | Iran | TUS | 110 / 0 | Dilated CBD in 65.5% of OA |
| Zahedi-Nejad et al[11] | 2010 | Case-Control | Iran | TUS | 121 / 142 | Dilated CBD in OA |
| Sharma et al[10] | 2013 | Case series | India | EUS | 15 / 0 | Dilated CBD in OA |
| Dadpour et al[12] | 2016 | Cross-sectional | Iran | TUS, ERCP | 50 / 0 | Dilated CBD in OA |

Abbreviations: TUS, transabdominal ultrasonography; EUS, endoscopic ultrasonography; ERCP, endoscopic retrograde cholangiopancreatography; CBD, common bile duct; OA, opium addict.

In Table 3 we summarize the pancreatobiliary abnormalities as reported in different study populations. In nearly all of the studies, the mean CBD diameter was increased amongst opium addicts compared with control groups.

To the best of our knowledge, this study is the largest one, having used EUS to compare abnormalities of the pancreatobiliary system in both patients with opium addiction and controls. These biliary changes include abnormalities in distal CBD wall thickness, ampulla of Vater diameter, and the PD diameters as measured in different parts of the pancreas - variables that cannot be properly evaluated with TUS.

We have shown that in comparison with control patients, patients with opium addiction exhibit larger ampulla of Vater, a finding compatible with that reported by Sharma et al.[10] However, the size of the ampulla of Vater in Sharma and colleagues' study was greater than that reported in our study (71.9 vs 39.1 $mm^2$). This difference might, at least in part, be due to the longer duration of opium addiction in their patient population. What is of great clinical relevance is that this enlarged ampullary size could be considered attributable to ampullary neoplasms as part of an important differential diagnosis. In these instances, EUS, especially when accompanied by fine needle aspiration/biopsy (FNAB), is a very helpful minimally invasive procedure for differentiating benign from malignant lesions. Moreover, it is possible at EUS to look for regional lymphadenopathy as well as perform FNAB for such findings when present - a procedure that cannot be as readily carried out when using other imaging modalities.[13]

Although in Sharma and colleagues' study,[10] CBD dilatation was noted in all 15 cases, PD dilation in the pancreatic body was detected in only two cases. In contradistinction, amongst our 56 cases, all patients exhibited both dilated CBDs and PDs. The mechanism of PD dilation in these cases might be due to SOD with or without pancreatic sphincter dysfunction. Dilation of both the CBD and PD also can mimic periampullary tumors and might require more investigation, including EUS-guided FNAB and side-view endoscopy for a complete investigation of the ampulla, taking endoscopic biopsies if needed. The portal vein diameter was significantly greater in patients with opium addiction when compared with controls. We do not have any explanation for this finding that has not been reported before and requires confirmation.

## Conclusion

In conclusion, dilation of both CBD and PD in patients with opium addiction is more prevalent than in control patients. As a result, opium addiction should be considered as a benign cause of dilated pancreatobiliary ducts as well as of enlarged ampulla. Recognition of such differences is clinically pertinent, and long-term follow-up studies are required to better characterize the clinical importance of these findings.

### Acknowledgments

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### Authors' Contribution

All authors participated in the study design and conception. Rasoul Sotoudehmanesh and Mohammad Bagheri performed EUS. Roya Rahimi collected the data; Ali Ali Asgari analysed the data. Rasoul Sotoudehmanesh wrote the first draft of the manuscript and all authors revised it critically.

### Competing Interests

The authors declare no conflict of interest related to this work.

### Ethical Approval

The study protocol was approved by the ethics committee of the Digestive Diseases Research Institute (DDRI) of the Tehran University of Medical Sciences (No. IRB28842-37-01-94).

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Original Article

# Efficacy and Safety of Peroral Endoscopic Myotomy (POEM) in Achalasia: An Updated Meta-analysis

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**Abstract**

**Background:** Heller myotomy has been considered the standard surgical treatment for patients with achalasia. Since the initiation of peroral endoscopic myotomy (POEM), it has represented an alternative for treating patients with achalasia. Over the years, numerous prospective and retrospective studies with POEM use for achalasia have been published. We performed a systematic review and meta-analysis to evaluate the efficacy and safety of POEM in patients with achalasia.

**Methods:** Publications investigating the safety and efficacy of POEM in patients with achalasia were searched in Medline, Ovid Journals, Medline non-indexed citations, and Cochrane Central Register of Controlled Trials and Database of Systematic Reviews. Pooling was conducted by both fixed and random effects models.

**Results:** The initial search identified 328 reference articles; of these, 34 relevant articles were selected and reviewed. Data was extracted from 20 studies (n=1753) which met the inclusion criteria. In pooled analysis, the clinical success of POEM at 3 months was 94% (95% CI=93–95). The pooled clinical success of POEM at 12 months was 91% (95% CI=90–92). The pooled rate of gastroesophageal reflux disease (GERD) was 21% (95% CI=19–23), esophagitis was reported in 16% (95% CI=15–18), pneumomediastinum in 4% (95% CI=3–6), cervical emphysema in 12% (95% CI=10–13), pneumoperitoneum in 8% (95% CI=7–10), pneumothorax in 5% (95% CI=4 – 6), pleural effusion in 3% (95% CI=2–3), post-operative bleeding in 4.29% (95% CI=1.91 –7.61) and aspiration pneumonia in 3.08% (95% CI=1.13–5.97) of the patients after POEM.

**Conclusion:** This meta-analysis suggests that POEM is a highly effective and safe endoscopic treatment for patients with achalasia and a reasonable alternative to Heller myotomy.

**Keywords:** Achalasia, Peroral endoscopic myotomy, Dysphagia

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## Introduction

Achalasia is an uncommon primary motor disorder of the esophagus that is characterized by insufficient relaxation of the lower esophageal sphincter (LES) as well as disorganized peristalsis of the LES. Symptoms include dysphagia, regurgitation, and chest pain.[1] The annual incidence rate of 1.6 cases per 100 000 individuals and the prevalence of 10 cases per 100 000 appears to be rising.[2] While the disease can occur at any age, the onset before adolescence is rare, and it is usually diagnosed between 25 and 60 years of age.[3]

Achalasia results from inflammation and degeneration of neurons in the esophageal wall.[4,5] Histological examination typically reveals decreased numbers of ganglion cells in the myenteric plexus with an increased number of lymphocytes surrounding the remaining cells.[6] The primary loss of inhibitory neurons within the wall of the esophagus leads to an increase in the basal LES pressure and affects its normal relaxation. This leads to progressive dilation of the esophagus, tortuosity, angulation, and even mega-esophagus. Patients with achalasia are also at an increased risk of developing esophageal cancer. Both squamous cell carcinoma and adenocarcinoma have been implicated, with squamous cell carcinoma typically having an increased prevalence.[7]

Treatment goals aim to improve the progression of the ingested contents into the stomach and alleviate dysphagia. Currently, the three main discussed therapeutic options are pneumatic dilatation (PD), laparoscopic Heller myotomy (LHM), and peroral endoscopic myotomy (POEM). The choice of treatment modality depends on many factors, including the type of achalasia, prior treatments, and the functional status of the patient.

Currently, the most common treatment modality employed by gastroenterologists is PD. It involves the passage of a dilating balloon across the LES attempting to disrupt the sphincter muscles. LHM is an alternative modality involving a laparoscopic approach to the LES myotomy. To prevent gastroesophageal reflux disease (GERD), concomitant partial fundoplication is performed. For patients who are not surgical candidates, Botox injections at LES can be offered for short-term

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symptom relief.

POEM is a novel endoscopic procedure that incorporates concepts of natural orifice transluminal endoscopic surgery and expands upon techniques used in endoscopic submucosal dissection in order to achieve a division of the esophageal circular muscle fibers across the gastroesophageal junction. As a result, POEM incorporates the advantages of both endoscopic dilation and LHM.[8] Previous literature and major society guidelines support it as a safe and effective treatment option, mainly for type 2 and type 3 achalasia.[9] When performed by an experienced operator, there is a low incidence of intra and post-procedure complications.[10]

Ortega et al in 1980, first described a technique for dissecting the LES using a needle-knife to cut the muscular fibers from the luminal side.[11] Later, Pasricha et al described the feasibility of an endoscopic mucosal esophageal myotomy in animal models.[12] Thereafter, in 2010 Inoue et al successfully performed the first POEM in humans. Inoue is also known for coining the term peroral endoscopic esophageal myotomy.[13] Since then, there have been a number of prospective and retrospective data in terms of outcomes and adverse events. The aim of this meta-analysis was to pool the results of previously published literature on the efficacy and safety of this novel technique.

## Materials and Methods

### *Search Methodology*

A literature search was conducted using the electronic database engines MEDLINE through PubMed, Ovid, Cochrane Library (Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews), EMBASE, Cumulative Index for Nursing & Allied Health Literature, ACP Journal Club, Database of Abstracts of Reviews of Effects (DARE), International Pharmaceutical Abstracts, OVID HealthStar, and Google Scholar from January 1974 to July 2021 to identify published articles and reports addressing the use of POEM in patients with achalasia. The combinations of keywords used were "Peroral Endoscopic Myotomy" or "POEM" and "Achalasia". The reference list of all eligible studies was reviewed to identify additional studies. The retrieved studies were carefully examined to exclude potential duplicates or overlapping data. Titles and abstracts selected from the initial search were first scanned, and the full papers of potentially eligible studies were reviewed.

### *Study Eligibility*

Published studies were eligible for inclusion if they reported the use of POEM for the management of achalasia. Articles were excluded if they were not available in English, no outcomes were reported, or they represented review articles or studies published as abstracts only. In studies using multiple modalities for the management of achalasia, data from the cohort of patients who underwent POEM were collected and analyzed. Two reviewers (AK, MB) independently performed study selections according to eligibility criteria. Disagreements were resolved by discussion or a third reviewer.

### *Data Extraction and Quality Assessment*

The following data was independently abstracted onto a standardized form: study characteristics (primary author, time period of study, year of publication, and country of the population studied), study design, baseline characteristics of the study population (the numbers of patients enrolled, participant demographics, pre-procedure dysphagia score), the intervention details and outcomes (clinical success at 3 months, efficacy at 1-year, post-procedure dysphagia score and complications). Risk of bias was rated for each study by two authors independently, using the Cochrane criteria for RCTs.[14]

### *Outcome Definition*

The primary outcome of interest was efficacy assessment 3 and 12 months after the procedure. This was defined as a post-POEM Eckardt score ≤3 or clinically relevant improvement of dysphagia. The secondary outcome of interest was safety assessment, including immediate and late complications. GERD was defined as symptomatic gastroesophageal reflux or abnormal acid exposure noted in a 24-hour pH monitoring study. Esophagitis was defined by the presence of erosions or ulcerations in the distal esophagus noted on upper gastrointestinal (GI) endoscopy.

### *Statistical Analysis*

This meta-analysis was performed by calculating pooled proportions. First, the individual study proportions were transformed into a quantity using Freeman-Tukey variant of the arcsine square root transformed proportion. The pooled proportion is calculated as the back-transform of the weighted mean of the transformed proportions, using inverse arcsine variance weights for the fixed effects model and DerSimonian-Laird weights for the random effects model. Forest plots were drawn to show the point estimates in each study in relation to the summary pooled estimate. The width of the point estimates in the Forest plots indicates the assigned weight to that study. The heterogeneity among studies was tested using $I^2$ statistic and Cochran Q test based upon inverse variance weights. $I^2$ of 0% to 39% was considered as nonsignificant heterogeneity, 40% to 75% as moderate heterogeneity, and 76% to 100% as considerable heterogeneity. If *P* value is > 0.10, it rejects the null hypothesis that the studies are heterogeneous. The effect of publication and selection bias on the summary estimates was tested by the Egger bias indicator.[15]

## Results

The initial search identified 328 reference articles; of these, 34 relevant articles were selected and reviewed. Data was extracted from 20 studies which met the inclusion criteria.

A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for details of the review process is shown in Figure 1. All the studies are published as full-text articles. All the pooled estimates given are estimates calculated by the fixed effects model.

The total number of patients included in this meta-analysis was 1753. Table 1 shows the baseline characteristics of the studies.

### *Primary Outcome*

In pooled analysis, the clinical success of POEM at 3 months was 94% (95% CI = 93–95). A forest plot diagram of the pooled analysis is shown in Figure 2. Publication bias calculated using the Harbord-Egger bias indicator gave a value of -0.26 (95% CI = -2.14–1.62, $P = 0.79$), indicating no publication bias. Figure 3 is a funnel plot assessing the publication bias for the same variable.

### *Secondary Outcomes*

#### *Clinical Success at 12 Months*

In the pooled analysis, the pooled clinical success of POEM at 12 months was 91% (95% CI = 90–92). A forest plot diagram of the pooled analysis is shown in Figure 4. Publication bias calculated using the Harbord-Egger bias indicator gave a value of -3.29 (95% CI = -9.59–3.01, $P = 0.30$), indicating no publication bias. Figure 5 is a funnel plot assessing the publication bias for the same

**Table 1.** Basic characteristics of the included studies

| Study | Year | Type of study | Country | N |
|---|---|---|---|---|
| Shiwaku et al [16] | 2020 | PCT | Japan | 233 |
| Kahaleh et al [17] | 2020 | PCT | Latin America | 69 |
| Hernández-Mondragón et al [18] | 2018 | PCT | Mexico | 50 |
| Martinek et al [19] | 2018 | PCT | USA | 132 |
| Li et al [20] | 2018 | PCT | China | 564 |
| Nabi et al [21] | 2017 | PCT | India | 408 |
| Minami e al [22] | 2014 | RCT | Japan | 28 |
| Khashab et al [23] | 2014 | RCT | USA | 9 |
| Hungness et al [24] | 2013 | RCT | USA | 18 |
| Verlaan at al [25] | 2013 | PCT | Netherlands | 10 |
| Kurian et al [26] | 2013 | PCT | USA | 40 |
| Rieder et al [27] | 2013 | RCT | USA | 4 |
| Chiu et al [28] | 2013 | PCT | China | 16 |
| Meireles et al [29] | 2013 | PCT | USA | 7 |
| Lee et al [30] | 2013 | RCT | Korea | 13 |
| Ujiki et al [31] | 2013 | RCT | USA | 18 |
| Von Renteln et al [32] | 2013 | PCT | International | 70 |
| Teitelbaum et al [33] | 2013 | PCT | USA | 36 |
| Costamagna et al[16,34] | 2012 | RCT | Italy | 11 |
| Inoue et al [13] | 2010 | PCT | Japan | 17 |

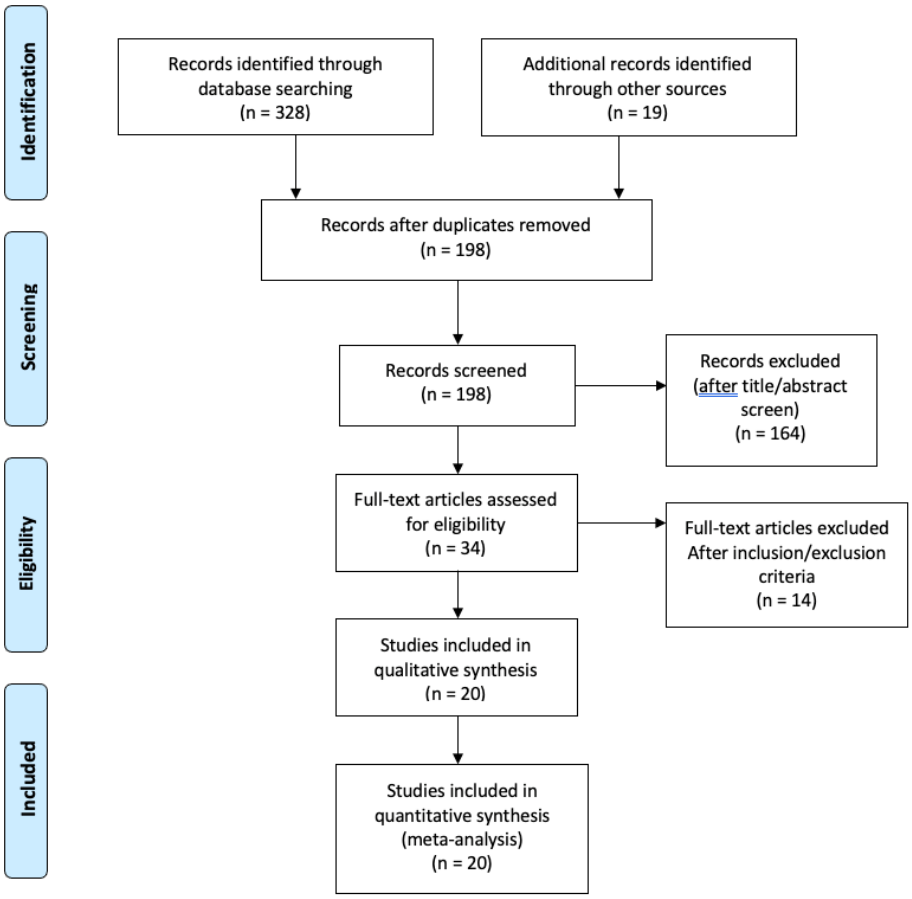


**Figure 1**. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram detailing the review process

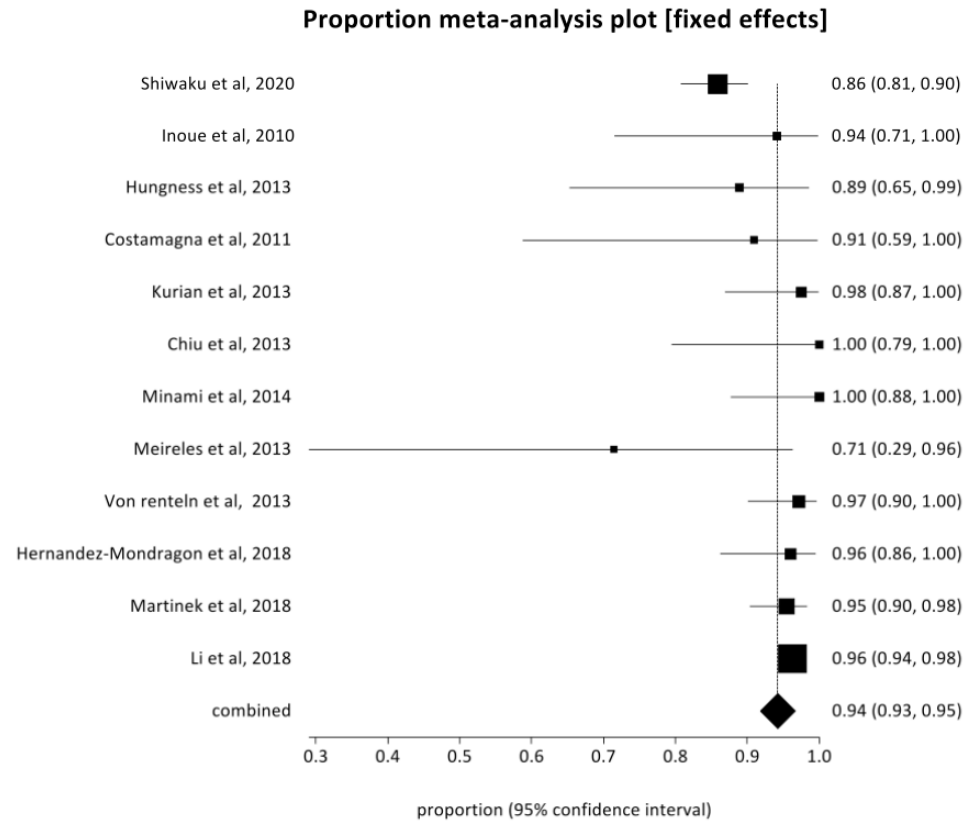


**Figure 2.** Forrest plot showing the pooled estimate of clinical success at 3 months with peroral endoscopic myotomy (POEM) in patients with achalasia

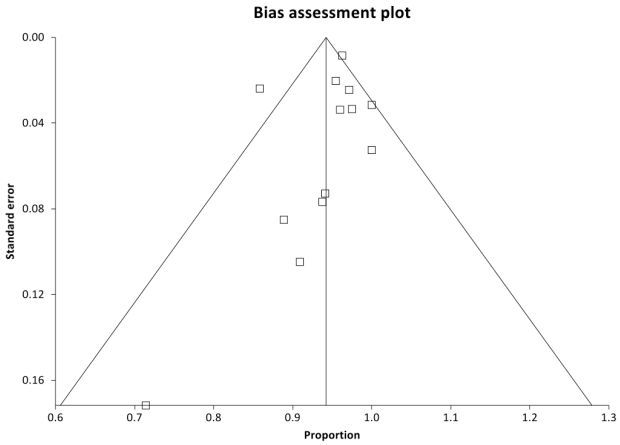


**Figure 3.** Bias assessment plot of publication bias in reporting clinical success at 3 months with peroral endoscopic myotomy (POEM) in patients with achalasia

variable.

Pooled change in Eckardt score at 12 months was noted to be -3.95 (95% CI = -4.10 – -3.80).

### *Rate of Immediate Complications*

Pooled rate of pneumomediastinum was 4% (95% CI = 3–6), cervical emphysema was reported in 12% (95% CI = 10–13), pneumoperitoneum in 8% (95% CI = 7–10), pneumothorax in 5% (95% CI = 4–6), pleural effusion in 3% (95% CI = 2–3), post-operative bleeding in 4.29% (95% CI = 1.91–7.61) and aspiration pneumonia in 3.08% (95% CI = 1.13–5.97) of the patients after POEM.

### *Rate of Late Complications*

The pooled rate of GERD was 21% (95% CI = 19–23), and esophagitis was reported in 16% (95% CI = 15–18) of the patients.

## Discussion

POEM is a relatively novel, minimally invasive technique that entails the creation of a submucosal tunnel, followed by myotomy of the muscular layer, reducing LES resting pressure.[35] The major alternatives to POEM for the treatment of achalasia are Heller myotomy and endoscopic pneumatic dilation. Since 2008, POEM has proven its efficacy in the treatment of patients with achalasia. POEM can be offered for different esophageal diseases, is cost-saving, and provides a longer myotomy with similar long-term benefits as compared to LHM, all while reducing post-procedural complications.[18] In addition, endoscopic myotomy has proven to be a promising technique for other esophageal conditions, such as Jackhammer esophagus, and as a "salvation technique" for patients with recurrent symptoms after LHM. Prior studies have demonstrated similar results comparing POEM and LHM and found that patients in the POEM group had lower Eckardt scores after the procedure compared with the LHM group.[35] Similarly, Schlottmann et al conducted a meta-analysis of LHM versus POEM for achalasia, confirming that overall, POEM is more effective than the Heller procedure based on short-term results.[36] Endoscopic pneumatic dilation is associated with a 4% risk of perforation, although it

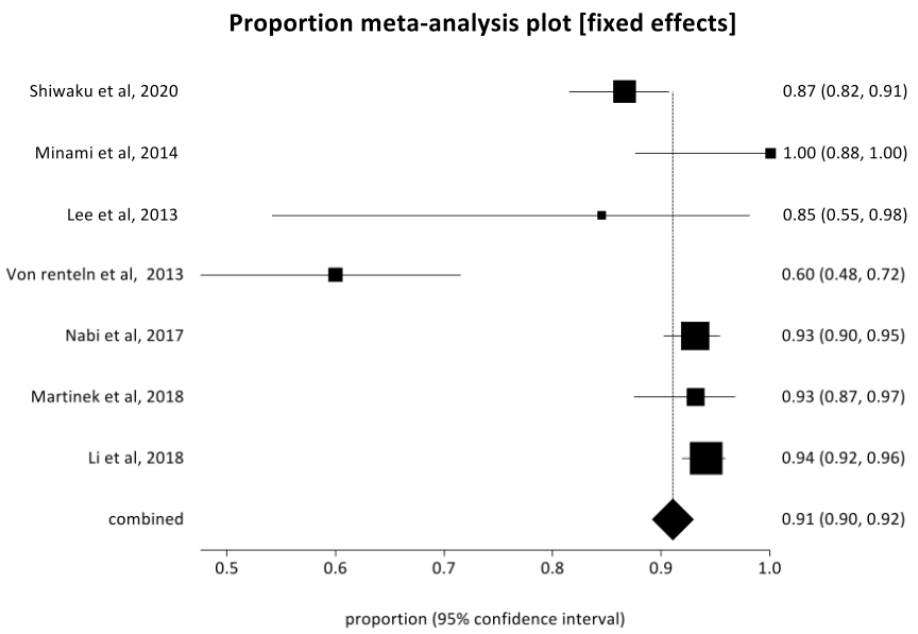


**Figure 4.** Forrest plot showing the pooled estimate of clinical success at 12 months with peroral endoscopic myotomy (POEM) in patients with achalasia

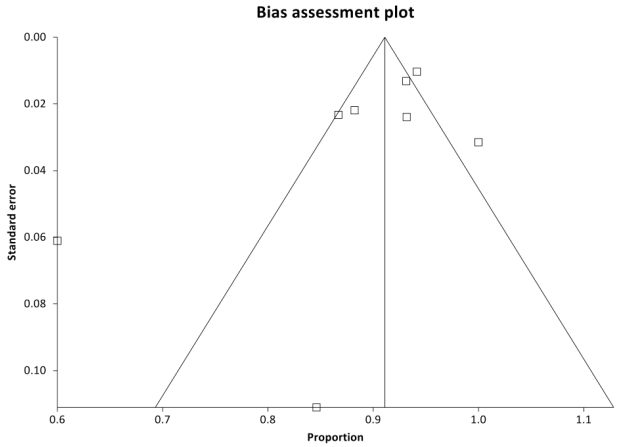


**Figure 5**. Bias assessment plot of publication bias in reporting clinical success at 12 months with peroral endoscopic myotomy (POEM) in patients with achalasia

appears to be as effective as Heller myotomy for at least 2–3 years.

In order to summarize the literature and assess for potential sources of heterogeneity, we conducted a systematic review and meta-analysis of available literature on the safety and efficacy of POEM.

This study further adds to the available evidence that POEM is an effective treatment for performing an endoscopic myotomy in patients with achalasia. In a pooled population of 1753, our meta-analysis demonstrated a pooled clinical success of 93% at 3 months and 91% at 1 year. Moreover, the risk of adverse events requiring surgical intervention was minimal and only observed in one patient.[24] Most of the adverse-related events were successfully managed conservatively.

As no anti-reflux procedure is performed in POEM, the development of GERD post-operatively has been a concern since its introduction. In our meta-analysis, post-POEM GERD was noted in 21% of the patients, which is higher than a rate of 11.5% with LHM noted in a large meta-analysis.[36] While the aim of POEM is to leave the layer of longitudinal muscle fibers intact, adverse events of pneumomediastinum, pneumoperitoneum and/or subcutaneous emphysema were noted in less than 10% of the patients.

This study has several limitations. The absence of individual patient data limited our ability to stratify patients according to the manometric subtype and previous treatments. Long-term follow-up was unavailable in most studies as POEM is a novel technique.

## Conclusion

In conclusion, our study adds to the current evidence that POEM is a safe and efficacious procedure for patients with achalasia. As a short-term follow-up, POEM resulted in a significant decrease in Eckardt score with minimal adverse events. At this time, further data would be beneficial in discussing the long-term outcomes of POEM.

### Competing Interests

The authors declare no conflict of interest related to this work.

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Original Article

# Predictors of Pathological Gastroesophageal Reflux among Emirati Patients with Reflux Symptoms Who Undergo Wireless pH Monitoring

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**Abstract**

**Background:** Diagnosis of gastroesophageal reflux disease (GERD) relies on recognizing symptoms of reflux and mucosal changes during esophagogastroduodenoscopy. The desired response to acid suppression therapy is reliable resolution of GERD symptoms; however, these are not always reliable, hence the need for pH testing in unclear cases. Our objective was to identify potential predictors of a high DeMeester score among patients with potential GERD symptoms to identify patients most likely to have pathological GERD.

**Methods:** We conducted a retrospective case-control study on patients who underwent wireless pH monitoring from January 2020 to April 2022. Cases were patients with a high DeMeester score (more than 14.7), indicating pathological reflux, and controls were those without. We collected clinical and demographic data, including age, sex, body mass index (BMI), smoking status, non-steroidal anti-inflammatory drugs (NSAIDs) use, and presence of atypical symptoms.

**Results:** 86 patients were enrolled in the study. 46 patients with high DeMeester scores were considered cases, and 40 patients with DeMeester scores less than 14.7 were considered controls. Esophagitis (grade A) was found in 41.1% of the cases and in 22.5% of the control group. In our study, age of more than 50 years compared with age of 20-29 years and being overweight appeared to be predictors of true pathological reflux among patients with reflux symptoms who underwent wireless pH monitoring.

**Conclusion:** Age above 50 years compared with age between 20-29 years and being overweight appeared to be predictors of true pathological reflux among patients with reflux symptoms who underwent wireless oesophageal pH monitoring. The presence of oesophagitis was approximately four times more likely to be associated with true pathological reflux.

**Keywords:** Gastroesophageal reflux disease, Epidemiology, Age, DeMeester score, Wireless PH capsule

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## Introduction

Gastroesophageal reflux disease (GERD) is a frequent disorder with various symptoms and a high cost of care. Population-based cross-sectional studies carried out globally are the primary source of our current understanding of the epidemiology of GERD.[1-7] Asthma, cough, hoarseness, and chest pain are atypical extra-oesophageal symptoms that people with GERD are more likely to experience.[8,9] These findings, however, are based on research that relied on patient-reported symptoms and their response to acid suppression therapy rather than a confirmed diagnosis of pathological reflux. As a result of this, they are subject to variation because patients perceive their symptoms differently. It is challenging to get a consensus regarding the incidence of true reflux due to the range of clinical symptoms associated with reflux.

According to previous studies, up to 20% of the general population suffers from heartburn and regurgitation at least once a week. Smoking, drinking alcohol, and being overweight are risk factors for GERD. Research has shown that obesity increases the incidence of GERD, particularly in women.[10,12] In general, patients with symptoms of reflux, regardless of the existence of oesophageal inflammation or confirmation of the presence of true pathological reflux, are given the diagnosis of suspected GERD. Heartburn or pyrosis, regurgitation, and, in advanced stages of the disease, dysphagia are suggestive symptoms of GERD; however, symptoms alone, including response to proton pump inhibitors (PPIs), can be unreliable and costly, especially when PPIs are continued long-term without a confirmed diagnosis.

PH monitoring has been used as a diagnostic tool in GERD and is considered the standard for diagnosis of pathological GERD; however, it is a costly and semi-

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invasive test. Recent studies have shown that wireless capsule pH monitoring is better tolerated and interferes less with daily activities as compared with traditional catheter-based pH monitoring. Moreover, prolonged recording time (48 or even 96 hours instead of 24 hours) is possible with wireless pH monitoring.[13]

## Materials and Methods

### *Study Design*

We conducted a retrospective case-control study on patients who underwent wireless oesophageal pH monitoring from January 2020 to April 2022 in Sheikh Shakhbout Medical City, Abu Dhabi. Our aim was to study the association between selected predictors/potential risk factors and the presence of a DeMeester score of > 14.7 vs. < 14.7. Cases were patients with a high DeMeester score ( > 14.7), indicating pathological reflux and controls were those without. Patients' data were de-identified throughout the data abstraction process to ensure patient privacy.

### *Participants*

All participants were referred for oesophageal pH measurement for various indications, including resistance to acid suppression therapy, typical as well as atypical GERD symptoms, and before GERD correction intervention. Capsule deployment was deferred if upper gastrointestinal (GI) endoscopy showed grade B or C esophagitis. Exclusion criteria were patients with a history of surgery for GERD, patients with inconclusive findings while reporting the study, those with less than 48 hours of pH monitoring data, and patients who were not compliant with the instructions given.

Patients who underwent the 96-hour wireless capsule study had GERD symptoms for more than three months. All patients underwent upper GI endoscopy. Patients were off acid suppression therapy for two weeks before the study.

Before capsule placement, experienced nurses/endoscopy technicians who assisted with the capsule placement did the calibration. During the upper endoscopy, the endoscopic finding of Barrett's esophagus, esophagitis, and hiatus hernia grade were reported if found. The distance between the squamocolumnar junction and the incisors was measured. The pH monitoring capsule was deployed blindly (6 cm above the squamocolumnar junction) using the delivery system guided by the measurements obtained from endoscopy. After wireless capsule placement, all patients remained off PPIs for 2 days and resumed their PPI therapy in the last two days of the study. They were encouraged to be on their usual daily activity and go to work. After verbal instructions, patients were given a patient instruction form to guide them regarding symptom recording. Patients were asked to identify a dominant symptom for symptom analysis. They typically chose one of the following symptoms as their prevalent complaint: heartburn, regurgitation, or chest pain. Patients were instructed to press the symptom indicator button on the pH recorder when experiencing only their one dominant GERD symptom.

Patients returned after 96 hours of capsule placement for the return of the receptor device. Data were downloaded using a standard computer software program (pH Capsule Data Analysis Workstation, Jinshan Science and Technology Co. Ltd, Chongqing, China).[14] The physician made the final review and diagnosis.

### *Data Collection*

Clinical and demographic data including age, sex, body mass index (BMI), nationality, smoking status, non-steroidal anti-inflammatory drugs (NSAIDs) use, presence of atypical symptoms, and history of chronic use of medication affecting lower esophageal sphincter (LES) such as nitro-glycerine, anticholinergics, β-adrenergic agonists, aminophylline, and benzodiazepines[15] were collected retrospectively from patients' electronic records. Endoscopic findings for the presence of Barrett's esophagus, esophagitis, and hiatus hernia were collected. Reports for wireless pH capsules were reviewed, and those with inconclusive results were excluded. According to the average DeMeester score on day one and day 2, the cohort was divided into cases with a score of more than 14.7, indicating pathological reflux, and controls with a score of less than 14.7. The data were stored on a deidentified spreadsheet.

The DeMeester score was chosen for the primary variable as it is the most reproducible of the commonly analyzed pH variables (similar to the percent total time pH < 4) and has an accepted cut-off point of 14.72.[16] Esophagitis grading was made according to LA classification, and hiatus hernia was reported as per Hill grade.

### *Statistical Analysis*

Logistic regression analysis was performed to ascertain the effects of age, sex, BMI, smoking, medications affecting LES, GERD atypical symptoms, Hill grade, esophagitis, and Barrett's esophagus on the likelihood of GERD patients who underwent the study of having a DeMeester score of > 14.7. Based on the Hosmer and Lemeshow test, the logistic regression model was considered to be an excellent fit for the data ($\chi^2 = 26.238$, $P$ value = 0.016). The model explained 35.1% (Nagelkerke R2) of the variance in patients with GERD who underwent the study and had a DeMeester score of > 14.7.[17]

## Results

Eighty-six patients were included in the study. All had symptoms over 3 months. 46 patients had DeMeester score of more than 14.7, and the 40 controls had DeMeester score of less than 14.7. Age ranged between 19 and 76 years. BMI ranged from 17.9 to 47 kg/m$^2$. Women comprised 59%, and 41% were men. Most of the cohort were Emirati (87.2%) and non-smokers (89.5%). 95.3% of the patients were not using NSAIDs regularly. 46.5% presented with atypical GERD symptoms, while 53.5%

presented with typical GERD symptoms. 11 patients (13%) were using medications affecting LES. Endoscopic examination demonstrated esophagitis in 32.6%. Three cases were found to have Barrett's esophagus. 34.9% of the total cohort had no hiatus hernia, while 41.9% had grade 1, 11.6% had grade 2, 7% had grade 3, and 4.7 % had grade 4 hiatus hernia (Table 1).

A comparison of cases and controls also appears in (Table 2). Of note, variables of age, BMI, and presence of esophagitis were significantly different between cases and controls. Unadjusted logistical regression analysis (Table 3) showed that age, BMI, and presence of esophagitis were all associated with a greater likelihood of a high DeMeester score among patients who underwent a wireless oesophageal pH capsule as part of the work-up for GERD. Logistic regression analysis (Table 4) adjusted for age, sex, nationality, and any variable with an effect size of greater than 15% demonstrated that having a high DeMeester score was associated with more than four times the odds of esophagitis ($P=0.02$). The multivariable logistic regression analysis model containing all the variables studied demonstrated that age, BMI, and mild esophagitis were independent predictors of pathological GERD. Patients aged 20-29 years were less likely to have DeMeester score of >14.7 compared with those aged above 50 ($P=0.017$*). BMI 25-29 was also more likely than those with BMI <25 to have GERD ($P=0.026$) with weaker, non-significant trends above BMI 30.

**Table 1.** Baseline characteristics of all patients

| Variables | | No. (%) |
|---|---|---|
| Age (y) | <20 | 1 (1.2) |
| | 20-29 | 30 (34.9) |
| | 30-39 | 28 (32.6) |
| | 40-49 | 17 (19.8) |
| | above 50 | 10 (11.6) |
| Gender | Male | 35 (40.7) |
| | Female | 51 (59.3) |
| Nationality | Non-Emirati | 11 (12.8) |
| | Emirati | 75 (87.2) |
| Smoking | No | 77 (89.5) |
| | Yes | 9 (10.5) |
| BMI | 18-24 | 30 (34.9) |
| | 25-29 | 29 (33.7) |
| | Above 30 | 27 (31.4) |
| Medications affecting LES | No | 75 (87.2) |
| | Yes | 11 (12.8) |
| NSAIDs | No | 82 (95.3) |
| | Yes | 4 (4.7) |
| Standard capsule protocol | No | 1 (1.2) |
| | Yes | 85 (98.8) |
| GERD atypical symptoms | No | 46 (53.5) |
| | Yes | 40 (46.5) |
| Hill grade | Normal | 30 (34.9) |
| | I | 36 (41.9) |
| | II | 10 (11.6) |
| | III | 6 (7.0) |
| | IV | 4 (4.7) |
| Hill grade | normal | 30 (34.9) |
| | I | 56 (65.1) |
| Esophagitis | No | 58 (67.4) |
| | Yes | 28 (32.6) |
| Barrett | No | 83 (96.5) |
| | Yes | 3 (3.5) |
| Symptoms duration | >3 Months | 86 (100.0) |
| Total | | 86 |

BMI: Body mass index, LES: Lower esophageal sphincter, NSAIDs: Non-steroidal anti-inflammatory drugs.

## Discussion

This study showed that patients aged 20-29 years were less likely to have DeMeester score of >14.7 compared with those aged above 50 years. When adjusted against all other variables, the study also showed that higher BMI was associated with pathological reflux. Esophagitis was found more in patients with true reflux, although notably, some patients labeled as having grade A esophagitis had no pathological reflux. The study showed that other parameters studied (some notable surprises) were found to have no significant association with a high DeMeester score.

This case-control study conducted in an Emirati cohort builds on and extends what has been reported in the literature regarding risk factors for GERD. The study showed that only 50% of patients who were referred for pH study were found to have true pathological reflux, as confirmed with a high DeMeester score. This demonstrates the importance of ensuring this diagnosis in such patients, especially if they are going for GERD correction surgery, endoscopic intervention, or having atypical reflux symptoms. Depending only on response to acid suppression is not enough as two other differentials, namely esophageal hypersensitivity and functional dyspepsia, both respond to PPI therapy in the absence of GERD. Most current literature that studied patients with GERD used symptom response to acid suppression for diagnosis. Esophageal pH measurement can be done either by pH capsule or by 24-hour pH catheter. The wireless pH capsule was chosen as patients preferred this type of study while they declined to have a catheter inserted for 24 hours, and both tests were covered by insurance.

We found that higher BMI and being overweight appeared to predict true reflux. Literature showed that an increase in symptoms was more correlated with BMI than with fat distribution (such as the waist-to-hip ratio), which suggests that hormonal factors associated with adiposity may play a more significant role in the pathogenesis of GERD symptoms compared with mechanical factors, at least in women.[18]

The study showed that patients aged 20-29 years were

**Table 2.** Comparison of characteristics and variables of cases vs. controls

| Variables | | Demeester score | | Test of Sig | *P* value |
|---|---|---|---|---|---|
| | | Control < 14.7 | Cases > 14.7 | | |
| Age (y) | < 20 | 1 (2.5) | 0 (0) | F = 11.022 | 0.026* |
| | 20-29 | 20 (50) | 10 (21.7) | | |
| | 30-39 | 12 (30) | 16 (34.8) | | |
| | 40-49 | 5 (12.5) | 12 (26.1) | | |
| | Above 50 | 2 (5) | 8 (17.4) | | |
| Gender | Male | 13 (32.5) | 22 (47.8) | $\chi^2 = 2.082$ | 0.149 |
| | Female | 27 (67.5) | 24 (52.2) | | |
| Nationality | Non-Emirati | 3 (7.5) | 8 (17.4) | $\chi^2 = 1.877$ | 0.171 |
| | Emirati | 37 (92.5) | 38 (82.6) | | |
| Smoking | No | 34 (85) | 43 (93.5) | F = 1.64 | 0.293 |
| | Yes | 6 (15) | 3 (6.5) | | |
| BMI | 18-24 | 18 (45) | 12 (26.1) | $\chi^2 = 5.015$ | 0.081 |
| | 25-29 | 9 (22.5) | 20 (43.5 ) | | |
| | Above 30 | 13(32.5) | 14(30.4) | | |
| Medications affecting LES | No | 34 (85) | 41 (89.1) | $\chi^2 = 0.327$ | 0.567 |
| | Yes | 6 (15) | 5 (10.9) | | |
| NSAIDs | No | 37 (92.5) | 45 (97.8) | F = 1.369 | 0.334 |
| | Yes | 3 (7.5) | 1 (2.2) | | |
| Standard capsule protocol | No | 1 (2.5) | 0 (0) | F = 1.164 | 0.281 |
| | Yes | 39 (97.5) | 46 (100) | | |
| GERD atypical symptoms | No | 24 (60) | 22 (47.8) | $\chi^2 = 1.275$ | 0.259 |
| | Yes | 16 (40) | 24 (52.2) | | |
| Hill grade | Normal | 16 (40) | 14 (30.4) | F = 3.175 | 0.529 |
| | I | 13 (32.5) | 23 (50) | | |
| | II | 5 (12.5) | 5 (10.9) | | |
| | III | 4 (10) | 2 (4.3) | | |
| | IV | 2 (5) | 2 (4.3) | | |
| Hill grade | normal | 16 (40) | 14 (30.4) | $\chi^2 = 0.862$ | 0.353 |
| | I | 24 (60) | 32(69.6) | | |
| Esophagitis | no | 31 (77.5) | 27 (58.7) | $\chi^2 = 3.445$ | 0.063 |
| | yes | 9 (22.5) | 19 (41.3) | | |
| Barrett | no | 39 (97.5) | 44 (95.7) | F = 0.217 | 0.641 |
| | Yes | 1 (2.5) | 2 (4.3) | | |
| Symptoms duration | > 3 Months | 40 (100) | 46 (100) | - | - |
| Total | | 40 | 46 | | |

BMI: Body mass index, LES: Lower esophageal sphincter, NSAIDs: Non-steroidal anti-inflammatory drugs, Sx: Symptoms
F: Fisher's exact test, * Significant.

less likely to have DeMeester score of > 14.7 compared with those aged above 50 years, when adjusted against all other variables. In 2010, Maxwell and colleagues showed that GERD and its associated complications were common in older patients. They concluded that the elderly tended to have fewer symptoms with more severe complications that may be life-threatening. These are important considerations regarding causation, evaluation, and treatment in older patients as compared with younger patients.[19] The possible mechanisms for increased incidence of GERD in the elderly population include weakened and impaired esophageal motility, decreased salivary and bicarbonate secretions, decreased LES pressure with advancing age, diaphragmatic weakness, increased incidence of hiatal hernia, presence of comorbidities such as diabetes and Parkinson disease, and concomitant use of medications such as nitrates, calcium antagonists, theophylline, or antidepressants.[20]

Yamasaki et al also showed that the proportion of patients with GERD using PPIs increased in all age groups, except for the ≥ 70 years group, with the most significant increase being in the 30–39-year age group.[21] On the other hand, in 2018, Yamasaki et al reported that GERD affected a growing number of the adult population and

**Table 3.** Unadjusted Odds of high DeMeester Score based on Variables Collected

| Variables | | OR | 95% CI | | *P* value |
|---|---|---|---|---|---|
| | | | Lower | Upper | |
| Age (y) | <20 (excluded) | NA | NA | NA | NA |
| | 20-29 | 0.125 | 0.022 | 0.702 | 0.018* |
| | 30-39 | 0.333 | 0.060 | 1.863 | 0.211 |
| | 40-49 | 0.600 | 0.093 | 3.885 | 0.592 |
| | above 50 (ref) | - | - | - | - |
| Gender | Male/Female | 0.525 | 0.218 | 1.265 | 0.149 |
| Nationality | Non-Emirati/Emirati | 0.385 | 0.095 | 1.565 | 0.171 |
| Smoking | No/Yes | 0.395 | 0.092 | 1.697 | 0.293 |
| BMI | 18-24 (ref) | - | - | - | |
| | 25-29 | 3.333 | 1.139 | 9.752 | 0.026* |
| | Above 30 | 1.615 | 0.565 | 4.618 | 0.37 |
| Medications affecting LES | No/Yes | 0.691 | 0.194 | 2.463 | 0.567 |
| NSAIDs | No/Yes | 0.274 | 0.027 | 2.746 | 0.334 |
| Standard capsule protocol | No/Yes | - | - | - | - |
| GERD atypical symptoms | No/Yes | 1.636 | 0.694 | 3.856 | 0.259 |
| Hill grade | Normal/Abnormal | 1.524 | 0.625 | 3.716 | 0.353 |
| Esophagitis | No/Yes | 2.424 | 0.941 | 6.243 | 0.063 |
| Barrett | No/Yes | 1.773 | 0.155 | 20.315 | 0.641 |
| Total | | 15.633 | 69.606 | | 4.047 |

BMI: Body mass index, LES: Lower esophageal sphincter, NSAIDs: Non-steroidal anti-inflammatory drugs.
* Significant.

**Table 4.** Logistic regression (Odds adjusted for age, sex, and any variable with an effect size>5%) of high DeMeester Score based on variables collected)

| Variables | | OR | 95% CI | | *P* value |
|---|---|---|---|---|---|
| | | | Lower | Upper | |
| BMI | | | | | 0.468 |
| | 25-29 | 0.790 | 0.198 | 3.150 | 0.738 |
| | Above 30 | 1.870 | 0.469 | 7.459 | 0.375 |
| Gender (female) | | 2.482 | 0.691 | 8.916 | 0.164 |
| Age | | | | | 0.124 |
| | less than 20 | 0.000 | 0.000 | . | 1.00 |
| | 20-29 | 0.069 | 0.008 | 0.620 | 0.017* |
| | 30-39 | 0.178 | 0.021 | 1.485 | 0.111 |
| | 40-49 | 0.324 | 0.033 | 3.174 | 0.333 |
| | Above 50 (ref.) | | | | |
| Nationality | Non-Emirati/Emirati | 0.077 | 0.005 | 1.090 | 0.058 |
| Smoking | No/Yes | 2.564 | 0.340 | 19.334 | 0.361 |
| NSAIDs | No/Yes | 1.704 | 0.087 | 33.461 | 0.726 |
| Medications affecting LES | No/Yes | 3.762 | 0.414 | 34.159 | 0.239 |
| Standard capsule protocol | No/Yes | 0.000 | 0.000 | . | 1.00 |
| GERD atypical symptoms | No/Yes | 0.480 | 0.155 | 1.489 | 0.204 |
| Hill grade | Normal/Abnormal | 0.613 | 0.183 | 2.055 | 0.428 |
| Esophagitis | No/Yes | 4.384 | 1.2 | 15.5 | 0.022* |
| Barrett | No/Yes | 0.107 | 0.005 | 2.407 | 0.160 |
| Constant | | 162.593 | | | 0.101 |

BMI: Body mass index, LES: Lower esophageal sphincter, NSAIDs: Non-steroidal anti-inflammatory drugs.
* Significant.

that younger people develop GERD very fast.[22] This study included various age groups and noted a high proportion of younger patients with GERD, especially those aged 30-39 years. Also, in 2018, Gwang and colleagues reported an increasing incidence of GERD in younger patients.[23]

The increased incidence of obesity, decreased prevalence of *Helicobacter pylori* infection, smoking, and heavy alcohol consumption can explain the recent increase in the incidence of GERD in the young age group.[22]

Our study showed that being between 20 and 29 years of age compared with being 50 years of age or older was associated with having a lower Demeester score. While those between the ages of 30-50 also appeared to have a lower likelihood of a high DeMeester score compared with those above the age of 50, this difference was not statistically significant. When we compare our results with the results reported by Khoder et al, we note that in the Emirates (UAE), young populations have higher rates of *H. pylori* infection,[24] and there is overall less consumption of alcohol and tobacco, possibly explaining the lower incidence of pathological reflux in this part of our cohort.

Reflux has been linked to alcohol use and tobacco smoking.[25] Smoking cigarettes likely worsens reflux disease by sharply increasing the frequency of acid reflux episodes. The presence of decreased LES pressure is crucial to the mechanisms of acid reflux during cigarette smoking. Alcohol also lowers LES pressure, much like smoking does. Additionally, it has been shown that alcohol decreases the amplitude of esophageal peristaltic waves, affects acid clearance for roughly 3.5 hours with a considerable acidic shift below pH 3 or 4 when the person is supine and decreases saliva production in healthy individuals.[25]

Despite these physiological effects of smoking and alcohol, we could not conclusively link either substance to GERD. Most likely, the results shown in our study were related to low alcohol and smoking consumption in our cohort.

The current study showed true pathological reflux was associated with four times higher odds of having esophagitis. The LA classification has been used to assess mucosal injury; however, symptoms and endoscopic findings are not always correlated. The intensity and frequency of reflux symptoms are poor predictors of the presence of severe reflux esophagitis.

Previous studies have shown that only one-third of patients with endoscopic LA grade A had GERD symptoms. Endoscopic findings of LA grade B esophagitis had significant inter-observer variability. Therefore, endoscopic LA grades C or D esophagitis, Barrett's esophagus, or peptic stricture are considered confirmatory evidence for GERD in the Lyon consensus. Furthermore, many GI experts consider LA grade B as an indication of definitive GERD needing treatment. Therefore, studies of the natural history and outcome of therapy based on GERD's endoscopic findings are required.[26-29]

The association between LA grade A esophagitis and true reflux in our study is expected and can be attributed to the observation that most of the cohort was using regular acid suppression therapy and stopped two weeks before performing the pH study, which may not be sufficient time to develop endoscopic finding of more severe esophagitis.

## Study Limitation

We did not consider the symptoms index from pH capsule results as our aim was to measure true pathological reflux rather than symptom association. Our sample size was overall small.

## Conclusion

In conclusion, we have described the epidemiology and clinical characteristics of GERD in the Emirati population. Several factors are associated with the increase in the prevalence of GERD in Emiratis. Increasing age above 50 compared with age between 20-29 and being overweight appeared to be predictors of true pathological reflux among patients with reflux symptoms who underwent wireless pH monitoring. The presence of even grade A esophagitis was associated with true pathological reflux. These data can be further used to guide which patients benefit most from pH testing. Those with either a very high or very low probability of GERD likely do not benefit, as they can be either empirically treated or reassured.

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### Authors' Contribution

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### Competing Interests

The authors declare no conflict of interest related to this work.

### Ethical Approval

All the studies were approved by the Institutional Review Board of SSMC, Abu Dhabi.

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Original Article

# Impact of Various Risk Factors on the Positive Fecal Immunochemical Test for Colorectal Cancer in the Iranian Population

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**Abstract**

**Background:** Colorectal cancer (CRC) is the most prevalent cancer with high mortality worldwide. We aimed to evaluate the incidence of CRC based on the positive fecal immunochemical test (FIT) result in the Iranian population.

**Methods:** The present study was conducted on the health assessment data recorded in the SINA (Integrated Health Information System) in 2018 and 2019 from individuals who had participated in the national program, including asymptomatic people aged 50-69 years or had risk factors of CRC such as family or past personal history of CRC as well as symptomatic individuals, for the early detection and prevention of CRC in Mashhad, Iran.

**Results:** The study participants included 140,463 eligible individuals, of whom 8258 (5.88%) and 145 (2.21%) were positive for FIT and diagnosed with colon cancer, respectively. Unfortunately, only 654 people had undergone colonoscopy. Our results indicated that age, fast food intake (≥two units per day), family history of CRC in first or second-degree relatives, some gastrointestinal diseases such as inflammatory bowel disease (IBD) and CRC, as well as bleeding per anus, constipation, abdominal cramp, and losing body weight were associated with increased risk of positive FIT. However, some other factors, including having a hard job, physical activity, and Iranian nationality (compared to non-Iranians), were associated with a low risk of positive FIT screening tests for CRC.

**Conclusion:** A high number of high-risk persons in Mashhad were positive for the FIT test in 2018-2019, and many of them were diagnosed with CRC, according to the colonoscopy results. Therefore, screening is highly recommended as the first step in the early detection of CRC.

**Keywords**: Colorectal cancer, Epidemiology, Fecal immunochemical test, Prevention, Screening

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## Introduction

Colorectal cancer (CRC) is a common cause of death before the age of 70 in different countries. Moreover, this cancer is one of the most prevalent cancers worldwide, including in Iran.[1] According to the global cancer burden (GLOBOCAN 2020), based on information from the International Agency for Research on Cancer in 2020, CRC is the 3rd most prevalent cancer in both men and women and is the second in terms of mortality in the world.[1] However, the incidence and mortality of CRC are declining in developed countries.[2]

Iran is one of the regions with a lower incidence of CRC, and based on the available evidence, the incidence of the disease in Iran is close to its incidence in other Middle Eastern countries but is lower compared with its rate in Western countries.[3] According to the information available in the Iranian population cancer registration systems, the incidence of this disease in Iran is higher in the northern provinces, such as Golestan and Mazandaran, compared with the central and southern provinces.[3] Between the years 2003 and 2008, the rate of cancer in Iran increased in both men and women (from 3.92 to 7.78 in women and from 5.56 to 12.7 per 100 000 people in men) due to changes in diet and lifestyle.[4] In Iran, nearly 4000 new cases of CRC are reported each year, with 1,150 fatalities annually.[5] A study conducted in Iran from 2003-2008 demonstrated that 61.83 %, 27.54%, 7.46%, and 3.10% of patients with CRC had colon cancer, rectal cancer,

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rectosigmoid cancer, and anal cancer, respectively.[4]

Genetic and environmental factors are among other causes of CRC. Several risk factors have been identified in association with this disease such as red meat intake, positive family history, alcohol use, tobacco smoking, and certain hereditary cancer syndromes. Protective factors include calcium, vegetables, folate, hormone replacement therapy, physical activity, and non-steroidal anti-inflammatory drugs.[6]

Colon cancer is known as a silent disease, and people affected by this disease usually do not show symptoms until the advanced stages of the disease; however, according to the available evidence, the most important symptoms of this disease, which should be taken into consideration, include rectal bleeding, weight loss, abdominal pain and changes in bowel movements. In addition to these, the most important laboratory symptoms are the presence of blood in stool and anemia.[7]

CRC is often diagnosed after the onset of symptoms or through screening tests for asymptomatic cases. Various screening tests are available in this regard, such as non-invasive stool-based testing or colonoscopy. A patient with any abnormal non-invasive stool-based screening test result for CRC requires a colonoscopy to be evaluated for CRC. Stool-based screening tests include guaiac-based fecal occult blood tests (g-FOBT), fecal immunochemical tests (FITs), and multi-target stool DNA testing (sDNA-FIT). The mentioned tests for CRC are different in terms of sensitivity and specificity, evidence of effectiveness, safety, convenience, cost, and availability.[8,9]

It should be noted that tumors have different prevalence around the world, and environmental exposures and racial factors may affect this prevalence. Therefore, it can be concluded that environmental exposures can play a key role in CRC. We surveyed the incidence of CRC in terms of the available non-invasive screening test (FIT) in the city of Mashhad, Iran, and compared the relative frequency of FIT test results (positive-negative-invalid) in eligible patients who had been referred to Mashhad Comprehensive Health Service Centers in 2018-2019 based on the presence of CRC risk factors and lifestyle. A spatial analysis of FIT-positive participants was conducted based on the participants' specific geography, culture, and ethnicity.

## Materials and Methods

### *Study Design*

The present study was performed based on the health assessment data recorded in the SINA (Integrated Health Information System) system in 2018-2019 related to individuals who participated in the national program for the early detection and prevention of CRC in Mashhad, Iran.

In this study, the sampling was performed based on the census method, and we included all patients who were eligible to enter the health centers and willing to participate in the study. We observed all ethical considerations in performing this study, and the participants were initially informed about the study objectives and procedure. Moreover, written informed consent was obtained from all of them.

### *Inclusion and Exclusion Criteria*

The study population was selected based on the inclusion criteria, including Iranians living in regions covered by the Mashhad University of Medical Sciences who were referred to Comprehensive Health Centers and were eligible for FIT. Criteria for entering the national program for the prevention and early detection of CRC with the FIT included: (1) the asymptomatic individuals with the age range of 50-69 years, (2) personal history of gastrointestinal cancer, adenoma, or inflammatory bowel disease (IBD), (3) family history of CRC or adenoma in the first-degree family or the same history in those under 49 years of age in the second-degree family, (4) any gastrointestinal symptom, such as bleeding from the lower gastrointestinal tract in the last year, and (5) constipation during the last month (with or without diarrhea, feeling full in the anus after defecation, and abdominal pain), and the weight loss of more than 10%. The exclusion criteria were incomplete information and the inability to give a history or visit a comprehensive health center, for instance in the case of those with acute mental or emotional disorders, or physical illness.

A total number of 140 463 patients with indications for colorectal screening via the FIT test were enrolled in this study. The FIT was performed for all eligible participants on a single stool sample from each participant. The mentioned test measured hemoglobin in the stool and was a single-stage test using a qualitative immunoassay method to detect human blood in the stool.

Additionally, demographic characteristics of individuals, physical activity, nutritional status, and other risk factors were assessed (using a questionnaire) and recorded in the SINA system by health caregivers. The FIT result was recorded for each participant, and those with positive FIT results were referred for colonoscopy. Unfortunately, out of the 8258 patients who tested positive for FIT, only 654 (12.6%) had undergone a colonoscopy. The relative frequency of FIT test results (positive, negative, and invalid) was determined, and the presence of CRC risk factors and lifestyle was compared between the groups.

### *Statistical Analysis*

Data analysis was performed using SPSS software (version 22.0). Descriptive statistics were used to assess the frequency and percentage of qualitative variables, and quantitative variables with normal distribution were presented with mean ± standard deviation (SD). The normal distribution of data was determined using the Kolmogorov-Smirnov test. The independent Student's *t* test was used to compare the quantitative variables between positive and negative FIT groups. The qualitative variables were analyzed using chi-square or Fisher's exact

tests. The logistic regression model was used to evaluate the relationship between independent variables and the positive results of FIT, and the odds ratio (OR), and 95% confidence intervals (CI) were reported for the significant risk factors. The level of significance was set at $P<0.05$.

## Results

The characterization of 140,463 participants according to the results of the FIT is summarized in Table 1. Our results demonstrated that 5.9%, 93.2%, and 1.0% of the included population had positive, negative, and invalid FIT results, respectively. The mean ± SD age of the subjects in the groups of positive, negative, and invalid FIT was 58.94 ± 10.92, 59.76 ± 10.92, and 62.1 ± 15.12, respectively, with a significant difference between positive and negative FIT groups ($P<0.001$). Overall, 55.8% of individuals were women, and a significant difference was observed between the two groups based on sex ($P<0.001$). Moreover, 82.6% of the subjects were married with a spouse, while 13.3% and 4% were married without a spouse and single, respectively ($P<0.001$). Furthermore, 96.5% of participants had Iranian nationality compared with 3.5% with non-Iranian nationality ($P<0.001$). Non-academic and academic education was observed in 55.8% and 9.1% of the subjects, and 35.1% of the subjects were illiterate ($P<0.001$). In total, 39% and 50.3% of the study population had hard jobs involving heavy physical activity or physical activities, respectively, and there was a significant difference between the negative and positive FIT groups ($P<0.001$).

Overall, 31.6%, 42.2%, and 33.5% of the subjects consumed dairy products, vegetables, and fruits two or more than two units per day, whereas 66.2%, 54.5%, and 63.4% had no or rare intake of dairy, vegetables, and fruits, respectively. In total, 77.2% used two or more units of fast food, and 76.3% never or rarely consumed salt per day. In our study, 51%, 14.1%, and 34.8% of the population used liquid oil, solid oil, and a combination of both, respectively. There was a significant difference between positive and negative FIT groups in terms of all lifestyle parameters ($P<0.001$).

The clinical symptoms, including bleeding per anus, constipation, abdominal cramp, feeling of residuum per defecation, and body weight loss, were observed in 71.6%, 11%, 1.3%, and 0.3% of the participants during the last month with significant differences between the results of negative and positive FIT groups. Additionally, 19%, 41.2%, 0.2%, 0.2%, and 0.1% of the enrolled subjects had diabetes, hypertension, IBD, CRC, and colorectal adenoma, respectively. A total of 1.7% and 0.5% of the subjects had first-degree or second-degree relatives with CRC, respectively. As presented in table 1, no significant difference was found in terms of diabetes mellitus between negative and positive FIT groups ($P<0.954$). However, there were significant differences between the mentioned groups in terms of other medical histories and symptoms.

Table 2 presents the significant effect of risk factors associated with the positive FIT results based on the logistic regression model with an OR at a CI of 95%. It was found that hard jobs (OR = 0.730, CI = 0.674-0.791), physical activity (OR = 0.763, CI = 0.703-0.829), and Iranian nationality versus non-Iranian nationality (OR = 0.768, CI = 0.655-0.901), independently reduced the risk of positive FIT. In contrast, bleeding per anus (OR = 4.169, CI = 3.502-4.963), loss of body weight (OR = 3.543, CI = 2.462-5.097), IBD (OR = 3.476, CI = 2.393-5.050), CRC (OR = 2.880, CI = 1.872-4.432), constipation (OR = 2.303, CI = 2.126-2.495), abdominal cramp, feeling of residuum per defecation (OR = 2.039, CI = 1.709-2.432), second-degree (OR = 2.203, CI = 1.610-3.016) or first degree (OR = 1.734, CI = 1.445-2.081) relatives with CRC, and hereditary diseases (OR = 1.891, CI = 1.079-3.314) were independently associated with a high risk of positive FIT results. Additionally, the non-academic (OR = 1.390, CI = 1.279-1.511) or academic (OR = 1.459, CI = 1.285-1.657) education of the subjects increased the odds of positive FIT by 1.4 fold, compared with illiterate participants. The consumption of fast food for two or more units (OR = 1.208, CI = 1.094-1.333) independently increased the risk of positive results compared with the less usage of fast food (less than two units). Furthermore, the increase in the age of the participants was related to an increase in the likelihood of a positive FIT test (OR = 1.005, CI = 1.001-1.009). Our results revealed that the bleeding per anus was associated with a 4.2-fold higher risk of positive FIT and was determined as the risk factor with the highest significant effect in this study.

## Discussion

The burden of common cancers, such as CRC, is changing in different regions.[10] In addition, incidence rates of CRC have been increasing in many countries in South-Central Asia, Eastern Europe, and South America.[11] According to data from 184 countries, the rate of CRC is regarded as a measure of community development.[12] The increase in the rate of this cancer likely reflects changes in lifestyle factors, including physical activity and diet.[13]

In the present study, the rate of CRC was estimated to be 2.21%, with a standardized incidence of 22.1 per 100 000 people. However, this rate was lower in a previous study in which CRC was estimated to be the fourth most common cancer among women with a standardized rate of 6.5 to 7.5 per 100 000 and the third most prevalent cancer among Iranian men with a standardized rate of 8.1-8.3 per 100 000 individuals.[14] Based on our data, only 654 individuals had undergone colonoscopy, and others with a positive FIT test either did not undergo colonoscopy, or there was no information regarding the performance of colonoscopy recorded in the SINA system, despite the thorough investigations performed by the health care professional. Accordingly, the mentioned results should be performed with caution. The present study recommended that the application of an appropriate national cancer control program seems to be of great importance in controlling

**Table 1.** Characteristics of 140463 subjects based on the results of the fecal immunochemical test (FIT)

| Variables | FIT | | | *P* value* |
|---|---|---|---|---|
| | Positive | Negative | Invalid | |
| **Demographic** | | | | |
| Age | 58.94±10.92 | 59.76±10.92 | 62.1±15.12 | <0.001 |
| Sex | | | | <0.001 |
| Male | 3303 (40.0) | 58152 (44.4) | 586 (43.9) | |
| Female | 4955 (60.0) | 72717 (55.6) | 750 (56.1) | |
| Marital status | | | | <0.001 |
| Single | 430 (5.2) | 5194 (4.0) | 63 (4.7) | |
| Married with spouse | 6792 (82.2) | 108276 (82.7) | 1024 (76.6) | |
| Married without spouse | 1036 (12.5) | 17399 (13.3) | 249 (18.6) | |
| Nationality | | | | <0.001 |
| Iranian | 7882 (95.4) | 126472 (96.6) | 1291 (96.6) | |
| Non-Iranian | 376 (4.6) | 4397 (3.4) | 45 (3.4) | |
| Education | | | | <0.001 |
| Illiterate | 2247 (27.2) | 46568 (35.6) | 563 (42.1) | |
| Non-academic | 5044 (61.1) | 72596 (55.5) | 668 (50.0) | |
| Academic | 967 (11.7) | 11705 (8.9) | 105 (7.9) | |
| Hard job | 2609 (31.6) | 51762 (39.6) | 444 (33.2) | <0.001 |
| **Lifestyle** | | | | |
| Dairy consumption | | | | <0.001 |
| Never or rarely | 4550 (60.7) | 80534 (66.6) | 688 (65.5) | |
| <Two units | 209 (2.8) | 2584 (2.1) | 26 (2.5) | |
| ≥Two units | 2739 (33.2) | 37870 (31.3) | 337 (32.1) | |
| Vegetable consumption | | | | <0.001 |
| Never or rarely | 2684 (47.6) | 49585 (55.0) | 300 (50.8) | |
| <Two units | 236 (4.2) | 2926 (3.2) | 36 (6.1) | |
| ≥Two units | 2721 (32.9) | 37724 (41.8) | 254 (43.1) | |
| Fruit consumption | | | | 0.005 |
| Never or rarely | 4624 (61.6) | 76775 (63.5) | 644 (61.2) | |
| <Two units | 256 (3.4) | 3758 (3.1) | 39 (3.7) | |
| ≥Two units | 2621 (34.9) | 40463 (33.4) | 370 (35.1) | |
| Salt consumption | | | | <0.001 |
| Never or rarely | 6066 (75.4) | 98318 (76. 4) | 953 (72.5) | |
| <Two units | 477 (5.8) | 5075 (3.9) | 70 (5.3) | |
| ≥Two units | 1503 (18.2) | 25277 (19.6) | 292 (22.2) | |
| Fast food consumption | | | | <0.001 |
| Never or rarely | 504 (6.3) | 6965 (5.4) | 86 (6.6) | |
| <Two units | 1228 (15.3) | 22545 (17.5) | 177 (13.5) | |
| ≥Two units | 6299 (78.4) | 99089 (77.1) | 1048 (79.9) | |
| Oil consumption | | | | |
| Solid | 1304 (16.2) | 18046 (14.0) | 207 (15.7) | |
| Liquid | 4214 (52.3) | 65485 (50.8) | 680 (51.7) | <0.001 |
| Both | 2545 (31.6) | 45288 (35.2) | 428 (32.5) | |
| Physical activity | 3474 (47.8) | 66679 (59.7) | 579 (53.9) | <0.001 |
| **Symptoms during last month and medical history** | | | | |
| Bleeding per anus | 469 (5.7) | 1002 (0.8) | 5 (0.4) | <0.001 |
| Constipation | 2143 (26.0) | 13240 (10.1) | 67 (5.0) | <0.001 |
| Abdominal cramp and feeling of residuum per defecation | 397 (4.8) | 1414 (1. 1) | 12 (0.9) | <0.001 |

**Table 1.** Continued.

| Variables | FIT | | | *P* value* |
|---|---|---|---|---|
| | Positive | Negative | Invalid | |
| Loss of body weight (>10%) | 97 (1.2) | 283 (0.2) | 4 (0.3) | <0.001 |
| Diabetes | 1657 (24.9) | 24724 (24.9) | 276 (27.3) | 0.954 |
| Hypertension | 3414 (51.2) | 53829 (54.2) | 598 (59.1) | <0.001 |
| IBD | 90 (1.1) | 253 (0.2) | 2 (0.1) | <0.001 |
| CRC | 58 (0.7) | 201 (0.2) | 1 (0.1) | <0.001 |
| Colorectal adenoma | 12 (0.1) | 93 (0.1) | 2 (0.1) | 0.034 |
| Hereditary diseases | 38 (0.5) | 148 (0.1) | 0 (0.0) | <0.001 |
| First- degree relatives with CRC | 284 (3.4) | 2161 (1.7) | 6 (0.4) | <0.001 |
| Second- degree relatives with CRC (<50 years) | 83 (1.0) | 553 (0.4) | 5 (0.4) | <0.001 |

IBD: Inflammatory bowel disease; CRC: Colorectal carcinoma; * Between positive and negative FIT.
The quantitative variables were presented as the mean±standard deviation (SD), and the qualitative variables were presented by frequency (percentage).

**Table 2.** The effect of significant risk factors on positive fecal immunochemical test results using the logistic regression model

| Variables | Odds ratio | 95% CI | | *P* value |
|---|---|---|---|---|
| | | Lower | Upper | |
| Age | 1.005 | 1.001 | 1.009 | 0.011 |
| Nationality (Iranian) | 0.768 | 0.655 | 0.901 | 0.001 |
| Education | | | | |
| Non-academic | 1.390 | 1.279 | 1.511 | <0.001 |
| Academic | 1.459 | 1.285 | 1.657 | <0.001 |
| Hard job | 0.730 | 0.674 | 0.791 | <0.001 |
| Fast food (≥Two units) | 1.208 | 1.094 | 1.333 | <0.001 |
| Physical activity | 0.763 | 0.703 | 0.829 | <0.001 |
| Bleeding per anus | 4.169 | 3.502 | 4.963 | <0.001 |
| Constipation | 2.303 | 2.126 | 2.495 | <0.001 |
| Abdominal cramp and feeling of residuum per defecation | 2.039 | 1.709 | 2.432 | <0.001 |
| Loss of body weight (>10%) | 3.543 | 2.462 | 5.097 | <0.001 |
| IBD | 3.476 | 2.393 | 5.050 | <0.001 |
| CRC | 2.880 | 1.872 | 4.432 | <0.001 |
| Hereditary diseases | 1.891 | 1.079 | 3.314 | 0.026 |
| First- degree relatives with CRC | 1.734 | 1.445 | 2.081 | <0.001 |
| Second- degree relatives with CRC (<50 years) | 2.203 | 1.610 | 3.016 | <0.001 |

CI: Confidence interval; IBD: Inflammatory bowel disease; CRC: Colorectal carcinoma.

the rate of CRC.

Currently, the IFOBT test is the most widely used CRC screening in the world. The performance of this test (FIOBT or FIT) leads to a two-fold increase in the diagnosis of assiduous and also a three to four-fold increase in the diagnosis of advanced adenomas.[15] Based on the evidence from different countries, the adoption of screening programs using this test significantly reduces the CRC incidence and mortality rate.[16,17] The present study showed the status of people screened for CRC in 2018-2019 in Mashhad using FIT, among whom 8258 (5.88%) individuals tested positive for FIT.

The results of similar studies in different countries indicate that this rate varies from about 1% to 11%. For example, the risk of a positive FIT result was 5.9% in Mexico,[18] 8.7% in Thailand,[19,20] 4.1% in Italy, 9.7% in Brazil,[17] 11.1% in Uruguay,[21] and 3.4% in Serbia.[15] This variation indicates the difference in the percentage of positive people in each country and region and can be explained by the difference in the age range of the people screened as well as the difference in the cut-off point used for the FIT. Accordingly, the lower cut-off points for positive FIT decrease the test sensitivity and decrease the test specificity.[18] In the present study, although a small percentage of the subjects were non-Iranians, the rate of positive FIT result was higher among them, compared with their Iranian counterparts. Therefore, it can be concluded that the Iranian nationality has a protective effect against CRC (OR=0.768), which can be explained by the lack of health insurance coverage and the late referral of non-Iranian people to health centers.

The evaluation of demographic features of participants who had undergone FIT showed that age had a positive association with the result of the FIT and that the chance of a positive FIT result increased with age (OR=1.005). In general, based on the evidence, the risk of developing polyps as well as cancer is expected to increase with age.[22] Therefore, as people get older, they need to pay more attention to cancer screening tests for CRC and perform them more regularly. In terms of education, the study results showed that the odds of positive FIT were increased by 1.4-fold among those with non-academic (OR=1.390, CI=1.279-1.511) and academic (OR=1.459, CI=1.285-1.657) education compared with the illiterate population. Moreover, those with higher awareness of the issue participated more in screening programs for the disease. Various studies and research have shown that the lack of knowledge and awareness, especially the misconception of not having symptoms and being healthy, can be considered the main obstacle to greater participation in screening programs.[23]

Lifestyle, including diet and physical activity, may contribute to the increased CRC incidence.[24] However, the relation between diet and predisposition to colon cancer is undeniable. The types of foods that can affect the risk

of these cancers are not yet fully recognized. Moreover, different studies have provided conflicting evidence for or against an association between eating vegetables and fruits and CRC.[25-27] Extensive cohort studies show that the incidence of these cancers decreases up to 25% with increased consumption of fish, fruits, vegetables, dietary fiber, and intake of vitamin D and calcium.[24,27,28] Our study demonstrated that the consumption of two units or more fast food (OR = 1.208, CI = 1.094-1.333) independently increased the risk of positive results of FIT.

Based on the obtained results, the risk of positive FIT in people who are physically active or have hard jobs is less compared with those who are not physically active. In other words, having physical activity is a protective factor in this regard. This result is consistent with those obtained in other studies.[29-31] Numerous biological mechanisms have been proposed to justify the association between physical activity and colon cancer.[31] In general, exercise reverses the mechanisms associated with the risk of CRC indirectly by controlling weight, insulin, and body mass index.[31]

The study results indicated that the signs and symptoms of colon cancer in the last month had a direct impact on the FIT test result and increased the chances of a positive FIT test result. These symptoms include rectal bleeding, constipation, abdominal pain, a feeling of residuum after defecation, body weight loss of more than 10%, personal history of CRC, history of IBD, family history of CRC in first-degree relatives, history of colon cancer in second-degree families under the age of 50, and history of inherited diseases. CRC is a preventable disease, and screening plays an important role in the early detection of this disease. However, given the balance between cost-effectiveness, potential benefit, and the extent of harm, FOBT tests are the simplest, cheapest, and most non-invasive way of diagnosing CRC by detecting human blood in the lower intestines.[15,17] Selective screening in people with positive symptoms and medical history can be very effective in the prevention and early detection of CRC.

Many studies worldwide have shown a correlation between a family history of cancer and CRC. This result was confirmed in the present study, given the higher number of positive cases of FIT in people with a family history of colon cancer, particularly among first-degree relatives. The increased risk of CRC may be justified by genetic commonalities or by shared exposure to certain environmental factors over time.[32] The high prevalence of a family history of CRC among Iranian patients suggests that a high number of CRCs arise among the family members and relatives of patients with CRC.[33] Therefore, screening should be performed regularly in families with a member affected by CRC, and they should be provided with relevant information and awareness.[33]

In this study, we investigated the association of chronic diseases with CRC. However, some studies have shown that diabetes, metabolic syndrome, and increased insulin resistance are related to an increased risk of CRC.[34,35] Some evidence revealed that diabetes treatment did not affect the risk of cancer in patients with type 2 diabetes. Based on our findings, diabetes treatment has no impact on the risk of cancer associated with type 2 diabetes. Accordingly, an increase in cancer rate does not justify the prescription of glucose-lowering treatment for type 2 diabetic patients.[36]

## Study Strengths and Limitations

The large sample size is one of the strengths of this study, which allows for the generalizability of the results and a more comprehensive view of the subject. The data used in this study was made available by Mashhad University of Medical Sciences to determine the relative frequency and risk factors of colon cancer in the covered population for the first time. The limitations of the present study include the inactive collection of information by physicians and health care providers, incorrect or incomplete health information in some cases, lack of full coverage of the urban population in the health care system, and incorrect or low-quality sampling for the FIT test. In addition, only 654 individuals had undergone colonoscopy, and others with a positive FIT test either did not undergo colonoscopy, or there was no such information regarding the performance of colonoscopy recorded in the SINA system, despite the thorough investigations performed by the health care professional. Another limitation of this study is the lack of access to pathology and the number of polyps detected in the colonoscopy of the patients. Further studies are suggested to follow up on these as well.

## Conclusion

Although the incidence and mortality of CRC are declining in developed countries, the prevalence of CRC in recent years has increased in the Iranian population. Our results revealed that bleeding per anus, body weight loss, and some gastrointestinal diseases, including IBD or previous history of CRC, first-degree or second-degree relatives with CRC, and hereditary diseases, as well as constipation and abdominal cramp symptoms were independently associated with a high risk of positive FIT result for CIC. According to the present study, bleeding per anus was associated with 4.2-fold odds of positive FIT and considered the risk factor with the highest significant effect. It can be concluded that early detection of CRC or premalignant polyps through convenience cancer screening and diagnosis of associated risk factors for CRC leads to the reduction of mortality rate and an increase in the level of public health.

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### Authors' Contribution

NM and TJD drafted the manuscript and provided the data related to the study population. NM was the principal investigator and project leader. EMF, TJD, and LG contributed to data gathering from

SINA. NM and MK critically revised the text. MK performed the data analysis. All authors read and approved the final manuscript.

## Competing Interests
The authors have no relevant financial or non-financial interests to disclose.

## Consent to Participate
Written informed consent was obtained from the subjects.

## Consent to Publish
The authors affirm that participants provided informed consent for publication.

## Data Availability Statement
All data are included in the present article.

## Ethical Approval
This study was reviewed by the Ethics Committee of the School of Medicine at Mashhad University of Medical Sciences (IR.MUMS.MEDICAL.REC.1399.047). The data were provided to the researchers anonymously and without specifications.

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Original Article

# Epidemiological, Endoscopic, Clinical, and Pathological Features of Patients with Celiac Diseases in Southern Littoral of Caspian Sea

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**Abstract**

**Background:** Celiac disease is an autoimmune disorder resulting from gluten consumption in genetically predisposed individuals. The present study investigated the epidemiological, endoscopic, and clinicopathological features of patients with celiac disease in the southern littoral of the Caspian Sea.

**Methods:** 140 patients with celiac disease were interviewed and examined regarding demographic characteristics, clinical symptoms, and serologic, endoscopic, and pathological findings.

**Results:** 44 (31.4%) of the patients were male and 68.6% were female. The mean age of the patients at diagnosis was 27.13 ± 13.4 years (ranging from 2 to 60 years). The most common gastrointestinal (GI) symptoms were bloating (47.8%), abdominal pain (47.1%) and diarrhea (30.7%), respectively. Also, 17 (12.1%) patients did not complain of any GI symptoms.18 (12.8%) patients had aphthous stomatitis, 10.7% had dermatitis herpetiformis, 3.6% suffered from itching without a rash, two (1.4%) mentioned psoriasis and one (0.7%) had lichen planus. 19 (19.7%) of the female patients complained of menstrual bleeding disorders, 4% mentioned infertility, and 2% experienced primary amenorrhea. The most common comorbid condition was hypothyroidism in 16 (11.4%) patients. The most common endoscopic finding was duodenal scalloping (37.25%). In addition, 7.8% of the patients had a normal endoscopic appearance. 43 (30.7%) patients were classified as Marsh IIIC, 25.7% Marsh IIIB, 17.8% Marsh IIIA, 12.8% Marsh II and 12.8% were classified as Marsh I.

**Conclusion:** Since celiac disease can present with non-GI manifestations and the majority of our patients had Marsh III classification, it seems that celiac disease must be considered as a routine screening test in GI clinics, and also, it should be kept in mind as a differential diagnosis in other specialty fields.

**Keywords:** Celiac, Epidemiology, Pathology, Endoscopy

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## Introduction

Celiac disease is a chronic autoimmune disease of the small intestine, characterized by mucosal inflammation, villous atrophy, and crypt hyperplasia. The disease is due to gluten sensitivity, a protein found in wheat and some other grains.[1] Although genetic predisposition is very important in its development, many other environmental factors contribute to its occurrence.[2,3] In the classic form of celiac disease, the patient presents with malabsorption symptoms, including steatorrhea, weight loss, and signs related to nutrient and vitamin deficiencies. However, the disease also has atypical and silent forms.[4] In the atypical form, the patients have mild digestive symptoms, and they present with non-gastrointestinal (GI) symptoms, including neurological symptoms, anemia, tooth disorders, osteoporosis and/or infertility. In the silent form, the patients have no symptoms, and the disease can only be diagnosed via screening tests,[5] but these patients face a greater risk as they develop digestive malignancies, especially intestinal lymphoma.[3,6,7] Consequently, this disease is very important for various reasons, including its effects on the quality of life and life span of the patients.[3]

Many studies have so far been conducted on the prevalence of celiac disease in Iran. Based on a recent

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review and meta-analysis of 63 patients, the general prevalence of celiac disease in Iran was 3% based only on biochemical tests and 2% when the biochemical findings were histologically confirmed.[8] In the study region (Mazandaran province), a study by Fakheri et al in 2004 on 1438 residents of Sari county reported that the prevalence of celiac disease in this population was 1%.[9]

However, the research performed in Iran has mainly dealt with the prevalence of this disease in various parts of the country, and few studies have investigated the frequency of its clinical manifestations and its relationship with the demographic characteristics of the patients. In a study conducted in Mashhad in 2014, celiac disease was more prevalent in female patients, and its initial demonstration was mostly accompanied by non-GI symptoms, and diarrhea was not a dominant symptom.[10] Contrary to the research in Mashhad, diarrhea was the most prevalent symptom among the patients when they visited the clinic in another study that was carried out in southern Iran (Ahvaz).[11]

In our geographic region (Mazandaran province, situated in the littoral of the Caspian Sea), no research has been conducted on clinical manifestations of celiac disease. Meta-analyses have shown that the risk of celiac disease and their presentations not only vary among different countries but also vary within countries. Therefore, the present study intended to determine the demographic, clinical, endoscopic, and pathological features of patients with celiac disease in Mazandaran province. Of course, the results of this research can help in determining the groups at risk of celiac disease and in earlier diagnosis.

## Materials and Methods

In this descriptive research, all the patients with celiac disease referred by adult and pediatric GI specialists in Sari and the other Counties in Mazandaran province to the National Center for Registration of Celiac Disease at the Mostafavian Clinic of Imam Khomeini Hospital in Sari during 2018-2021 were studied with respect to demographic features, clinical symptoms, serological and pathological findings of duodenal biopsies and endoscopic findings.

To this end, the patients visiting this clinic were interviewed in person, and their laboratory, endoscopic, and pathological records were examined, and the information was recorded in the questionnaires designed for this purpose.

The exclusion criteria included the unwillingness of the patients to disclose this information and the incompleteness of the records that had confirmed the celiac diagnosis. Accordingly, histological findings from the duodenal biopsy based on the Marsh classification indicating the presence of celiac disease were needed in addition to positive serologic testing (presence of one of the IgA and/or IgG antigliadin, anti-endomysial, or anti-tissue transglutaminase antibodies) for the diagnosis of celiac disease. The only exception was the patients with celiac disease who had dermatitis herpetiformis together with high titers of the antibodies associated with celiac disease and hence did not need intestinal biopsy.

Finally, the information obtained from the patients was analyzed by SPSS software (version 16) and using descriptive statistical tests (determination of frequency and mean) and the chi-square test.

## Results

Based on the results, 140 patients were entered into the research, of whom 44 (31.4%) were male, and 96 (68.6%) were female. The mean age of the patients at diagnosis was 27.13 ± 13.4 years. The mean age of the female patients was 30.4 ± 12.3 years, and the mean age of the male patients was 20.06 ± 13.2 years. This indicated that there was a statistically significant difference in mean age between the female and male participants ($P < 0.05$). The youngest and oldest patients at diagnosis were aged 2 and 60 years. 12 (8.6%) patients said they had a history of celiac disease in their first-degree relatives. The mean body mass index (BMI) values of the patients was 22.37 kg/m$^2$ (41.4%, 21.4%, and 26.4% of the patients had normal, lower than normal, and higher than normal BMI values, respectively). As for the type of nutrition when they were infants, 71.4% received only breast milk, 10.7% received only infant forma, and 5.7% had both breast milk and infant formula.

Regarding GI symptoms at diagnosis, 17 (12.1%) patients did not exhibit any GI symptoms, 43 (30.7%) complained of diarrhea at the time of diagnosis, 32 (22.8%) mentioned constipation, 67 (47.8%) patients complained of bloating along with changes in bowel movements, 66 (47.1%) patients felt abdominal pain besides other GI symptoms and three patients only experienced nausea when they visited the GI clinic. However, 31 (22.1%) patients suffered from nausea along with other GI symptoms, including diarrhea and bloating. 26 (18.5%) patients suffered from weight loss at the time of diagnosis, and 19 (13.5%) patients mentioned gastroesophageal reflux together with the other GI symptoms. It must be mentioned that as some of the patients presented with a number of GI symptoms, the overall frequency of the above symptoms exceeded 100%. Table 1 presents the frequencies of the GI symptoms.

Also, significant numbers of patients had concomitant non-gastrointestinal symptoms at the time of diagnosis,

**Table 1**. The frequencies of gastrointestinal symptoms at the time of diagnosis

| Clinical presentations | | No. (%) |
|---|---|---|
| Gastrointestinal | Diarrhea | 43 (30.7) |
| | Constipation | 32 (22.8) |
| | Bloating | 67 (47.8) |
| | Abdominal pain | 66 (47.1) |
| | Weight loss | 26 (18.5) |
| | Gastroesophageal reflux | 19 (13.5) |
| | No gastrointestinal symptoms | 17 (12.1) |

including rheumatologic, mucocutaneous, neurologic, gynecological, and renal problems (Table 2).

The most common non-GI symptoms were peripheral neuropathy, muscle weakness, headache, abnormal uterine bleeding, and aphthous stomatitis.

Also, based on the results of the present research, a number of diseases were accompanied by celiac disease. The most prevalent concomitant diseases were hypothyroidism in 16 (11.4%) patients, diabetes in 14 (10%), rheumatoid arthritis in 4 (3.5%) patients, hyperthyroidism in 2 (1.4%), Down syndrome in 3 (1.2%), and lymphoma in 1 (0.7%) patient. Among the above-mentioned diseases, two patients had concomitant diabetes and hypothyroidism accompanying celiac disease, two suffered from concomitant rheumatoid arthritis and hypothyroidism that accompanied celiac disease, and one experienced diabetes together with hypothyroidism and Down syndrome accompanying celiac disease.

Regarding laboratory tests, 42.3% of the patients had anemia (31.5% microcytic hypochromic anemia and 68.5% normocytic normochromic anemia). In addition, the levels of aminotransferase levels were normal in 77.3% of the patients, but they were 2-3 times higher than the normal level in 18% of the patients, 3-5 times higher than the normal level in 1.8% of the patients and more than five times higher than the normal level in 1.8% of the patients.

Also, regarding endoscopic examination, the most common findings were duodenal scalloping in 38 (37.25%) patients, duodenal atrophy in 15 (14.5%), hiatal hernia in 14 (13.7%), bulbar erosions in 11 (10.7%), gastric erythema in 11 (10.7%), bulbar nodularity in 1 (0.9%), duodenal ulcer in 2 (1.9%), evidence of gastroesophageal reflux in 7 (4.9%), duodenal erythema in 4 (3.6%) and gastric ulcer in 3 (2.9%) patients. In addition, 8 (7.8%) of the patients had a normal endoscopic appearance. Unfortunately, endoscopy reports of 38 patients were not available (Figure 1).

Moreover, based on the Marsh classification, the pathological findings were as follows: 43 (30.7%) patients were classified as Marsh IIIC, 36 (25.7%) as Marsh IIIB, 25 (17.8%) had Marsh IIIA, 18 (12.8%) had Marsh II and 18 (12.8%) were classified as Marsh I. It must be mentioned that no relationship was found between the severity of pathological involvement and the endoscopic findings or between the severity of pathological involvement and the clinical symptoms in the patients.

**Table 2.** The frequencies of non-gastrointestinal problems at the time of diagnosis

| Clinical presentations | | No. (%) |
|---|---|---|
| Rheumatologic | Arthritis | 5 (3.6) |
| | Arthralgia | 9 (6.4) |
| | Muscle cramps | 12 (8.6) |
| | Bone pain | 13 (9.2) |
| | Muscle weakness | 32 (22.8) |
| Mucocutaneous* | Aphthous stomatitis | 18 (12.8) |
| | Dermatitis herpetiformis | 15 (10.7) |
| | Itching | 5 (3.6) |
| | Psoriasis | 2 (1.4) |
| | Non-specific dermatitis | 2 (1.4) |
| | Hair loss | 3 (1.2) |
| | Lichen planus | 1 (0.7) |
| Neurologic | Headache | 23 (16.4) |
| | Ataxia | 1 (0.7) |
| | Seizures | 5 (3.5) |
| | Peripheral neuropathy | 34 (24.2) |
| | Depression | 9 (6.4) |
| Gynecological (only among females) | Abnormal uterine bleeding | 19 (19.7) |
| | Infertility | 4 (4) |
| | Primary amenorrhea | 2 (2) |
| Renal | Stone | 5 (3.6) |
| | Proteinuria | 1 (0.7) |

*Dermatologic diseases were diagnosed and confirmed by dermatologists.

## Discussion

This research was conducted on 140 patients with celiac disease who visited the Celiac Clinic of Mazandaran University of Medical Sciences whose demographic, clinical, endoscopic, and pathological features were investigated.

Most patients (68.8%) were women. This sex ratio is in concordance with the reports from others (79, 80). This may be somewhat due to the fact that women use healthcare services more frequently compared with men, and therefore, more female patients are diagnosed with celiac disease than men.[12,13]

The mean age of the patients at diagnosis was 27.13 years. However, the mean age among the female patients was 10 years older, and the oldest age at recognition was 60 years. Recent research indicates a rise in the age at which celiac disease becomes symptomatic and diagnosed. A study performed in Italy showed that 15% of the patients recently diagnosed with celiac disease were more than 60 years old.[14] Also, in another study from Finland, 2% of the patients with celiac disease were diagnosed between 52-74 years of age.[15]

Seventy-one percent of the patients in the present

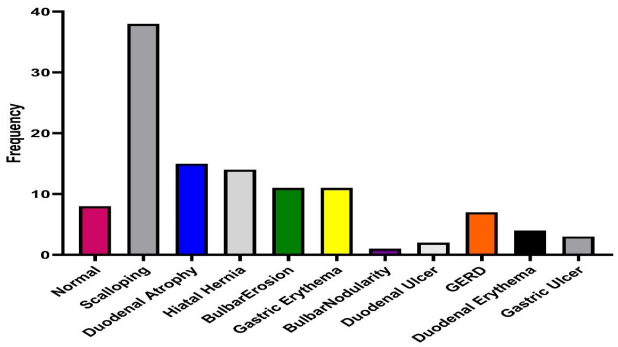


**Figure 1.** The frequencies of endoscopic findings in the patients with celiac disease

research were breastfed during their first two years of life. In the past, it was believed that long-term breastfeeding of children might reduce their chances of developing celiac disease in the future. This opinion was formed during the 1980s and 1990s when the incidence of celiac disease rose sharply in Sweden, where newborns received more food or infant formula and less breast milk.[16] However, later large-scale research projects did not support this idea.[17,18]

Regarding clinical symptoms, although celiac disease is mainly considered an intestinal disease, 12% of the patients did not exhibit any GI symptoms. Among the patients whose primary manifestations of the disease were the GI symptoms, bloating was the most common complaint (47.8%) followed by abdominal pain (47.1%), diarrhea (30.7%), constipation (22.8%) and nausea (22.1%). Of course, most patients presented with many simultaneous symptoms, and therefore, the overall percentage of the symptoms exceeded 100%. Recent studies indicate an increasing shift from GI symptoms to atypical symptoms in patients with celiac disease so that many adults diagnosed with this disease rarely complain of obvious diarrhea and/or metabolic disorders or malnutrition.[19,20] This points out the need for paying attention to the atypical symptoms of celiac disease when patients visit GI clinics.

The most frequent non-GI symptoms were peripheral neuropathy in 24.2% of the patients, muscle weakness in 22.8%, menstrual disorders in 19.7% of the female patients, headache in 14.4%, and aphthous stomatitis in 12.8% of the patients. Of course, aphthous stomatitis can be considered among the GI symptoms, but it was put among the cutaneous-mucosal symptoms of celiac disease in the present research. The frequency of these symptoms also emphasizes that it is necessary to pay attention to the atypical symptoms of this disease.

Based on previous research, there is a close relationship between celiac disease and its neurological manifestations. In a study by Chin et al on the neurological manifestations of celiac disease, peripheral neuropathy was reported in 50% of the patients, and this symptom was, in some cases, observed even before the other manifestations of celiac disease.[21] The cause of this neuropathy can be a deficiency of vitamins B2, B3, B6, and B12. The other important neurological manifestations of celiac disease are depression and seizures.[22,23] In the present research, 6.4% of the patients with celiac disease who were diagnosed with depression received psychiatric treatment, and 3.5% of the patients with celiac disease had a history of seizures. The causes of these symptoms in patients with celiac disease are not very clear.

In our study, rheumatologic manifestations included muscle weakness in 22.8% of the patients, bone pain in 9.2%, and arthralgia in 6.4% of the patients. In addition, 3.6% of the patients had arthritis when they were diagnosed with this disease, which is because they simultaneously suffered from rheumatoid arthritis. Although celiac disease is accompanied by rheumatologic manifestations, especially rheumatoid arthritis, it is not clear yet whether there is a causal relationship between these two diseases.[24,25]

In 2019, Abenavoli et al conducted a review study on the cutaneous manifestations of celiac disease. Based on the results of this research, including more than 7000 articles, a strong relationship was found between celiac disease and only dermatitis herpetiformis or psoriasis. Other reported cutaneous manifestations were not based on the results of randomized clinical trials and were mainly according to case reports. These manifestations included urticaria, aphthous stomatitis, rosacea, cutaneous malignancies, and vitiligo.[26] Based on the results of our research, the most common cutaneous-mucosal manifestations accompanying celiac disease were aphthous stomatitis followed by dermatitis herpetiformis, itching without a rash, and psoriasis. As for the pathogenesis of these symptoms, it seems that improper function of the small intestine acting as a barrier prevented entry of antigens, caused special antigens to enter the body, and stimulated immunological responses involved in the appearance of cutaneous manifestations in patients with celiac disease.[27]

Based on the results of the present research, concomitant diseases accompanying celiac disease were hypothyroidism, followed by diabetes, rheumatoid arthritis, and Down syndrome. Previous research indicated that patients with celiac disease faced a greater risk of developing autoimmune thyroid diseases, including hypothyroidism. In addition, a very close relationship was observed between celiac disease and type 1 diabetes and autoimmune polyglandular syndrome type 3.[28] These findings are in concordance with the results of the present research.

Furthermore, based on the results of previous studies, the risk of developing celiac disease in patients with Down syndrome is 20 times greater compared to the healthy population.[29] In our research, also, Down syndrome was the fourth most common condition associated with celiac disease, and three (2.1%) of the patients had Down syndrome. It should also be mentioned that the two above-mentioned patients with primary amenorrhea had Down syndrome. Therefore, the pathogenesis of amenorrhea might have been related to this genetic syndrome, not celiac disease itself.

According to the laboratory findings in the present study, 42.3% of the patients had anemia when they first visited the Celiac Clinic (31.5% had iron deficiency anemia and 68.5% normocytic normochromic anemia). Unfortunately, we did not have any information on folate and vitamin B12 levels in these patients to make a good interpretation of anemia in patients with celiac disease.

Based on research carried out by Martín-Masot et al on anemia in patients with celiac disease, anemia was a multifactorial complication in these patients. But in most cases, it was caused by iron, folic acid and/or vitamin B12 malabsorption, and also, in some cases, it was caused by GI bleeding resulting from the diseases, including

inflammatory bowel diseases associated with celiac diseases.[30]

Another important finding in the present research was that 22.7% of the patients with celiac disease had higher than normal levels of aminotransferases. In a study by Castillo et al in 2015, about 40% of the 463 patients with celiac disease had elevated levels of transferases, but in most patients, the levels of aminotransferases returned to normal soon after they started a gluten-free diet.[31] However, the related pathogenesis is not completely clear yet.

In the present study, the most frequent endoscopic finding was scalloping of the duodenal mucosal folds (37.2% of the patients). The other frequent endoscopic appearances of duodenal mucosa were atrophy of duodenal folds in 15 patients (14.5%), bulbar erosions in 11 (10.7%), and gastric erythema in 11 (10.7%) patients. Although celiac disease can have various endoscopic appearances, the endoscopic sensitivity for the diagnosis of this disease varies from 59% to 94%, and the specificity of these appearances for celiac disease is in the range of 92%-100%. In fact, these endoscopic findings may also be observed in other conditions, including giardiasis, autoimmune enteropathy, and HIV infection.[32] Therefore, in addition to endoscopic appearance, histological findings play an important role in diagnosing celiac disease.

In our study, histologic evaluation showed that more than 86% of the patients were in advanced stages of Marsh classification (Marsh II or III), with Marsh III being the dominant type. This finding may indicate delays in the diagnosis of celiac disease, caused by both the physicians and the patients for delay in seeking medical visits. Although Marsh II and III are not sufficient for making a definitive diagnosis of celiac disease, they considerably help in its diagnosis.[33] It is noteworthy that, in the present study, no significant relationship was found between the endoscopic findings and the extent of the histologic involvement. This lack of a relationship has also been reported in other studies.[34]

The present study has some limitations. First of all, most of our patients had been diagnosed with celiac disease many years ago, and therefore, they probably would make mistakes in remembering their initial symptoms. Another limitation resulting from this gap was that a percentage of the patients had lost the results of their endoscopic examination performed at the beginning of the diagnosis. However, the strong point of our study is that it is the first research on epidemiological, clinical, endoscopic, and pathological features of celiac disease in the southern littoral area of the Caspian Sea.

In conclusion, the estimated prevalence of celiac disease in the north of Iran is 1%.[35] Celiac disease can have atypical GI or even non-GI manifestations, and also, regarding the advanced stages of Marsh classification in most of our patients, it seems that the screening tests for celiac disease must be included in the routine screening strategies of GI clinics and also, be taken into account in other sub-specialty clinics such as rheumatology, dermatology, neurology, gynecology, and psychiatry.

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## Competing Interests

The authors declare no conflict of interest related to this work.

## Ethical Approval

This project was approved by the Ethical Committee of Mazandaran University of Medical Sciences.

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Original Article

# Do Serological Tests Eliminate the Need for Endoscopic Biopsy for the Diagnosis of Symptomatic Patients with Celiac Disease? A Retrospective Study with Review of Literature

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**Abstract**

**Background:** Celiac disease is one of the most common genetic allergies worldwide. The prevalence of celiac disease in Iran is similar to or even higher than the global prevalence. Celiac disease is a chronic inflammatory disease that affects the small intestine. Affected patients are allergic to gluten protein that exists in some grains, such as wheat and barley.

**Methods:** Serological endomysial IgA antibody (EMA-AB) and tissue transglutaminase IgA antibody (TTG-IgA) tests were performed on 114 patients aged the ages of 0–18 years with histopathological findings of celiac disease. The results of these tests were compared to the results of the histopathological study of the duodenal biopsy.

**Results:** Based on the receiver operating characteristic (ROC) curve and a calculation of the TTG-IgA test's sensitivity and specificity, the best diagnostic limit for the TTG-IgA test is 144, which has the best sensitivity and specificity. At this value (cut-off), the test's sensitivity was 62%, and the specificity was 93.7%. For the endomysial test, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 80%, 93%, 90%, and 75%, respectively.

**Conclusion:** The diagnostic accuracy of the endomysial test is better than that of the TTG-IgA test in general for diagnosing patients with celiac disease. In the TTG-IgA test, false-positive cases are high due to a cut-off of 20, reducing the test's specificity. In these false-positive cases, the endomysial test helps in better diagnosis.

**Keywords:** Celiac disease, EMA-AB, TTG-IgA

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## Introduction

Celiac disease is a chronic inflammatory disease that affects the small intestine. The affected patients are sensitive to a protein called gluten, found in some cereals, such as wheat, barley, rye, etc. It is one of the most common food allergies worldwide, affecting approximately 1% of the world's population. Most cases of celiac disease are not diagnosed.[1-4]

In celiac disease, the gold standard for diagnosis is the histopathological study of the sample obtained from endoscopy and biopsy of the early part of the small intestine, usually the duodenum.[5,6] Two samples are taken from each area. The best locations are the bulb and the second part of the duodenum.

Microscopic findings show a range of changes in the epithelial surface and structure of the intestinal mucosa.[7,8] So, celiac disease is not the only disease with microscopic signs. Other diseases may exhibit the same histopathological signs. Therefore, in order to diagnose celiac, we often need the clinical signs, laboratory results, genetic tests, histopathological findings, and finally, the patient's response to a gluten-free diet to be consistent as pieces of a puzzle.[9] As was already said, the gold standards for diagnosing celiac disease are an endoscopy and a biopsy of the small intestine.

However, endoscopy is an expensive and invasive examination and requires general anesthesia in children, with associated risks. In addition, screening is recommended in susceptible populations, such as first-degree family members with celiac disease and those with type I diabetes and autoimmune thyroid disease. As a result, effective screening tests that can identify suitable endoscopic candidates are needed. The European Society of Gastroenterology, Hepatology, and Pediatric Nutrition has also remarked that serological tests can diagnose celiac disease without a biopsy.[10,11] Therefore, patients with celiac disease can avoid the risks of this invasive test, the cost of general anesthesia, and other costs by using serological tests and doing less endoscopy and sampling.[12,13]

By looking at the antibodies to endomysial IgA antibody (EMA-AB) and tissue transglutaminase IgA antibody (TTG-IgA) in the serum of people who might have celiac

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disease, we hope to compare the results of small bowel biopsy, which is the gold standard for diagnosing celiac disease, with the results of these tests and figure out how sensitive and specific they are.

The role of EMA and TTG-IgA in diagnosing celiac disease is well established in previous studies.[14,15] The goal of this study was to determine whether the positive results of these two tests will be able to correctly diagnose the disease in people who are likely to have celiac disease based on clinical findings and eliminate the need for endoscopy. We calculate the sensitivity and specificity of this test in quantities of test results and, if possible, determine which cut-off of the test results is possible to diagnose celiac correctly. We also want to determine if there is a link between the amount of antibody titer in the TTG-AB test and the amount of mucosal damage in the biopsy.

## Materials and Methods

### *Patient Selection*

This study was a retrospective cross-sectional study that compared the diagnostic power of the TTG test with the ELISA method and the results of the EMA test with the indirect immunofluorescent method in the diagnosis of celiac disease. Children aged 0 to 18 years who had signs of celiac disease and were referred to Nemazee hospital and Motahari clinic in Shiraz were included in the study.

### *Inclusion Criteria*

Inclusion criteria were typical clinical signs and symptoms of celiac disease, including diarrhea, weight loss, fatigue, abdominal pain, nausea, and vomiting. Due to changes in the expression of antibodies in people treated for celiac, patients should not have been on a gluten-free diet before.

### *Exclusion Criteria*

Cases whose microscopic examination of the biopsy specimen was suspicious or undetectable, and it was not possible to rule out or confirm celiac disease based on pathology, were excluded from the study. If the biopsy result was mild and at the level of Marsh 1 and 2, considering that similar pathology in these people may be found in other diseases and conditions, these patients were also excluded. IgA-deficient patients were also excluded from the study due to the possibility of negative tests.

### *Sampling Method*

Patients were visited by a pediatric gastroenterologist, and endoscopy was requested due to the signs and symptoms of celiac disease, along with elevated or normal TTG-IgA levels. A sample was taken from the patients during a routine visit to the endoscopy room. The amount of TTG-IgA and EMA-AB in the patient's serum was measured from this sample. The patient's form, including name, age, TTG-IgA level, and signs and symptoms of patients referred by a gastroenterologist, was completed. Test serum should be clear and non-hemolyzed.

### *Description of the Experiment*

We used the indirect immunofluorescence tests from the EUROIMMUN kit (Germany) to perform an indirect immunofluorescence test to find IgA antibodies against endomysial tissue. Positive and negative controls are needed to ensure that the test steps are performed correctly and that the mixtures and solutions used in the test are safe. For positive control, we used a mixture containing human antibodies against endomysial tissue, and for the negative control, we used a mixture without these antibodies. When adding the patient's serum to the slides, these mixtures should be in contact with the monkey's esophageal tissue instead of the patient's serum. Both mixes were provided by the kit manufacturer. Fluorescent-labeled antibodies find endomysial antibodies that bind to the endomysium tissue of smooth muscle in the sample to make a specific fluorescence pattern. Based on the fluorescence intensity seen and the kit brochure, the test result can be announced relatively quantitatively. The level of staining was graded (strong reaction) using a scale ranging from zero (no reaction) to three (strong reaction) (i.e., + 1 (weak reaction), + 2 (moderate reaction)).

TTG-IgA was measured by AESKULISA ELISA kit (Germany). Human recombinant tissue transglutaminase is bound to microwells. The determination is based on an indirect enzyme-linked immune reaction. Specific antibodies in the patient's sample bind to the antigen coated on the surface of the reaction wells. After incubation, a washing step removes unbound and unspecifically bound serum or plasma components. Subsequently, the added enzyme conjugate binds to the immobilized antibody-antigen complexes. After incubation, a second washing step removes unbound enzyme conjugate. After adding the substrate solution, the bound enzyme conjugate hydrolyzes the substrate, forming a blue-colored product. The addition of an acid stops the reaction, generating a yellow end-product. The yellow color's intensity correlates with the antibody-antigen-complex concentration and can be measured photometrically at 450 nm. The reference amount announced by kit:

- Negative: Less than 20 u/mL
- Positive: Equal or more than 20 u/mL

### *Pathological Examination*

All patients' slides were taken out of the file, evaluated by a pathologist, and re-graded using the Marsh criteria. Histological findings in this study define celiac disease. The Marsh type 3 lesion has three subgroups: 3a mild villous atrophy and pathological increase of intraepithelial lymphocytes (IEL); 3b moderate villous atrophy and pathological increase of IEL; 3c total villous atrophy and pathological increase of IEL.

### *Statistical Analysis*

The SPSS software version 23 was used to analyze the

data, and the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of EMA-AB and TTG-IgA were calculated using the receiver operating characteristic (ROC) curve.

## Results

The study population included 114 children aged 0 to 18 years with symptoms of celiac disease who were referred to Nemazee hospital and Motahari clinic in Shiraz. The mean age of the patients was 8.8 years, and the standard deviation was 6.7. The average age of female patients was 9.2 years with a standard deviation of 7.6, and the mean age of male patients was 8.3 with a standard deviation of 7.6. A total of 49 (43%) children had histopathological changes of celiac disease in the biopsy, and 65 (57%) did not have such changes in duodenal histology. In terms of sex, 49 (43%) were boys, and 65 (57%) were girls. In the celiac group, the ratio of girls to boys was 1.8 (32 girls and 17 boys), and in patients without the disease, this ratio was 1.06 (33 girls and 32 boys).

### *Histopathological Findings*

Among patients with celiac disease, 15 (13%) had Marsh 3a, 26 (23%) had Marsh 3b, and 8 (7%) had Marsh 3c. Of these patients, 37 showed two microscopic changes in the bulb and D2. Regarding this group of patients, where there is a difference between the degree of celiac disease in the two parts, D1 and D2, we diagnosed based on the higher grade of the disease.

### *TTG-IgA Levels*

Based on the information in the kit, values of less than 20 were normal, and those of 20 or above were positive. In this study, the range of TTG-IgA obtained was 0-436, with an average of 60.

In our study, the number of false-positive TTG-IgA cases (values greater than 20 without pathology in the duodenum) was 48 (42.1%). Of these 48 cases, four patients had an EMA-AB test (+1), and the number of false-negative cases (values less than 20 with pathology in the duodenum) was five. In all these false negatives, the amount of TTG-IgA was less than 17. Of these five cases, two patients had a positive EMA-AB test (+1).

The one-way analysis of variance (*P* value: 0.05) showed that increasing the amount of TTG-IgA from normal to celiac is significantly related. However, there was no clear link between the levels of antibodies and the severity of the disease in the Marsh 3a, 3b, and 3c celiac groups.

Quantitative values for each level of TTG values are given in Table 1. For each level of identification of TTG values and sensitivity and specificity, the number of PPV and NPV was calculated. According to this curve and also Table 1 of sensitivity and specificity, the best diagnostic limit for the TTG-IgA test is 144, in which there is the best specificity against the best sensitivity. At this value (cut-off), the sensitivity of the test was 62%, and the specificity of the test was 93.7%.

**Table 1.** Quantitative diagnostic values for each level of TTG cut-off

| TTG Result | Sensitivity | Specificity | Positive predictive value | Negative predictive value |
|---|---|---|---|---|
| 6 | 100.00 | 17.19 | 48.5 | 100.0 |
| 17 | 90.00 | 23.44 | 47.9 | 75.0 |
| 41 | 84.00 | 56.25 | 60.0 | 81.8 |
| 45 | 80.00 | 57.81 | 59.7 | 78.7 |
| 60 | 74.00 | 70.31 | 66.1 | 77.6 |
| 85 | 66.00 | 79.69 | 71.7 | 75.0 |
| 100 | 64.00 | 85.94 | 78.0 | 75.3 |
| 144 | 63.00 | 93.7 | 88.6 | 75.9 |
| 200 | 50.00 | 96.87 | 92.6 | 71.3 |
| 259 | 46.00 | 100.00 | 100.0 | 70.3 |

### *EMA-AB Values*

According to the information in the kit brochure, the positive result of the kit is shown as the presence of a special fluorescence design in the form of a beehive under the texture of the mucosa layer, and the mucosa layer, which lacks fluorescence, is black (Figure 1).

For the endomysial test, sensitivity, specificity, PPV, and NPV were 80%, 93%, 90%, and 75%, respectively (Table 2). In an indirect immunofluorescence study, out of 65 people without celiac disease, four had a false-positive result (+1), but no higher amount of fluorescent was seen in these patients. Two of these patients were female, and their TTG test results were 295 and 139. The results of TTG for the other two male patients were 215 and 73. False-negative results were seen in nine patients. Among these people, six had a positive result for the TTG test, and among these, only two cases had TTG values higher than the cut-off value of 144 and TTG values higher than 340.

Among those with severe disease (3a), three cases had a negative indirect immunofluorescence test, and nine, two, and one cases showed +1, +2, and +3 results. Among those with the 3b stage of celiac disease, five cases had a negative result, two cases showed a +1 result, 16 out of the 26 patients with grade 3b had a positive result (+2), and three showed a +3 result. Among those with grade 3a, one case showed a negative result in indirect immunofluorescence. The result of +1 was not seen; one person had a result of +2, and six patients showed a +3 result.

### *The diagnostic accuracy of both EMA and TTG tests together in the diagnosis of celiac disease*

In all patients, if we consider the EMA and TTG IgA cut-off test 144, patients with either an EMA-AB or TTG-AB positive result are considered to have celiac disease, and those with both tests or one test negative are considered to have celiac disease, the sensitivity will be 93.8%, specificity 93.8%, PPV 93.8%, and NPV 93.8% (Table 3).

## Discussion

Celiac disease is a distinct gastrointestinal disorder

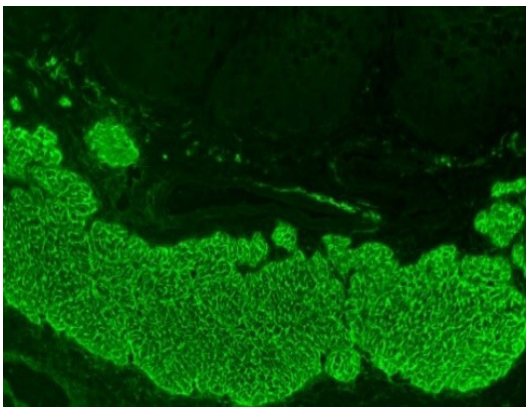

**Figure 1.** Honeycomb-like fluorescence pattern for EMA-IgA along muscolaris mucosa of monkey esophagus

because, apart from its clinical and pathophysiological characteristics, sensitive and specific serological markers allow its diagnosis. A significant milestone in the history of celiac disease was the discovery of the EMA serological biomarker for the disease in 1980. In 1997, Dieterich and colleagues identified the transglutaminase 2 autoantibody that targets endomysial antibodies. Then, autoantibodies to tissue transglutaminase were introduced by ELISA with high sensitivity and specificity, and as a result, celiac disease was recognized as a common global disease.[16]

This study was performed on children aged 0 to 18 years, suspected of having celiac disease, who were referred to the endoscopy department of Motahari Clinic by a pediatric gastroenterologist. These people were clinically suspected of having celiac disease.

Regarding the EMA test, the sensitivity was 80%, the specificity was 93%, and a significant relationship was found between the severity of the disease based on the pathology and the amount of fluorescent observed in the test. Also, regarding TTG-IgA, according to the ROC curve, for calculating the sensitivity and specificity, the best diagnostic limit for the TTG-IgA test is 144, in which there is the best specificity against the best sensitivity. At this value (cut-off), the test's sensitivity was 62%, and the specificity of the test was 93.7%.

Although the TTG test is widely used by laboratories as a first-line due to its high sensitivity and repeatability, false-positive TTG tests are usually seen in low values of the titer of this antibody and in titrations up to about twice the diagnostic cut-off. Therefore, due to false positive results that are relatively common due to the high specificity of reverse immunofluorescence for the detection of EMA antibodies, the EMA test for patients with suspected celiac disease is often performed as a confirmatory test before biopsy in individuals who have a TTG-positive test.[17] The sensitivity and specificity of the TTG test in the diagnosis of celiac disease when the EMA test is also positive is about 100%.[18] Reverse immunofluorescence detection causes problems for EMA antibody observation due to different levels of observer skill, interference with anti-nuclear or anti-smooth muscle antibodies, as well as different standards from laboratory to laboratory in interpreting

**Table 2.** Sensitivity, specificity, positive predictive value, and negative predictive value for IgA endomysial test

| Test | Sensitivity | Specificity | Positive predictive value | Negative predictive value |
|---|---|---|---|---|
| EMA-AB | %80 | 93.75% | 90.9% | 75.7% |

**Table 3.** Sensitivity, specificity, positive predictive value, and negative predictive value for EMA- IgA and TTG-AB

| Test | Sensitivity | Specificity | Positive predictive value | Negative predictive value |
|---|---|---|---|---|
| EMA-AB and TTG-AB | %93.8 | 93.8% | 93.8% | 93.8% |

EMA testing. Also, there are ethical questions about how the endomysial tissue bed from the monkey's esophagus is prepared.[15]

In our study, with increasing disease severity, the mean Marsh as well as the upper and lower limits of the TTG test result, increase to grade 3b in proportion to the severity of the disease, but these values decrease in more severe diseases (Marsh 3c).

TTG test results in other studies[19-25] show different sensitivity and specificity values. Table 4 shows that even though the PPV of the TTG test varies and is sometimes low (between 70% and 99%), In our study, the sensitivity and specificity stood at 63% and 93.7%, respectively. The specificity is close to one, but the inconsistency between the sensitivities might be related to the difference in the volume of samples, the sensitivity of kits, or the difference in the stage of the disease.

De Chaisemartin et al in 2015[26] assessed 100 patients with celiac disease who were under treatment and showed that endomysial testing was best associated with villi atrophy and Marsh grading compared with TTG-IgA and TTG-IgG and a few lesser-known serological markers. In this study, the cut-off was 17.9, with a sensitivity of 53.1 and a specificity of 96.2.

Ganji and colleagues conducted a study in northeast Iran and found a linear relationship between increased TTG-AB titers and disease severity. The highest mean TTG-AB titer was seen among patients with Marsh 3. Also, based on the ROC curve, the TTG-AB test at a cut-off of 140 had a sensitivity of 83% and a specificity of 56%.[27]

In another study by Donaldson et al, the TTG-AB test was more than 98% specific for the diagnosis of celiac disease, and the EMA test with a titer above 1:1280 was more than 98% specific. They showed that higher TTG-AB values, as well as high EMA titers, were more likely to be associated with atrophy of the gastrointestinal villi.[28]

The results of the EMA test in other studies[29-34] show different sensitivity values ranging from 64% to 100%. The specificity of this test also varies from 93% to 100% (Table 5). In our study, the sensitivity and specificity stood at 80% and 93.7%. The specificity is close to one, but the inconsistency between the sensitivities might be related to the difference in the volume of samples, the sensitivity of kits, or the difference in the stage of the disease.

Based on the positive results of the EMA test and the

**Table 4.** TTG test results in other studies

| Study | TTG | | | | | |
|---|---|---|---|---|---|---|
| | Test cut-off | Year | sensitivity | specificity | Positive predictive value | Negative predictive value |
| Abdollahi et al[19] | Not stated | 2008 | 28% | 95% | - | - |
| Alessio et al[20] | 100 U/mL | 2012 | 98% | 97% | 97.9% | 98% |
| Lodhi et al [21] | 25 U/mL | 2017 | 91% | 29% | 76% | 57% |
| Taneja et al[22] | 84.6 U/mL | 2021 | 91.7% | 68.4% | 94.2% | 50% |
| Bansal et al[23] | 70 U/mL | 2018 | 83.9% | 56.1% | 86.8 | 50.2 |
| Tortora et al[24] | 62 U/mL | 2014 | 69% | 100% | 100% | 31% |
| Meena et al[25] | 115 U/mL | 2019 | 76% | 100% | 100% | 17% |
| Our study | 144 U/mL | 2022 | 63% | 93.7% | 88.6% | 75.9% |

**Table 5**. The results of the EMA test in other studies

| Study | EMA | | | |
|---|---|---|---|---|
| | Sensitivity | Specificity | Positive predictive value | Negative predictive value |
| Abdollahi et al[19] | 64% | 96% | - | - |
| Carroccio et al[29] | 100% | 100% | 100% | 100% |
| Baudon et al[30] | 90% | 100% | 100% | 97% |
| Tesei et al[31] | 86% | 100% | 100% | 83% |
| Wolters et al[32] | 92% | 90% | - | - |
| Dickey et al[33] | 80.8% | 96.6% | - | - |
| Dahele et al[34] | 86.8% | 100% | - | - |
| Our study | 80% | 93% | 90% | 86% |

severity of celiac disease, none of the people without celiac disease show fluorescence higher than + 2, and also, among people whose disease was grade 3a, 64% (9 out of 14 people) had a test of + 1. In cases with grade b3, this test was + 2 positive in 61% of patients (16 out of 26 people), and 75% of patients with severe disease (6 out of 8) showed + 3 positive results. So, in most cases, the severity of a positive test is related to how bad the disease is.

Serological screening for celiac disease is usually based on anti-TTG-IgA.[35,36] These antibodies are the most sensitive for celiac disease.[22] On the other hand, EmA-IgA is used to confirm a positive TTG test because it is more specific.[23]

False positives for TTG have been observed in patients with inflammatory bowel disease, food allergies, irritable bowel syndrome, anemia, giardiasis, other intestinal infections, and autoimmune disorders.[24-26] These false positives are not always addressable, as EMA test results are only reliable in laboratories with skilled personnel with experience in immunofluorescence assays. Commercial ELISA assays for TTG may vary depending on antigen quality, and there are differences between different kits in cut-off values. False negatives can be seen in celiac serological tests in children under two years of age, use of a gluten-free diet, IgA deficiency, use of corticosteroids, and laboratory error.[27,28]

The diagnostic accuracy of both the EMA and TTG tests together in the diagnosis of celiac disease increases in comparison with each test alone.[29] As seen in our results, the sensitivity and specificity increased. However, it does not eliminate the need for endoscopy, and patients with positive serology will still require a confirmatory endoscopy.

The current study has limitations, including a small sample size, an incomplete examination of patients' clinical symptoms, and the exclusion of asymptomatic patients. But there were some strengths, like looking at the samples' pathology, doing TTG and endomysial serological tests together, figuring out the cut-off based on the samples' pathology, and having patients of different ages, from 0 to 18 years.

## Conclusion

According to the results, the sensitivity and specificity of the endomysial test are better than the TTG-IgA test to identify those individuals who require an intestinal biopsy examination to diagnose CD while avoiding unnecessary biopsy examinations in those who do not have the condition. In the TTG-AB test, false-positive cases are higher. In these cases, the endomysial test helps better diagnose, especially when the TTG-IgA is between 18 and 100, which includes false positives of TTG-IgA. It is better to check the endomysial antibody. Also, in cases where we are clinically suspected of having celiac disease but the TTG-IgA level is negative, checking the endomysial test has a high PPV. Finally, according to the obtained results, checking both of these tests for patients with suspected celiac disease will increase the diagnostic accuracy of serological tests to diagnose these patients. However, it does not eliminate the need for endoscopy, and patients with positive serology will still require a confirmatory endoscopy.

### Authors' Contribution

**Conceptualization:** Mohammad Hossein Anbardar.
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**Supervision:** Mohammad Hossein Anbardar.
**Validation:** Sahand Mohammadzadeh.
**Visualization:** Sahand Mohammadzadeh.
**Writing–original draft:** Sahand Mohammadzadeh.
**Writing–review & editing:** Sahand Mohammadzadeh.

## Competing Interests
The authors declare no conflict of interest related to this work.

## Data Availability Statement
All data generated or analyzed during this study are included in this published article.

## Ethical Approval
The research was conducted in accordance with the World Medical Association Declaration of Helsinki and approved by the Ethics Committee of Shiraz University of Medical Sciences (No. IR.SUMS.MED.REC.1398.628). Additionally, informed consent was obtained from the patients.

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Original Article

# Diabetic Markers, Five Years after Bariatric Surgery

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**Abstract**

**Background:** Bariatric surgery delivers substantial weight loss for obese patients with comorbidities like diabetes mellitus. We aimed to investigate the impacts of bariatric surgery on diabetic markers after 5 years of follow-up.

**Methods:** This is a retrospective study on patients with diabetes and a history of bariatric surgery between 2016-2017. The diabetic markers before and 5 years following surgery, including a lipid profile, glucose level, and the required antidiabetic medications, were evaluated.

**Results:** 34 consecutive patients were included, 30 (88.2%) women, with a mean age of 52.71 ± 8.53 years. The majority (65%) of surgeries were Roux-en-Y gastric bypass (RYGB), and the remaining were one anastomosis gastric bypass (OAGB) and sleeve gastrectomy (SG). The serum levels of diabetic markers reduced during follow-up ($P=0.001$), except for high-density lipoprotein levels and serum total cholesterol, which increased ($P=0.011$, $P=0.838$). Low-density lipoprotein levels reduced, but it was insignificant ($P=0.194$). Surgery types had affected the changes of diabetic markers ($P>0.05$). Demand for oral medication was reduced significantly, but insulin injection reduction was not significant ($P=0.006$ and $P=0.099$, respectively).

**Conclusion:** Our study showed favorable bariatric surgery results on patients with diabetes in long-term follow-up. However, dyslipidemia is still a concern.

**Keywords:** Bariatric surgery, Diabetes mellitus, Morbid obesity, R-Y gastric bypass, Sleeve gastrectomy, One anastomosis single bypass

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## Introduction

Type 2 diabetes mellitus (T2DM) is associated with obesity. While more than 60% of patients with diabetes are obese, weight loss is attractive.[1,2] Additionally, T2DM is heterogeneous and progressive,[3] and often, a combination of two or more interventions is needed for controlling diabetes.[4] Intensifying treatment could induce weight gain. So, managing obese diabetic patients requires careful consideration.[5,6] Also, dietary regimens alone cannot reduce long-term weight loss due to the low adherence of patients to modified lifestyle efforts during the time.[7,8] This highlights the role of biological and clinical manipulation of the gastrointestinal tract in treating T2DM.[9,10]

Bariatric surgery, also called metabolic surgery, leads to diabetic remission in several studies by increasing insulin sensitivity in the pancreas, favorable glucose levels, and weight reduction.[11-15] Also, bariatric surgeries reduce other obesity-related comorbidities such as dyslipidemia, cardiovascular disease, and cancers.[16,17] T2DM remission rate varies in surgery-submitted obese patients (25% to 75%) versus medical management (0-6%).[11] It seems that remission and disease-free rates in patients with diabetes rely on surgery type and glycemic index.[18] Hutter and colleagues, in a study on 28 616 patients with diabetes, demonstrated that Roux-en-Y gastric bypass (RYGB) led to a higher remission rate than sleeve gastrectomy (SG) (83% vs 55%) in one-year follow-up, respectively.[19]

Despite evidence of the role of metabolic surgery in diabetic remission, associated baseline characteristics and diabetic markers affecting diabetic remission are still under debate. At least 35-50% of recovered patients experience a relapse in long-term follow-up.[20] A recent study demonstrated that after 10 years of follow-up, 53% of patients with a history of RYGB experienced a relapse of T2DM.[21] Furthermore, the relapse definition must still be fully elucidated.[22] However, poorer diabetes control before surgery, longer disease duration, and insulin injection before surgery can compromise long-term remission.[20] The role of weight regain several years after bariatric surgery is uncertain.[23] It should also be noted that following bariatric surgery, the relapse period increases in long-term observation, especially in RYGB.[24,25]

Inconsistent results of previous studies are associated with a lack of long-term follow-up, high population study, and a variety of remitting definitions that influenced the results of bariatric surgery. In this long-term observational

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study, we aimed to evaluate changes in diabetic markers, antidiabetic agents' prescription, and diabetic remission rate following bariatric surgeries.

## Materials and Methods

### *Study Design and Participants*

This retrospective observational study was conducted on patients with diabetes aged > 18 years who underwent bariatric surgery from March 2016 to July 2017 in Imam Reza hospital, a tertiary academic hospital affiliated with Mashhad University of Medical Sciences, Mashhad, Iran. Patients were divided into three groups by well-experienced bariatric surgeon who would perform RYGB, one anastomosis gastric bypass (OAGB), and SG surgery due to the amount of required weight reduction, anesthesia complications, and comorbidities. Patients who needed consensus to participate in the study or lack of medical data were excluded.

The data collected from the patients' medical records, including age, sex, surgery type, height, weight, body mass index (BMI), waist circumference (WC), abdominal circumference (BC), lipid profile (e.g., triglyceride [TG], low-density lipid [LDL], high-density lipid [HDL]), total cholesterols (TC), fasting blood sugar (FBS), HbA1C, insulin resistance, oral medications, and insulin regimen before and 5 years after bariatric surgery.

Diabetic partial remission was defined as FBS between 100-125mg/dL and HBA1C < 6.5%. Diabetic remission was defined as HBA1C < 6.0 and FBS < 100 mg/dL without ongoing medical therapy.[26] Insulin resistance was calculated by the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR).[26]

### *Statistical Analysis*

Categorical variables were expressed as frequencies and percentages, and continuous variables were presented as mean ± standard deviation. Normal distribution was evaluated using Kolmogorov-Smirnov. Categorical data were compared by chi-square test or Fisher's exact test, as appropriate. The quantitative data were compared using the Student's t-test or Mann-Whitney test, as appropriate. For comparing qualitative variables between more than two groups, one-way analysis variance (ANOVA) was used. A *P* value less than 0.05 was considered statistically significant. All data were analyzed using SPSS software version 26.

## Results

This study was conducted on 34 patients (88% female) with a mean age of 52.71 ± 8.53 years. The mean abdominal circumference was 109.29 ± 10.44 cm and WC was 115 ± 13.03 cm, respectively. BMI, lipid, glycemic profile, IR, and HOMA-IR were evaluated before and 5 years after surgery (Figure 1). Serum total cholesterol and LDL levels had not changed significantly during the follow-up. Overall, 22 (64%) patients had RYGB, 9 (27%) had OAGB, and 3 (9%) had SG. Additionally, no significant differences were observed in metabolic variables between the three types of surgeries. However, lower LDL reduction and increasing cholesterol serum levels were found in the RYGB group (Table 1).

Of our 34 patients, 24 patients (71%) (14 RYGB; 7 OAGB; and 3 SG) had experienced remission (50% complete remission, 21% partial remission) during 5 years of follow-up. We found no predictive factors associated with diabetic remission (Table 2). Also, we found that BMI changes in the remitted group were slightly higher versus the non-remitted group, but it was insignificant (-16.07 ± 6.22 vs -13.31 ± 6.25, *P* = 0.289). IR changes in the non-remitted group were slightly higher versus the remitted group, but it was also not significant (14.16 ± 9 vs 12.85 ± 14.5, *P* = 0.749).

In this study, despite the higher female population, no significant sex-related differences were observed in diabetic markers (*P* > 0.05). Insulin injection and consuming antihyperglycemic drugs as confounding variables that affected the metabolic panel were evaluated before and in follow-up time (Figure 2).

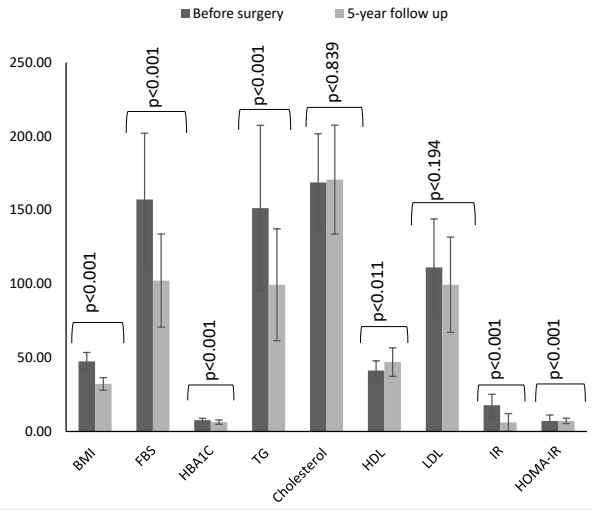


**Figure 1.** Comparison of metabolic markers before and 5 years after the operation. BMI: Body mass index, FBS: fasting plasma glucose, HbA1c: hemoglobin A1c, TG: triglyceride, HDL: High density lipoprotein, LDL: low density lipoprotein, IR: insulin resistance, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance

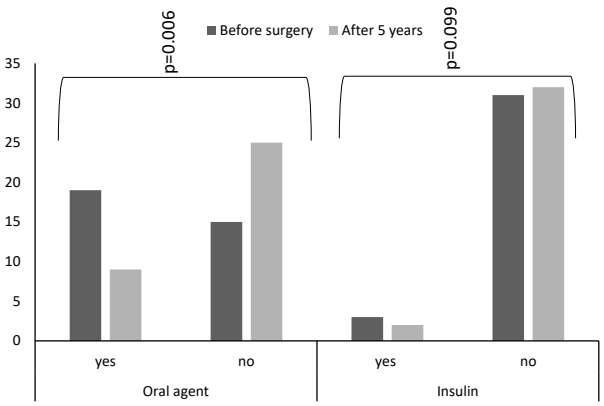


**Figure 2.** Comparison of oral agent and insulin injection before and 5 years after surgery

**Table 1.** Comparison of metabolic panel changes in three surgery types

| Variables | Sleeve | RYGB | OAGB |
|---|---|---|---|
| BMI (kg/m$^2$) | -18.0±4.4 | -13.8±5.9 | -18.0±6.90 |
| FBS (mg/dL) | -58.3±34.4 | -56.0±61.2 | -51.5±44.5 |
| HbA1c (%) | -2.2±1.1 | -1.4±1.9 | -0.94±1.9 |
| TG (mg/dL) | -112.3±50.8 | -44±69.4 | -51±46.8 |
| Cholesterol (mg/dL) | 12±6.2 | -11.5±59.9 | 16±37.2 |
| HDL (mg/dL) | 13±6.0 | 5.8±13.7 | 3.1±10.3 |
| LDL (mg/dL) | -45.7±12.7 | -4.1±59.5 | -19.1±32.9 |
| IR (μIU/dL) | -7.5±2.2 | -11.8±10.9 | -11.9±7.5 |
| HOMA-IR | 5.2±1.5 | 8.9±7.7 | 5.9±1.9 |

BMI: Body mass index, FBS: Fasting blood sugar, Hb A1c: Hemoglobin glycosylated A1C, TG: Triglyceride, HDL: High-density lipoprotein, LDL: Low-density Lipoprotein, IR: Insulin resistance, RYGB: Roux-en-Y gastric bypass, OAGB: One anastomosis gastric bypass.

**Table 2.** Different factor discrepancy between the two remission groups

| Variables | Remission (n=24) | Non-remission (n=10) | *P* value |
|---|---|---|---|
| Age | 53.5±8.8 | 60±7.5 | 0.434 |
| Gender (female) | 22 (64.7) | 8 (80.0) | 0.334 |
| BMI | 48.3±6.0 | 45.4±5.9 | 0.208 |
| Weight reduction | -45.3±25.4 | -38.2±17.7 | 0.549 |
| Surgery | | | 0.288 |
| Sleeve | 3 | 0 | |
| OAGB | 7 | 2 | |
| R-Y GB | 14 | 8 | |
| FBS | 155.1±43.8 | 161.4±46.5 | 0.642 |
| HBA1C | 7.6±1.3 | 7.6±1.1 | 0.669 |
| IR | 6.6±6.3 | 5.3±4.6 | 0.254 |
| HOMA-IR | 7.7±6.9 | 7.9±5.5 | 0.780 |
| TG | 153.9±6.7 | 145±38.1 | 0.838 |
| Chol | 171.2±34.2 | 168±34.7 | 0.445 |
| HDL | 41±6.9 | 42±5.9 | 0.454 |
| LDL | 112.9±34 | 106.9±31.4 | 0.589 |

RYGB: *Roux-en-Y Gastric Bypass; OABG:* one anastomosis gastric bypass

Among our patients included in the study, in 15 patients, T2DM was diagnosed for the first time preoperatively, and they were candidates for bariatric surgery due to high BMI. 19 (60%) patients were taking antihyperglycemic agents before surgery (five patients used 500 mg metformin, eight patients used 1000 mg, and six patients used 1500 mg metformin), while just for nine (26%) patients, this situation remained after the operation ($P=0.006$). For one patient without a history of taking oral agents despite poor control of diabetes, 1000 mg of metformin was prescribed. Eight patients had continued the previous oral agents regimen, but this time with near-optimal blood glucose control. Insulin was administered prior to surgery for three patients. Two patients used ten units of glargine, and one patient used 60 units of glargine with ten units of glulisine). Insulin was simultaneously prescribed with 500-1000 mg of metformin for patients. Among three patients, only one still used insulin post-operatively, and the insulin was changed to oral agents for two other ones. During follow-up, one patient who was taking metformin and glibenclamide for about 4 years after surgery, insulin was administered due to a high HBA1C level ($P=0.999$).

## Discussion

With the trend of utilizing metabolic surgery to alleviate metabolic markers in patients with diabetes, the role of bariatric surgery is still under debate in long-term follow-up. This was a retrospective observational study that consisted of early and late diagnosis of diabetes in patients who were candidates to undergo metabolic surgery. Our findings present that metabolic surgery plays a key role in robust alteration in three category measurements: weight loss, lipid profile, and glycemic indices. Our presentation confirmed the previous studies on weight loss and glycemic index in long-term bariatric surgery follow-ups.[27,28]

Our interesting findings were an insignificant decrease in LDL and an insignificant increase in total cholesterol. Also, in the RYGB group, LDL level reduction is lower than in other groups. The effect of bariatric surgery on reduction of cholesterol level in morbid obesity is discussable. A study by Adam and colleagues showed that LDL levels decreased by about 26% because of RYGB surgery after 6 years.[29] Another meta-analysis study on 1551 patients demonstrated a significant reduction of serum LDL levels following bariatric surgery, especially after RYGB.[30] However, Hu et al, in a meta-analysis on 7443 subjects who underwent RYGB and SG, revealed that, in more than 3 years of follow-up, comorbidities such as dyslipidemia and hypertension had not been improved significantly.[31] Also, Coleman and co-workers, in a study of 8265 patients, found lower dyslipidemia relapse in 4 years of follow-up in RYGB versus the SG group (21% vs. 24%).[32] Dyslipidemia relapse was not the scope of our study. A person would be considered as having dyslipidemia relapse if he/she has LDL level ≥ 160 mg/dL, HDL level < 40 mg/dL for men or less than 50 mg/dL for women, TC level ≥ 240 mg/dL, or triglyceride levels ≥ 200 mg/dL.[31,32] Our findings demonstrated a relapse of dyslipidemia in about 23% of our patients, 20% in the RYGB group, and 3% in the OAGB group, considering that most of our patients had undergone RYGB surgery. Noticeably, a high level of serum TC was also found in most patients who experienced dyslipidemia relapse. Since we did not follow the patients gradually, other causes, such as diet regimen adherence, may be associated with dyslipidemia progression in our patients, while taking saturated fatty acids increases LDL levels following bariatric surgery.[33,34] Albeit, after bariatric surgery, the patients' meal frequency increases.[35] Furthermore, patients' preference for low-calorie diets and sweets may fall after 18 months.[36] So, nutrition counseling is essential for maintaining the normometabolic situation following bariatric surgery.[37]

Although bariatric surgery increases diabetic remission, the advantages and disadvantages of the type of surgery, such as mortality and diabetic reversibility, remain under

discussion.[38,39] In this study, we found 70% diabetic remission in our patients during 5 years of follow-up, but the type of surgery does not affect remission in our survey. Following all patients in SG and the remaining patients in another surgery group, this result is related to our patient population. A recent meta-analysis showed that SG, OAGB, and RYGB impact diabetic remission and OAGB has a higher effect on diabetic remission.[40] However, the diabetic remission mechanism is attributed to several factors, such as gastrointestinal hormones, patient adherence and compliance with treatment, and patient lifestyle.[41] Gloy et al found that bariatric surgery had a major impact on diabetic improvement, HDL level, obesity, metabolic syndrome, and quality of life compared with drug medications.[42] Among metabolic surgeries, RYGB was superior to other types of surgery.[43-45] However, Balamurugan and colleagues, in their systematic review of 82833 patients who underwent metabolic surgery, showed that SG is more effective in diabetic remission and weight loss compared with OAGB and RYGB. Despite this, the rate of SG procedures was lower than other surgeries. The heterogenicity of studies interprets the data so difficult.[46] In a study by Gentileschi et al on 78 patients with RYGB and OAGB, OAGB was found to be superior by facilitating more diabetic remission compared with RYGB in a 6-month follow-up.[47] We did not find any factors related to diabetic remission. Previous studies demonstrated that age, insulin injection, preoperative HbA1C, C-peptide level, baseline BMI, and diabetic duration were predictive factors of diabetic remission after bariatric surgery.[48-50] In a study by Stenberg et al, the authors demonstrated that diabetic remission was lower in patients who had a higher duration of diabetes, HbA1c, age, and dyslipidemia during 10 years of follow-up of RYGB surgery.[51] We collected the data from the first laboratory tests of patients. Some participants had no concerns about diabetes and did not have any history of diabetes before our first diagnostic session. So, we could not estimate the duration of diabetes and its association with the remission rate. Additionally, in our diabetic patients, the non-remitted group had higher pre-operation BMI, but it was insignificant ($P=0.208$). Although weight loss is a prior factor in alleviating diabetic markers, BMI reduction has not been considered a predictive factor for diabetic remission.[51] We found weight reduction in 5-year follow-up has not affected diabetic remission.

Adipose tissue reduction in bariatric surgery attenuates IR.[52] IR is the most important factor in glucose tolerance in patients with diabetes. Early diagnosis of T2DM with higher Beta cell remnant function and lower hepatic IR is associated with diabetic remission in a 5-year follow-up.[53] Also, bariatric surgery affects polypeptide tyrosine-tyrosine, which is associated with pancreas function, adiponectin, glucagon-like peptide 1, and C-reactive protein, which may contribute to improvements in IR.[54] Our study confirmed previous reports in the literature, which demonstrated a significant reduction in HOMA-IR following different types of metabolic surgeries.[55-58] However, it is not a predictive factor of diabetic remission in our study. Ekberg et al also demonstrated that despite evidence of HOMA-IR level reduction, it is not a predictive factor of keeping HbA1C in the normal range.[59]

Moreover, in this study, we observed a significant reduction of required oral antidiabetic agents during follow-up, which confirmed diabetic remission. This also clears the role of gastrointestinal manipulation on hormonal changes and further medications. We also observed that maintaining a metformin prescription in follow-up visits did not prevent diabetic relapse. Souteiro and colleagues also demonstrated that keeping metformin in a patient with HBA1C < 6% does not show T2DM relapse.[60] These findings show that bariatric surgery requires a multidisciplinary team even after reaching a significant weight reduction.

Long-term follow-ups and three types of bariatric surgery were the strengths of this study, while the best surgery method for patients with diabetes is still the subject of debate.

One of the limitations of this study was being retrospective, and it contained bypass as the major type of surgery. The other main limitation of our study was poor patients' adherence to follow-up visits, mostly due to the COVID-19 pandemic, leading to a low study population.

Although most patients in our study were women, like the systematic review by Wang et al, sex did not affect diabetic remission during follow-ups.[18] Our study attracted attention to investigating oral drug prescriptions while selecting patients for surgeries. Despite good control of diabetes after the operation, we recommend future randomized controlled studies to evaluate medical treatment in long-term follow-ups, which involve all kinds of bariatric surgeries.

## Conclusion

Our study showed favorable results of bariatric surgery on patients with diabetes in long-term follow-up. Patients who used oral antidiabetic drugs before surgery had better blood sugar control compared with patients taking insulin. Although the present study found no metabolic changes based on the three types of surgeries, it should be considered that taking oral medications after bariatric surgery were reduced. Further studies inquiring into which bariatric surgery is efficient for diabetic remission through conducting long-term follow-ups are required.

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### Authors' Contribution

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## Competing Interests

The authors declare no conflict of interest related to this work.

## Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Ethical Approval

The Ethics Committee of Mashhad University of Medical Sciences approved this study (IR.MUMS.MEDICAL.REC.1400.426). All participants of the study signed the informed consent.

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Original Article

# Comparison of the Effectiveness of Mindfulness-Based Stress Reduction and Compassion-Focused Therapy on the Cognitive Emotion Regulation in Patients with Irritable Bowel Syndrome

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**Abstract**

**Background:** We aimed to compare the effectiveness of mindfulness-based stress reduction and compassion-focused on the cognitive regulation of emotion in patients with irritable bowel syndrome (IBS). The research method was the semi-experimental type, with pre-test, post-test, follow-up, and experimental and control groups.

**Methods:** The population included patients with IBS in Isfahan city; 45 of them were selected by convenience sampling method and randomly assigned to 3 groups (15 in each group). Then, the patients of one experimental group received eight sessions of 90 minutes of a mindfulness-based stress reduction program, while the other experimental group received eight sessions of 90 minutes of compassion-focused therapy. The measurement tools included the Cognitive Emotion Regulation Questionnaire (Garnefski and Kraaij, 2002) and a short clinical interview. Research data were analyzed using variance analysis with repeated measures on one factor (mixed design).

**Results:** Both intervention methods were equally effective in changing the cognitive regulation of adaptive emotion mean scores ($P<0.01$), but the effect of compassion-focused therapy on improving the mean scores of cognitive regulation of adaptive emotion was more than mindfulness-based stress reduction therapy ($P<0.05$).

**Conclusion:** It was concluded that both intervention methods can be used as complementary treatment for patients with IBS.

**Keywords:** Mindfulness-based stress reduction, Compassion-focused therapy, Cognitive regulation of emotion, Irritable bowel syndrome

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## Introduction

Irritable bowel syndrome (IBS) is characterized by altered bowel habits in association with abdominal discomfort or pain in the absence of detectable structural and biochemical abnormalities. The prevalence of IBS has been reported differently in different countries. Epidemiological studies show an approximate prevalence of 3.5% to 5.8% in the Iranian population, with a higher prevalence in women.[1] Since IBS does not have a specific physical or biological cause, it is classified as a psychosomatic disease; therefore, these patients eventually need to receive psychological services after consecutive visits to numerous doctors and repeated tests.[2]

The etiology of IBS is complex and multifactorial, and reasons such as abnormal gastrointestinal movements, visceral hypersensitivity, and psychological factors have been confirmed in studies.[3]

While IBS is considered to be a benign disease usually not associated with any excess mortality, it is associated with a significant decrease in the quality of life of patients and causes significant economic problems for them. Numerous studies show that IBS has a strong relationship with psychological disorders such as anxiety, depression, and disease symptom disorder.[4] Therefore, not only does this syndrome severely reduce the patients' quality of life and face them with numerous problems in their daily lives, but it also creates a significant burden for the individual and society and brings about significant material and non-material damages (cost of treatment or luck of work).[5]

Despite the relatively high prevalence of IBS, this disorder is not well managed in the healthcare system due to its heterogeneous nature, which can explain the frustration and dissatisfaction among patients and physicians.[5]

These problems range from poor diagnostic processes to treatment failures. Also, the prevalence and severity of psychological disorders in IBS are closely related to the onset and severity of symptoms of the disease.[6]

Thus, it seems that cognitive regulation of emotion can greatly help people improve psychological conditions when facing IBS symptoms.[7] Research showed that there is a strong relationship between digestive diseases and cognitive emotion regulation. It seems that intervention methods that effectively influence the cognitive regulation

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of emotions, in addition to the biological aspects and symptoms of the disease, may be beneficial in controlling and improving IBS.[8,9] Theoretically and fundamentally, the psychological causes of digestive diseases lead psychologists and counselors to investigate the most common digestive diseases, IBS, from the psychological point of view.[10]

More specifically, the results of various research have also shown that people with IBS show excessive sensitivity to environmental issues, making them more vulnerable to difficult emotions.[11]

According to the research, the probability of using positive (adaptive) emotion regulation strategies to modify or change multiple emotional states among people with IBS is very low.[12] The resulting psychological stress, depression, anxiety, stress, and confusion from the lack of optimal cognitive-emotional regulation can further damage the emotional regulation mechanisms of patients with IBS. Emotion regulation refers to the process by which we influence what emotions we experience when we experience them and how we express them.[13]

Emotion regulation is one of the fundamental factors of well-being, playing an important role in adaptive coping with life events.[14] In fact, some characteristics of people suffering from psychosomatic diseases, including emotional disorders, make the person unable to process and perceive the emotional information caused by that event correctly in different situations and, as a result, give an appropriate response to the.[15] Several clinical and experimental studies have shown that emotion regulation as an indicator reduces the stress effects on emotional well-being in psychosomatic disorders. And the inability to deal efficiently with emotions is the most important factor in psychopathology.[16] Nowadays, various psychological treatments have been used to reduce anxiety, depression and pain in psychosomatic disorders , including these interventions mindfulness-based stress reduction therapy and compassion-focused therapy, which belong to the new third wave of cognitive-behavioral treatments. In a completely integrated manner, these two types of interventions control and balance physical, cognitive, and emotional functions.[17,18]

Examining the effectiveness of mindfulness-based and compassion-focused stress reduction therapies has shown that both independently and comparatively present an opportunity for researchers and psychologists to assess the utility of these intervention methods in the cognitive emotion regulation process as a mediating factor in the development and severity of psychological symptoms associated with IBS. The mindfulness-based stress reduction program, initially suggested by Kabat-Zinn for individuals with specific medical conditions and those experiencing chronic pain and related stress, can yield advantageous outcomes.[19]

In fact, people with the disease may react in a dysfunctional way when faced with stress and anxiety. Such emotional and behavioral reactions are commonly referred to as automatic stress responses. However, mindfulness interventions have been shown to facilitate a more mindful and efficacious response in such circumstances.[20] Mindfulness interventions reduce negative repetitive cognitive processing and negative memory by activating cognitive and emotional self-regulation skills, which in turn have a positive effect on the final physiological, psychological, and behavioral responses.[21,22]

Compassion-focused therapy is a comprehensive experimental behavioral therapy that draws upon developmental psychology, neuroscience, Buddhist philosophy, and evolutionary theory. This therapeutic approach emphasizes the regulation of emotions. Interventions are employed to establish particular emotional regulation patterns, mental states, and personal experiences that serve as the foundation for the process of transformation.[17] However, despite the fact that many studies have been conducted regarding the effectiveness of mindfulness-based and compassion-focused stress reduction treatments on IBS, there are few comparative studies in which the effectiveness of the two mentioned methods in the cognitive regulation of emotion has been investigated. Therefore, the current research seeks to determine the effectiveness of mindfulness-based and compassion-focused stress reduction therapy on cognitive emotion regulation in patients with IBS.

## Materials and Methods

It was a semi-experimental study with a pre-test, post-test, a control group, and a 3-month follow-up. The population consisted of all people suffering from IBS in Isfahan city who visited one of the gastroenterology clinics during March to September 2022. The sampling method was purposeful because only those who visited gastroenterology clinics were included in the research. Then, the patients were interviewed and clinically evaluated by gastroenterologists based on the Rome-IV diagnostic criteria, and 45 patients who were diagnosed with IBS and met other criteria for entering the study were randomly assigned into two experimental groups and a control group (15 in each group and a total of 45).

The inclusion criteria were: receiving a definitive diagnosis of IBS by a gastroenterologist, having an age range between 20 and 40 years, having a minimum education level, providing written consent to enter the research, having an absence of severe psychological diseases, lack of psychiatric medication, and non-attendance at other psychoeducational programs at the same time.

Exclusion criteria were receiving drug treatments for physical and psychological disorders during the research, absence in two consecutive sessions, and failure to perform homework. It should be noted that ethical considerations such as providing full information about the conditions of the research, confidentiality, obtaining informed consent for all participants, and using data exclusively for the purposes of the current research were fully observed in this research. In the present study, a symptom severity questionnaire and a short clinical interview were used to collect information.

Clinical interview: A structured clinical interview by a Ph.D. student in psychology based on DSM-5 diagnostic criteria was used to check and diagnose the absence of severe mental disorder or personality disorder and the presence of a substance abuse history.[23]

The Cognitive Emotion Regulation Questionnaire is a self-report tool developed by Garnefski et al[24] to identify the cognitive coping strategies of people after experiencing negative events or situations with 36 items and 9 different dimensions. This questionnaire is very easy to administer and can be used for people over 12 years old (both normal people and clinical populations). Unlike other questionnaires that lack clarity in differentiating between individuals and their actual behaviors, this questionnaire evaluates an individual's cognitive responses following a negative experience or traumatic event. The questionnaire comprises two categories of maladaptive strategies, namely self-blame, blaming others, rumination, and catastrophizing, as well as positive adaptive strategies, including acceptance, positive refocusing, refocusing on planning, positive re-evaluation, and perspective-taking.

The scale scores of this questionnaire range from 1 (never) to 5 (always), with each scale comprising four items. The total score for each scale is calculated by summing the scores of the individual items. Therefore, the range of scores of each of the subscales will be between 4 and 20, and the sum of the total scores will be in the range of 36 to 180.[25] The authors of this questionnaire have reported its reliability through Cronbach's alpha for positive strategies 0.91, negative strategies 0.87, and the entire questionnaire 0.93. The Persian version of this questionnaire was evaluated for validity through internal consistency methods, resulting in subscale scores ranging from 0.76 to 0.92. Retest scores ranged from 0.51 to 0.77, and criterion validity was determined by correlating scores with Beck's second Depression Inventory (1996), resulting in a range of 0.25 to 0.48. and its structure was reported to be favorable based on principal component analysis using Varimax rotation (explaining 74% of the variance).[25,26] In this study, reliability was assessed using Cronbach's alpha coefficient, resulting in scores ranging from 0.72 to 0.89, as described in Table 1.

### *Procedure*

After content preparation and reviewing the background of the research, the necessary coordination was made with the Isfahan Gastroenterology Clinics Association, and the necessary explanations were given regarding the objectives of the study and the type of collaboration.

After the implementation of the questionnaires, patients with IBS who received a definitive diagnosis of the disease were invited, and after providing the necessary explanations regarding the objectives, structure, and content of the training sessions, 45 people who agreed were selected and randomly divided into two experimental groups and a control group.

One of the experimental groups received 8 sessions of 90 -minute of a mindfulness-based stress reduction program based on Kabat-Zinn's protocol. The other experimental group received 8 sessions of 90-minute compassion-focused therapy based on the Gilbert protocol (Tables 2 ,3), while the control group did not receive any

**Table 1.** Questions regarding the components of the Cognitive Emotion Regulation Questionnaire (Garnefski and Kraaij, 2002)

| Row | Dimension | Related questions | Alpha Cronbach |
|---|---|---|---|
| 1 | Acceptance | 2,11,20,29 | 80 |
| 2 | Positive refocusing | 4,22,13,4 | 83 |
| 3 | Refocus on planning | 5,14,23,32 | 74 |
| 4 | Positive reevaluation | 24,33,15,6 | 72 |
| 5 | Perspective taking | 7,34,25,16 | 74 |
| | Adaptive strategies (positive) | questions of the above 5 strategies | 79 |
| 6 | Blaming others | 9,36,27,18 | 80 |
| 7 | Self-blaming | 28,19,10,1 | 83 |
| 8 | Rumination | 30,21,12,3 | 74 |
| 9 | Catastrophizing | 26,35,17,8 | 72 |
| | Maladaptive strategies (negative) | questions of the above 4 strategies | 74 |

**Table 2.** Treatment sessions of mindfulness-based stress reduction program (Kabat-Zinn, 2003)

| Sessions | Process and therapeutic focus in sessions |
|---|---|
| First session | Communicating and conceptualizing, explanation of disease symptoms and the need to use mindfulness training, explanation of the automatic pilot, body scan exercise, mindful eating (raisins), presenting CD No. 1 (body scan) |
| Second session | Confronting obstacles, giving feedback on exercises done, doing breathing mindfulness meditation, 10-15 minutes sitting meditation practice. |
| Third session | Standing stretching exercise, mindful walking, mindful seeing and hearing, describing being in the present moment, and paying attention to thoughts only as thoughts and not as facts. |
| Fourth session | Doing sitting meditation with an emphasis on the body sensations perception, deep listening to others, giving explanations regarding the judgment and the reasons for the negative judgment, homework, and presentation of CD No. 2 (mindful yoga). |
| Fifth session | Mindful breathing at the beginning of each session and giving feedback. Describing the acceptance concept and using it in dealing with problems and unpleasant experiences. Mindful sitting, body scan, reviewing of homework exercises. |
| Sixth session | Long-term sitting meditation, awareness of breath, sounds, and then thoughts, reviewing of homework exercises, mindful walking, standing stretching exercises, presentation of CD #3: Sitting meditation. |
| Seventh session | The day of silence, loving-kindness meditation training, exercises, and mindful attention to repetitive daily tasks. |
| Eighth session | Practicing body scan, practicing doing nothing, examining obstacles to applying techniques, reviewing past material and summarizing, preventing disease recurrence (discussing the signs of recurrence and noting important points about this), discovering potential ability in oneself, reminding, as much as you can practice. |

intervention during the study and only received two sessions of mindfulness-based and compassion-based combined therapy after the study termination.

It should be noted that all interventions were presented in person. In addition, the data related to the three phases of the research (pre-test, post-test, and 3-month follow-up) were entered into the SPSS software and finally analyzed.

### *Data Analysis*

To analyze the data obtained from the research tools, descriptive and inferential statistics were used. The relevant statistical analyses were performed using the SPSS software version 25.

Descriptive statistics indicators included frequency table and frequency percentage, mean, and standard deviation. To verify research hypotheses, analysis of variance with repeated measurements on one factor (mixed design) was used, and Bonferroni's post hoc test was used to compare the mean scores of different groups.

As can be seen in Table 4, the mean and standard deviation of the maladaptive (negative) cognitive regulation scores in the pre-test did not differ much from each other. However, in the post-test and follow-up, the mean scores of the test groups decreased compared with the control group.

At the same time, the mean scores of the total cognitive regulation of the adaptive (positive) emotions did not differ from each other in the pre-test stage but increased in the post-test and follow-up stages. These differences are subject to further examination in the subsequent tables and in the analysis of the primary hypotheses of the study.

The results of Table 5 show that the result for the mean scores of the total adaptive cognitive emotion regulation the measurement time (pre-test, post-test, and follow-up) as ($F = 57.77$ and $P = 0.001$) and the interaction of the measurement time with the group as ($F = 6.62$ and $P = 0.001$) have been obtained, which shows that the mean scores of adaptive cognitive regulation were significantly different not only in different measurement times but also in different groups.

The results of Table 5 show that the mean scores of the total maladaptive cognitive emotion regulation at the time of measurement (pre-test, post-test, and follow-up) were obtained as ($F = 74.60$, $P = 0.001$). The interaction of the time of measurement with the group was ($F = 27.80$, $P = 0.001$), which was analyzed in Table 5 using intergroup analysis. The results of Levene's test to measure the equality

**Table 3.** Content of compassion-focused therapy sessions (Gilbert, 2014)

| Sessions | Process and therapeutic focus in sessions |
|---|---|
| First session | Greetings and initial familiarization among group members, reviewing the structure of meetings, introducing the general principles and distinguishing compassion from self-pity, conceptualizing self-compassion training. |
| Second session | Mindfulness training along with body and breathing exercises, familiarity with brain systems based on compassion, empathy training, and introducing visualization. |
| Third session | Describing the characteristics of compassionate people, compassion towards others, cultivating a feeling of warmth and kindness towards oneself, cultivating and understanding that others also have defects and problems (cultivating a sense of human commonalities) in contrast to the self-destructive feelings of shame, training the empty chair technique, homework assignment. |
| Fourth session | Reviewing the previous session exercise, encouraging the subjects to self-knowledge according to the learned topics and investigating their personality as a non-compassionate or compassionate person, identifying and applying exercises to building a compassionate mind, training forgiveness, and homework assignments. |
| Fifth session | Introducing the three-dimensional behavioral model to express the common relationship between behavior/emotions, psychological functions, and observable behavior and discussion about efforts to change behavior based on it, receiving feedback and homework assignments, nurturing a compassionate mind exercise, and non-judgmental acceptance. Tolerance training. |
| Sixth session | Reviewing the previous session exercise, creating compassionate images, techniques, and methods of expressing compassion training (verbal, practical, and continuous compassion), integrating these practices in daily life, training the development of valuable and sublime feelings, and homework assignments. |
| Seventh session | Reviewing the previous session exercise, training how to write compassionate letters for oneself and others, and training how to record and keep a diary of real situations based on compassion and individual performance in that situation. |
| Eighth session | Training and practicing skills, reviewing and practicing the skills presented in previous sessions, training how to create a safe place, cultivating self-compassion, and finally summarizing and guidelines to integrate this method in everyday life. |

**Table 4.** The mean and standard deviation of the cognitive emotion regulation of adaptive and maladaptive emotions (positive and negative) of the experimental and control groups in the pre-test, post-test, and follow-up

| Variable | Stage | Pre-test, post-test, 3-month follow-up | | | | |
|---|---|---|---|---|---|---|
| | | Mean | SD | Mean | SD | Mean |
| Adaptive cognitive regulation scores | Mindfulness 8.39 | 40.33 | 12.81 | 63.93 | 14.30 | 66.06 |
| | Compassion 9.70 | 40.06 | 9.20 | 65.26 | 9.52 | 64.86 |
| | Control 7.27 | 41.33 | 11.13 | 46.20 | 9.74 | 48.60 |
| Maladaptive cognitive regulation scores | Mindfulness 7.61 | 41.66 | 6.58 | 29.00 | 8.44 | 29.20 |
| | Compassion 3.54 | 38.60 | 6.21 | 22.40 | 3.54 | 21.46 |
| | Control 7.52 | 39.93 | 7.19 | 42.26 | 7.77 | 41.13 |

of variances of adaptive cognitive emotion regulation in different groups are presented in Table 6.

According to Table 6, the mean scores of the adaptive cognitive emotion regulation of the experimental and control groups had a significant difference from each other ($F=14.20$ and $P=0.001$). The obtained eta coefficient is also equal to 0.386. The mean scores of the maladaptive cognitive emotion regulation of the experimental and control groups had significant differences from each other ($F=20.76$ and $P=0.001$). The obtained eta coefficient is equal to 0.497.

Thereby, it was found that there was a significant difference between the mean scores of adaptive and maladaptive cognitive emotion regulation in the three groups. These differences were subsequently examined in pairs utilizing Bonferroni's test, as presented in Table 7.

The results of Table 7, using Bonferroni's paired test, show that there exists a significant difference between the mean scores of the total adaptive cognitive emotion regulation of the experimental groups (mindfulness-based stress reduction and compassion-focused therapy) and the control group ($P=0.001$), while there was no significant difference between the mean scores of the mindfulness group and the compassion therapy group ($P<0.01$). Thus, it was concluded that both mindfulness-based stress reduction and compassion-focused therapy were equally effective in increasing the adaptive cognitive emotion regulation mean.

The results of Table 7, using the paired Bonferroni test, show that there exists a significant difference between the mean scores of the total maladaptive cognitive emotion regulation of the test groups (mindfulness-based stress reduction and compassion-focused therapy) with the control group ($P=0.001$). Also, there was a significant difference between the mean scores of the mindfulness group and compassion therapy ($P<0.01$).

## Discussion

Thus, it was concluded that both mindfulness-based stress reduction and compassion-focused therapy, particularly compassion-focused therapy, were effective in reducing the maladaptive cognitive emotion regulation mean, although the effectiveness of compassion-focused therapy was higher. Therefore, the research hypothesis is confirmed. This study sought to determine the effectiveness of mindfulness-based stress reduction program and compassion-focused therapy in the cognitive regulation of emotions in patients with IBS.

The findings of the research showed that both mindfulness-based stress reduction program and compassion-focused therapy are equally effective in the emotion cognitive regulation of patients. This finding is in line with the research results of Hassannezhad and colleagues,[27] Pashing and Khosh Lahjeh Sedgh,[28] Ghandi

**Table 5.** Within-subject effects of adaptive and maladaptive cognitive regulation

| Variable | Source | Sum | df | Mean squares | F | *P* value | Eta coefficient |
|---|---|---|---|---|---|---|---|
| Adaptive cognitive Regulation | Measurement time | 10396.72 | 2 | 5198.36 | 57.77 | 0.001 | 0.579 |
| (assumed sphericity) | Group *time | 238.29 | 4 | 596.07 | 6.62 | 0.001 | 0.240 |
| | Error | 7557.64 | 84 | 89.97 | | | |
| Maladaptive cognitive regulation | Measurement time | 2523.43 | 1.50 | 1676.80 | 74.60 | 0.001 | 0.640 |
| (Greenhouse) | Group *time | 1881.23 | 3 .01 | 625.03 | 27.80 | 0.001 | 0.570 |
| | Error | 1420.66 | 63.20 | 22.47 | | | |

**Table 6.** The intergroup effects test of the mean scores of adaptive and maladaptive cognitive regulation

| Variable | Source | Sum | df | Mean squares | F | *P* value | Eta coefficient |
|---|---|---|---|---|---|---|---|
| Adaptive cognitive regulation | Constant | 37867.18 | 1 | 37867.18 | 25.74 | 0.001 | 0.984 |
| | Group membership | 3883.65 | 2 | 1941.83 | 14.20 | 0.001 | 0.386 |
| | Error | 6178.48 | 42 | 147.10 | | | |
| Maladaptive cognitive regulation | Constant | 15572.18 | 1 | 15572.18 | 137.57 | 0.001 | 0.973 |
| | Group membership | 0 | 2 | 0 | 20.76 | 0.001 | 0.497 |
| | Error | 4263.60 | 101.27 | | | | |

**Table 7**. Pairwise comparison of the mean scores of adaptive and maladaptive cognitive emotion regulation of the groups

| Variable | Means pairwise comparison | Comparison | Mean Difference | Standard error | *P* value |
|---|---|---|---|---|---|
| Adaptive cognitive | Mindfulness | Compassion | 1.044 | 2.55 | 0.900 |
| Emotion regulation | | Control | 11.40 | 2.55 | 0.001 |
| | Compassion | Control | 12.35 | 2.55 | 0.001 |
| Maladaptive cognitive | Mindfulness | Compassion | 5.80 | 2.12 | 0.027 |
| Emotion regulation | | Control | -7.82 | 2.12 | 0.002 |
| | Compassion | Control | -13.62 | 2.12 | 0.001 |

et al,[11] and Tiwari and colleagues[29] in regard to the effectiveness of compassion-focused interventions.

In explaining these findings, it can be said that contrary to old beliefs, psychological literature suggests that emotions have useful functions and are essential for adaptation in everyday life, and according to what studies have shown if emotions are expressed at the right time, place, and situation, they will lead to positive consequences. Given the significant impact of emotional distress and tension on the exacerbation of symptoms in individuals with IBS, interventions that effectively address their psychological and emotional disturbances may prove beneficial in mitigating the symptoms experienced by these patients.[30]

As previously stated, the implementation of the mindfulness-based stress reduction program and compassion-focused therapy, utilizing the structural and content capabilities of third-wave cognitive behavioral therapies, resulted in enhanced adaptive cognitive emotion regulation through distinct mechanisms of action.

In fact, cognitive emotion regulation includes a number of cognitive, behavioral, and physiological mechanisms that are used unconsciously and consciously. Some emotion regulation strategies are activated before or at the beginning of an event, and some of them are activated after the occurrence of an event or after the formation of an emotion.[31]

The evidence indicates that the present-moment awareness and non-judgmental acceptance that is cultivated by mindfulness play an important role in promoting self-control. This increases sensitivity to emotional cues within one's experiential field and improves response to early emotional cues that contribute to effective emotional regulation and increases brain theta wave activity in the anterior cingulate cortex, middle prefrontal cortex, and emotional regulation.[32]

On the other hand, compassion-focused therapy, which is generally known as emotional self-regulation therapy, helps a person with a type of emotion-focused coping style to cope with situations where problem-focused coping strategies are ineffective so that by using these strategies he or she can adjust to the upcoming issues.[33] Another finding of this research is that the interventions are stable during the 3-month follow-up period. This finding is in line with Moghtadaei et al,[34] Khosh Chin Gol et al,[35] and Tiwari et al[29] findings. In explaining this finding, it can be said that the cognitive regulation of positive emotions improves individuals' ability to deal with emotions, thereby enabling them to recognize emotions in themselves and others so that they can show an appropriate reaction in stressful situations.[36]

In general, the goal of mindfulness-based interventions is not just to reduce tension but to be present in the present moment and acceptance without judgment, which is cultivated through mindfulness. In this way, mindfulness can be seen in two ways: as a process of sensitization and desensitization.

In fact, mindfulness desensitizes people by reducing avoidance of negative, unpleasant aspects, and it creates a sensitivity in them by paying attention to the relationship between emotional states and experiencing automatic responses. The desensitization quality of mindfulness increases people's mental adaptability and reduces people's mental occupations.[37]

According to another finding of the current study, both mindfulness-based and compassion-focused stress reduction methods are effective in reducing adaptive and maladaptive cognitive emotion regulation, although compassion-focused therapy's effectiveness in adaptive cognitive regulation is higher. This finding is somewhat consistent with the results of Dabbaghi Zarif et al,[38] Pashing and Khosh Lahjeh Sedgh,[28] Naliboff et al,[39] and Henrich et al[21] and their colleagues, who have confirmed the effect of mindfulness-based interventions in improving emotional processes and cognitive regulation of emotion.

This finding is also in line with the results of the research of Sepanta et al,[40] and Khalife Soltani and colleagues,[41] which have confirmed the effectiveness of compassion-focused therapy in improving the cognitive regulation of uncompromising emotion. Mindfulness and compassion-based interventions possess a unique capability to address psychological problems and disorders due to their multidimensional cognitive-emotional and physiological structure.

These interventions are mainly based on emotional self-regulation training programs, whose goal is to reduce emotional reactivity to perceived stress and the consequences of chronic disease. In addition, daily compassionate behaviors in patients serve as a coping approach to alleviate negative stress, which helps them manage their emotions more easily and use positive strategies optimally.[42] Regarding the higher effectiveness of compassion-focused therapy compared with mindfulness-based stress reduction therapy in uncompromising cognitive regulation strategies such as self-blame and blaming others, it can be stated that compassion-focused therapy is not solely focused on adjusting emotion-oriented coping strategies,[28] but also involves compassion and flexibility towards oneself and others, which leads to improvement in these emotion regulation strategies.

In fact, when people resort to negative strategies, they tend to blame and criticize themselves and others, get stuck in the issue for an extended period, and make a disaster about it.[43] Conversely, mindfulness and compassion-based treatments due to the acceptance of thoughts and feelings, and bodily sensations can set the stage for accepting such thoughts.

Compassion-based interventions prepare the ground for accepting negative thoughts and less use of incompatible and negative strategies by increasing kindness towards oneself and others.[44]

## Conclusion

According to the results of the present study, cognitive emotion regulation strategies are an important and

effective factor that can contribute to the exacerbation and persistence of IBS symptoms.

The results of the present study indicate the effectiveness of mindfulness-based stress reduction therapy and especially compassion-focused therapy in the cognitive regulation of emotion on promoting and improving positive strategies of cognitive emotion regulation and reducing negative strategies of cognitive emotion regulation in patients with IBS. Therefore it is recommended that psychological treatments, especially mindfulness-based stress reduction therapy and compassion-focused therapy, be utilized as an adjunct to common medical treatments. This necessitates the cooperation of gastroenterologists, psychologists, and psychiatrists so that patients can benefit from psychological therapies as complementary treatments in a safe treatment environment.

A limitation of the study is that the statistical population was confined to a small number of participants, which may limit the generalizability of the results. This study employed a convenience sampling method, which should be considered. According to the limitations of the current study, it is recommended to conduct a similar study with a larger number of participants in the future.

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**Competing Interests**

The authors declare no conflict of interest related to this work.

**Ethical Approval**

This study was approved by Shahrekord Islamic Azad University under the code of ethics IR.IAU.SHK.REC.1401.069.

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Case Report

# A Rare Case of Cystic Artery Pseudoaneurysm because of Cholecystitis Managed with Non-invasive Technique

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**Abstract**

Cystic artery pseudoaneurysm due to acute on chronic cholecystitis is very rare in spite of the high incidence of cholecystitis, and very few cases have been reported in the literature. Most of the pseudoaneurysms are symptomatic at the time of diagnosis due to rupture. Very few cases of unruptured cystic artery pseudoaneurysm caused by cholecystitis have been reported in the literature. We present a case of a 41-year-old man who presented in the Intervention Radiology Department with the diagnosis of cholecystitis and cystic artery pseudoaneurysm. Three treatment options are available for such cases. The first approach is surgical clipping of the pseudoaneurysm and cholecystectomy. The second approach is endovascular management of pseudoaneurysm and cholecystectomy. We chose the third approach, endovascular management of the pseudoaneurysm, percutaneous cholecystostomy, and elective laparoscopic cholecystectomy.

**Keywords:** Embolization, Image-guided procedures, Cystic artery pseudoaneurysm

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## Introduction

Cystic artery pseudoaneurysm is a very rare entity, and most of the pseudoaneurysms are iatrogenic due to complications of biliary procedure.[1] Cystic artery pseudoaneurysms due to acute on chronic cholecystitis are very rare in spite of the high incidence of cholecystitis, and approximately 36 cases have been reported in the literature.[2] Most of the pseudoaneurysms are symptomatic at the time of diagnosis due to rupture. Very few cases of unruptured cystic artery pseudoaneurysm caused by cholecystitis have been reported in the literature.[3] The presumed etiology of the formation of pseudoaneurysm is the erosion of the arterial wall by inflammation or direct pressure by calculus.[4] We present a rare case of cystic artery pseudoaneurysm incidentally detected during the workup of cholecystitis, which was managed with minimally invasive techniques followed by planned laparoscopic cholecystectomy.

## Case Report

A 41-year-old male patient presented in the Intervention Radiology Department with the diagnosis of cholecystitis and cystic artery pseudoaneurysm. He had a history of right upper quadrant abdominal pain, and contrast computed tomography (CT) in the venous phase showed a distended gallbladder (GB) measuring up to 10×3.5 cm with thickening and edema of the GB wall up to 8 mm thick. Multiple variable size calculi were noted in the GB lumen. A hyperdensity of size 9×7 mm in the wall of the GB appeared to be continuous, with a branch of the cystic artery suggestive of pseudoaneurysm. This finding was further confirmed with the follow-up CT performed in the arterial phase, and the diagnosis of acute cholecystitis with pseudoaneurysm of the superficial branch of the cystic artery was established (Figure 1). No obvious sign of pseudoaneurysm rupture was seen. Laboratory investigation showed borderline high white blood count, and C-reactive protein (CRP) was very high 150 mg/L.

Using right femoral artery access, an angiogram was performed with a Cobra catheter (5F, Cook, Bloomington, IN, USA) from the common hepatic artery, and a cystic artery was identified (Figure 2). The cystic artery originated from the right hepatic artery, traveled superiorly, and divided into the superficial branch and deep branch in a V-like fashion. No attempt was made to demonstrate pseudoaneurysm on angiogram due to the fear of rupture of the pseudoaneurysm because of strong injection, and we already knew from the preprocedural CT that pseudoaneurysm was arising from the superficial branch of the cystic artery. Superselective cannulation of the superficial branch of the cystic artery with Progreat microcatheter (Progreat, Terumo, Tokyo, Japan) and microwire (0.016 Fathom wire, Boston Scientific, Natick, MA, USA) and embolization with the 3-mm microcoils (vortex 0.018", Boston Scientific, Natick, MA, USA, 4 in number) was done. A follow-up angiogram showed complete embolization of the superficial branch of the cystic artery and patent deep branch (Figure 3).

Under ultrasonography and fluoroscopy guidance,

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**Figure 1.** Contrast computed tomogram in arterial phase axial section confirms the diagnosis of cystic artery suggestive of pseudoaneurysm (thin arrow). Signs of cholecystitis, such as thickened gall bladder wall and pericholecystic fluid, are seen (thick arrow)

**Figure 2.** Angiogram of hepatic artery shows the cystic artery (thin arrow) originates from the right hepatic artery, travels superiorly, and divides into the superficial branch (thick black arrow) and deep branch (thick white arrow) in a V-like fashion

a pigtail catheter (8.5F, Cook, Bloomington, IN, USA) was placed in the GB lumen. The catheter position was confirmed with injecting contrast under fluoroscopic guidance. Contrast injection showed a good position of the drainage catheter, with opacifying the intrahepatic and extrahepatic duct and filling defects in the GB lumen representing calculi (Figure 4). The patient was significantly improved and discharged after 5 days with oral antibiotics. The cholecystostomy catheter was removed after 4 weeks when the patient was asymptomatic. Follow-up CT and magnetic resonance imaging (MRI) demonstrated collapsed GB with multiple calculi and no radiological sign of cholecystitis. Elective uneventful laparoscopic cholecystectomy was performed after 3 months.

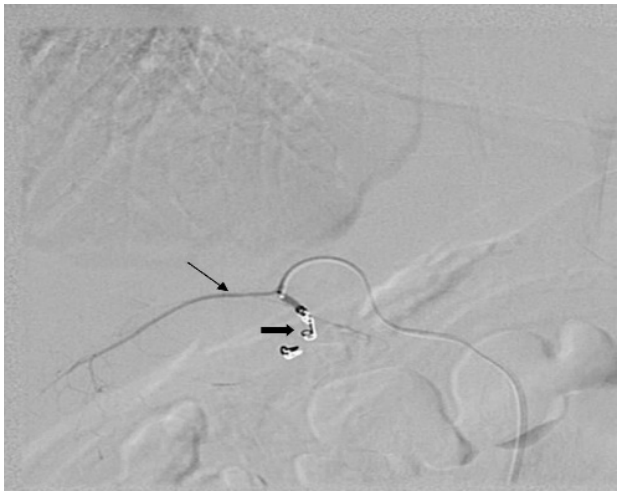

**Figure 3.** Post-embolization angiogram shows complete embolization of the superficial branch of the cystic artery with coils (thick arrow) and patent deep branch (thin arrow)

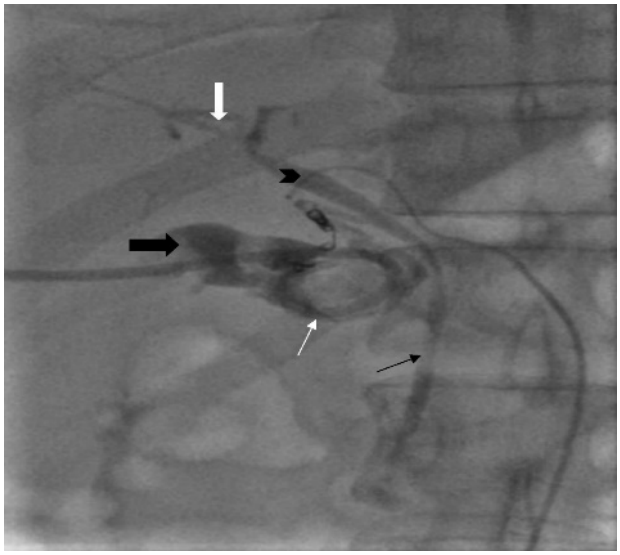

**Figure 4**. Contrast injection shows the good position of the drainage catheter (white arrow) with opacifying the intrahepatic (thick white arrow) and extrahepatic duct (black arrow) and filling defects (black thick arrow) in the gall bladder lumen representing calculi. Microcatheter tip (thick arrowhead) is seen in the cystic artery during cholecystostomy

## Discussion

Cystic artery pseudoaneurysm is most commonly seen as a complication of cholecystectomy. Other causes include cholecystitis, pancreatitis, and liver trauma. Cystic artery pseudoaneurysm is a rare complication of cholecystitis, which increases the morbidity. Incidental diagnosis is rare, and most of the cases present with the clinical triad of hemobilia consist of jaundice, colicky abdominal pain, and upper gastrointestinal hemorrhage due to ruptured pseudoaneurysm.[5,6] In our case, the patient presented with pain in the upper abdomen, and pseudoaneurysm was diagnosed incidentally with the diagnosis of cholecystitis.

Contrast CT/MRI with arterial phase has high sensitivity and specificity over ultrasonography, but conventional angiography is the gold standard with the benefit of therapeutic role.[7] Because of the rarity of this disease, there are currently no guidelines on the management of

this condition; however, two approaches to the treatment are mentioned in the literature. The first approach mentioned surgical clipping of the pseudoaneurysm and cholecystectomy,[8,9] and the second approach mentioned endovascular management of pseudoaneurysm and cholecystectomy.[10] We chose the third approach, endovascular management of the pseudoaneurysm, percutaneous cholecystostomy, and elective laparoscopic cholecystectomy. This approach is mentioned in the literature but not performed frequently because the procedure involves a high risk of pseudoaneurysm rupture during cholecystostomy.[8,11]

Endovascular treatment of an aneurysm and percutaneous cholecystostomy catheter insertion was reported as effective, with less trauma to the patient and no need for general anesthesia compared with the first approach.[3,12] Case reports are available where the patient was scheduled for laparoscopic clipping of cystic artery pseudoaneurysm and laparoscopic cholecystectomy, but because of the underlying significant inflammation, the laparoscopic procedure turned to open cholecystectomy. In a few case reports, laparoscopic cholecystectomy was performed successfully, but major laparotomy and a vascular instrument set were kept on standby.[4] In our patient, we used the third approach, where we embolized the pseudoaneurysm and a percutaneous cholecystostomy catheter was placed to control the source of infection, and the patient was scheduled for elective laparoscopic cholecystectomy when GB was not distended and no sign of infection on blood examination and no sign of GB inflammation on radiological imaging existed.

Reports are available on the use of different embolic agents, but in our case, we used micro coils to achieve superselective and controlled embolization. We were aware that there had been no case report available in the literature for GB ischemic complications, likely due to collateral blood supply from the epicholedochal artery.[13] Still, we took extra precautions during the embolization regarding the patency of the deep branch of the cystic artery. We kept the microcatheter in the cystic artery during cholecystostomy to deal with any arterial complications during cholecystostomy. We removed the microcatheter from the cystic artery when infected bile was drained well by a drainage catheter, and there was no sign of arterial complication.

## Conclusion

Cystic artery pseudoaneurysm associated with cholecystitis is a rare entity. Pseudoaneurysms can be safely treated with transcatheter techniques, and cholecystitis can be managed by percutaneous cholecystectomy followed by elective laparoscopic cholecystectomy.

### Authors' Contribution

**Conceptualization:** Gunjan Jindal.
**Data curation:** Amit Shrivastava.
**Formal analysis:** Lukman Khan, Rohan Chaube.
**Funding acquisition:** Lukman Khan.
**Investigation:** Amit Shrivastava.
**Methodology:** Amit Shrivastava.
**Project administration:** Gunjan Jindal.
**Resources:** Amit Shrivastava.
**Software:** Gunjan Jindal, Rohan Chaube.
**Supervision:** Gunjan Jindal.
**Validation:** Amit Shrivastava.
**Visualization:** Amit Shrivastava.
**Writing–original draft:** Gunjan Jindal.
**Writing–review & editing:** Amit Shrivastava.

### Competing Interests

The authors declare no conflict of interest related to this work.

### Consent for Publication

Informed written consent was obtained from the patient for publication of this report.

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Case Report

# Caroli's Disease Associated with Autosomal Dominant Polycystic Kidney Disease with Acute Pancreatitis: A Case Report

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**Abstract**

A rare congenital hepatobiliary disorder called Caroli's disease is characterized by multifocal segmental dilatation of intrahepatic bile ducts that can affect the entire liver or only specific areas of it. Coexisting conditions with Caroli's disease include autosomal dominant polycystic kidney disease (ADPKD) and autosomal recessive polycystic kidney disease (ARPKD). ADPKD results in the development of cysts, which are tiny fluid-filled sacs, in the kidneys. Caroli's disease is considered a rare disorder, affecting a small number of individuals worldwide. The symptoms of Caroli's disease can vary from person to person and it also may overlap with other liver and biliary disorders. As a result, it may be challenging to diagnose and manage the condition due to limited awareness and expertise. Increased awareness, research, and specialized medical care are crucial in improving outcomes for individuals affected by this rare disorder. This study involves the case of a 60- year-old woman presented with abdominal pain, fever, weight loss, and jaundice. Her imaging test endoscopic retrograde cholangiopancreatography (ERCP) signifies Caroli's disease with pancreatic duct (PD) calculi and management involves supportive care with antibiotics. Antibiotics were prescribed to prevent or treat infections such as cholangitis and nutritional supplement was recommended in managing Caroli's disease. The patient underwent pancreatic stent placement and was discharged with regular follow-up. So, this case highlights the clinical and diagnostic aspects to improve disease understanding and the progression of Caroli's illness along with ADPKD.

**Keywords:** Autosomal dominant polycystic kidney disease, Caroli's disease, Common bile duct, Endoscopic retrograde cholangiopancreatography, Magnetic resonance cholangiopancreatography

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## Introduction

Caroli disease is a rare genetic condition known as congenital communicating cavernous ectasia of the biliary tree, causing segmental dilation of the major intrahepatic bile duct, which, on imaging and histopathological examination, looks like cysts.[1] It is now understood to be a hereditary illness caused by the PKHD1 gene, which alters the fibrocystin protein and causes polycystic kidney and hepatic disease. The pancreas, liver cholangiocytes, and renal tubular cells are three organ systems where this protein is expressed. Fibrocystic alteration in the kidney and liver is brought on by genetic abnormalities in this protein.[2] Caroli disease only affects 1 in 100 000 people on average. A highly useful diagnostic test is magnetic resonance cholangiopancreatography.[3] Clinical features include jaundice, fever, and/or right hypochondrium pain.[4] Complications include recurrent attacks of cholangitis, abscesses, intrahepatic calculi, and growth of cholangiocarcinoma.[1] Caroli disease is treated with ursodeoxycholic acid for hepatolithiasis and antibiotics for cholangitis. Patients with mono- lobar disease have successfully undergone surgical resection. The preferred medical option for patients with diffuse disease is orthotopic liver transplantation.[5]

## Case Report

A 60-year-old lady presented to our outpatient clinic with complaints of fever, pain in the abdomen, and loss of appetite for the last 2-3 months. She had a high-grade, continuous fever associated with chills and headaches. The abdominal pain was near the periumbilical region, which was insidious in onset, intermittent, non-progressive, non-radiating, and associated with tenderness in the umbilical region. She had lost 6 kg weight over the last 6 months. She was lean built, afebrile to touch, with a heart rate of 74 beats per minute and blood pressure of 130/80 mm Hg. She was pale and icterus positive. She had an earlier diagnosis of jaundice and comparable symptoms, including recurring fever episodes accompanied by chills, stomach discomfort, inadequate sleep, and firm stools that necessitated hospitalization 6 months prior. During her previous hospitalization, her abdominal ultrasound scan revealed Caroli's disease, suggesting focal cholangitis. The patient encountered menopause 15 years

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ago. Her familial history was unremarkable. Meropenem 250 mg twice daily, linezolid 600 mg twice daily, metronidazole 400 mg thrice daily, paracetamol 500mg twice daily, and herbal supplements were among the previous medications in the patient's medication history. Currently, from the imaging test ERCP, it was confirmed that the patient has Caroli's disease with PD calculi. ERCP was performed to assess the extent of bile duct involvement, identify biliary stones or obstructions, and potentially treat certain complications, such as removing stones or placing stents to relieve strictures. Endoscopic ultrasound (EUS) was indicated to obtain high- resolution images, allowing for better visualization of the bile duct, identify any structural abnormalities or masses, and helping to differentiate between Caroli's disease and other conditions. Hospitalization treatment included intravenous (IV) pantoprazole 40 mg daily, ondansetron 4 mg daily, tramadol 50 mg SOS (taken as required), vitamin D3 60 000 IU once a week, pheniramine maleate 2 mL SOS (taken as required), diclofenac 50 mg in 100 mL normal saline (NS) SOS (taken as required), ceftriaxone 1gm twice daily, vitamin supplements, and IV fluids. The patient received a blood transfusion due to consistently low levels of hemoglobin (Hb), packed cell volume (PCV), mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH), which indicated anemia as shown in (Table 1). She had persistent abdominal pain and fever spikes with chills during the hospital stay, which were resolved with medications, and at the time of discharge, the patient was vitally stable without new complaints.

### *Laboratory Assessment*

The complete laboratory values are shown in Table 1.

**Table 1.** Laboratory values

| Variables | Date | | | |
|---|---|---|---|---|
| | 19/1/2023 | 30/1/2023 | 1/2/2023 | 6/2/2023 |
| HB (g/dL) | 9.30↓ | 9.90↓ | 9.50↓ | 8.70↓ |
| WBC (/µL) | 6300 | 5800 | 10700↑ | 10600↑ |
| ESR (mm/h) | 54↑ | 10 ↓ | 59↑ | |
| Neutrophil (%) | 62 | 69 | 96↑ | 83↑ |
| Lymphocytes (%) | 30 | 19 ↓ | 2↓ | 10↓ |
| PCV (%) | 28.90↓ | 30.00↓ | 29.10↓ | 26.70↓ |
| MCV (fL) | 65.20↓ | 66.50↓ | 65.90↓ | 64.10↓ |
| MCH (pg) | 21.10↓ | 21.90↓ | 21.40↓ | 20.90↓ |
| TIBC (µg/dL) | 196.00↓ | | | |
| RDW (%) | 17.10↑ | 17.60↑ | 18.20↑ | 18.40↑ |
| T. Bili (mg/dL) | 0.16↓ | | 1.27↑ | |
| D. Bili (mg/dL) | 0.10 | | 0.87↑ | |
| I. Bili (mg/dL) | 0.06↓ | | 0.40 | |
| AST (U/L) | 19 | | 75 | |
| ALT (U/L) | 18 | | 32 | |
| ALP (U/L) | 79 | | 112 | |
| Amylase (U/L) | 120↑ | 93 | 244↑ | 85 |
| Lipase (U/L) | 109 | 136 | 2217↑ | 260 |
| IRON (µg/dL) | 10.00↓ | | | |
| Transferrin (%) | 5.10↓ | | | |
| HbA1c (%) | 6.2 ↑ | | | |
| Vit B12 | >2000↑ | | | |
| PT (s) | 11.5 | 12.30 | 16.50↑ | |
| INR | 1.01 | 1.02 | 1.43↑ | |

HB: hemoglobin, WBC: white blood cells, ESR: erythrocyte sedimentation rate, PCV: packed cell volume, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, TIBC: total iron binding capacity, RDW: red cell distribution width, T. Bili: total bilirubin, D. Bili: direct bilirubin, I. Bili: indirect bilirubin, AST: aspartate aminotransferase, ALT: alanine transaminase, ALP: alkaline phosphatase, HbA1c: glycated hemoglobin, PT: prothrombin time, INR: international normalized ratio.

### *Imaging*

Ultrasonography of abdomen and pelvis: Multiple anechoic cystic lesions were noted in bilateral kidneys with few specks of calcification /and septations within. EUS report: Calculi of size 7×3 mm in the head region of the pancreatic duct (PD), gall bladder was distended, and liver showed multiple anechoic cysts as shown in Figure 1. Magnetic resonance cholangiopancreatography (MRCP) demonstrated multiple small cystic formations in the liver and both kidneys, continuity of few cysts with intrahepatic biliary radicals at places, central dot sign is seen, and mild dilation of the common bile duct (CBD) with lower CBD calculus. PD stent was placed, as shown in Figure 2.

### *Outcome and Follow-up*

After 3 weeks of hospital stay and treatment, the patient's symptoms, such as fever with chills and abdominal pain, resolved, which showed she was able to ambulate home and to carry out her daily activities. The patient was prescribed oral pantoprazole 40 mg daily, tramadol 500 mg twice daily, cefixime 200 mg twice daily, and ondansetron 4 mg SOS to continue for 7 days, and was advised regular follow-up.

## Discussion

In 1958, a gastroenterologist named Jacques Caroli reported a rare congenital disease in France. He said it was "non-obstructive fusiform multifocal segmental dilatation of the intra-hepatic bile ducts".[6] Caroli disease affects more women than men. Family history includes kidney and liver disease due to the link between Caroli disease and autosomal recessive polycystic kidney disease (ARPKD).[6] Patients with Caroli syndrome have shown alterations in the PKHD1 gene related to ARPKD and autosomal dominant polycystic kidney disease (ADPKD).[6] According to researchers, this condition is inherited as an autosomal dominant genetic trait. However, the more severe type of Caroli disease seems to be inherited as an autosomal recessive genetic characteristic.[6] Its signs and symptoms, including hepatomegaly, fever, and intermittent abdominal pain, are usually present as the initial symptoms. Jaundice happens occasionally.

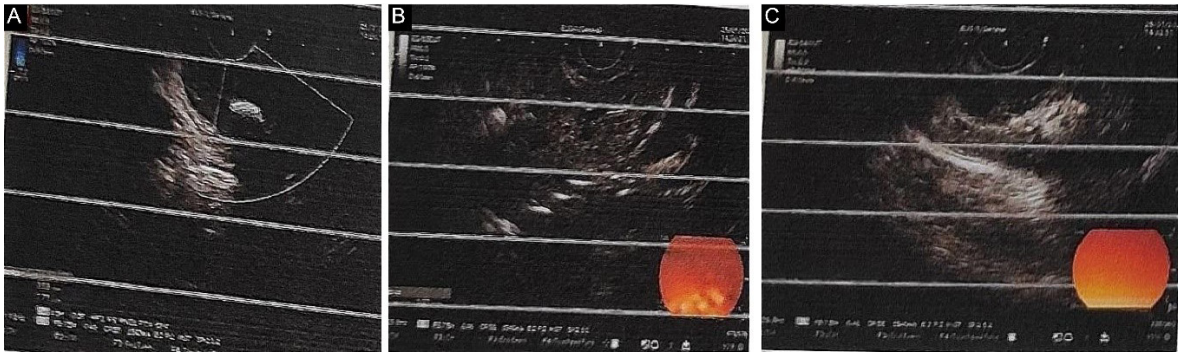


**Figure 1.** Endoscopic ultrasound report: Caroli's disease with PD calculi

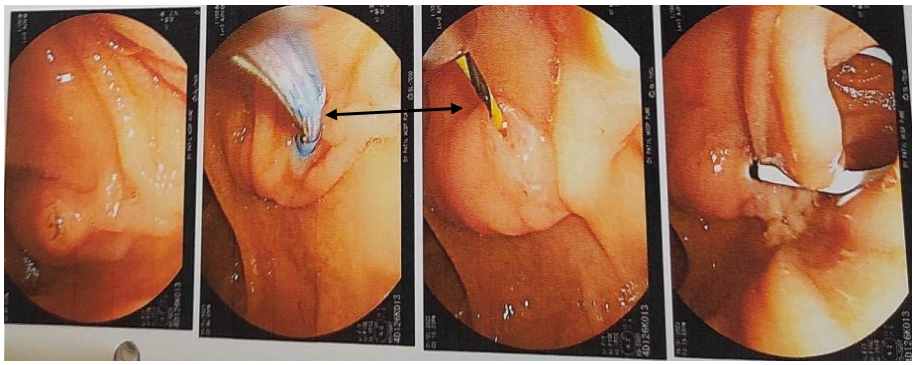

**Figure 2.** ERCP: Prominent pancreatic duct (PD)

Caroli disease usually develops in association with other conditions such as cholangitis, gallstones, biliary abscess, septicemia, liver cirrhosis, renal failure, and cholangiocarcinoma.[7] Histologically, Caroli disease's main microscopic and macroscopic features are non-obstructive, localized dilatation of the bile ducts, intra-ductal vascular tracts containing patent portal venous and hepatic arterial channels that traverse the true lumen, and intraluminal bulbar protrusions of the ductal wall.[8] The ability to demonstrate continuity between the cystic lesions and the biliary tree is consequently necessary for diagnosing CD. It can be carried out using imaging tests such as abdominal ultrasonography, computed tomography, isotope scan, ERCP, and MRCP.[9] Caroli disease can be complicated by the formation of liver abscesses, intra and extrahepatic lithiasis, and even cholangiocarcinoma.[8] The treatment of Caroli disease depends on the clinical features and the location of the biliary abnormalities.[8] Appropriate antibiotics for cholangitis and ursodeoxycholic acid therapy to prevent stone formation in case of intrahepatic cholelithiasis.[10] Radiological, endoscopic, and surgical intervention may be required for patients with biliary obstruction, abscess formation, and liver or gallbladder stones. Recurrent cholangitis may have a substantial impact on quality of life. The prognosis depends on the clinical course and the risk of cholangiocarcinoma.[10] As it is a rare genetic disorder, there are no preventive measures. In our case, multiple cystic forms were detected on the MRCP, endoscopic ultrasonography, and abdominal ultrasonography scans [as shown in Figures 1 and 2]. We have identified a dot sign in our patient. According to lab results, the patient had anemia and elevated amylase levels, indicating acute pancreatitis managed with antibiotics and hydration.

## Conclusion

In conclusion, polycystic kidney disease and various disorders affecting other organ systems may be linked to Caroli disease, an uncommon congenital abnormality of the intrahepatic bile ducts. Caroli disease should be included in the differential diagnosis of epigastric stomach pain despite its extremely low prevalence as well as recurrent cholangitis without risk factors or pertinent family history. Following a clinical suspicion, the diagnosis is always radiologic, with the preferred tests being MRCP and ultrasonography. Instead of the more typical manifestation of recurrent cholangitis, Caroli's illness can also manifest as a chronic, intractable stomach ache. Ursodeoxycholic acid should be used for medical therapy; however, surgical intervention may be beneficial. Despite this, the location and size of cystic dilations, the history of the disease, any complications, and any coexisting conditions all play a significant role in the care strategy that should be tailored to each patient. Early treatments and close follow-ups are necessary since complications from cholangiocarcinoma can be severe and frequent.

### Authors' Contribution

**Conceptualization:** Karishma M Rathi, Priyanka Pingat, Prachi Bansode, Shaili Dongare.
**Data curation:** Prachi Bansode, Shaili Dongare.
**Methodology:** Priyanka Pingat, Prachi Bansode, Shaili Dongare.

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The authors declare no conflict of interest related to this work.

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Letter to the Editor

# The Agreement between Endoscopic and Histopathological Findings of Esophageal and Gastroduodenal Lesions and Its Relationship with Endoscopists' Experience

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## Dear Editor,

Endoscopic and histopathological findings in diagnosing gastric diseases are complementary, and endoscopy alone cannot make a definitive pathognomonic diagnosis of gastric diseases.[1] In some cases, people with a normal endoscopy have abnormal histopathological findings, so combining endoscopic and histopathological findings is very useful for diagnosing precancerous gastric ulcers.[2]

As an early diagnosis reduces the disease's complications and the economic burden imposed on the country's healthcare system, studies on diagnosing gastrointestinal (GI) diseases via endoscopy are essential. Hence, we evaluated the agreement between abnormal endoscopic and histopathological findings of upper GI lesions and its relationship with the endoscopist's experience in adult patients referred to Afzalipour hospital in Kerman, Iran.

This cross-sectional, retrospective study was conducted from June 22, 2021, to August 23, 2021, in the Gastroenterology Department of Afzalipour hospital, affiliated with Kerman University of Medical Sciences, Kerman, Iran. The study population was patients who had undergone endoscopy and pathology sampling simultaneously. Inclusion criteria were age over 18 years and clarity of the final clinical diagnosis in the endoscopy report. Exclusion criteria were a previous definitive diagnosis of digestive problems or an incomplete clinical record. The gold standard for the final diagnosis of gastrointestinal lesions in our study was to perform a biopsy of the lesions. By referring to the hospital archives and carefully examining the patients' clinical records, upper endoscopy, and pathology results were recorded in separate checklists. After the checklists were filled, a gastroenterologist and a pathologist carefully checked all endoscopy and pathology reports to see whether they agreed with one another. They divided the cases into two groups: agreed and non-agreed.

In this study, 256 patients with a mean age of 51 ± 15 and an age range of 18-85 years participated. The largest number of endoscopies (38.3%) were performed by endoscopists with less than five years of experience. According to the type of endoscopic findings, erythematic and erogenous lesions (53.1%) were the most common. Regarding the site of involvement, the most frequent was the distal part of the stomach, i.e., incisura, antrum, prepyloric region, and pylorus (57.4%). Inflammation of the stomach and duodenum (gastritis) (82.4%) was the most common pathological finding (Table 1).

We found an agreement between endoscopic and pathological findings in 187 (73%) patients. There was no significant relationship between the endoscopists' experience and the agreement between endoscopic and pathological findings.

In terms of the type of endoscopic findings, the highest agreement was observed in gastric ulcers (81.7%), which was statistically significant ($P = 0.005$), and the lowest agreement was observed in normal endoscopy reports (30.8%), which also was statistically significant ($P = 0.001$). In terms of lesion location, the most and least agreement were seen in duodenal (81.3%) ($P = 0.022$) and esophageal involvement (54.1%) ($P = 0.005$), respectively (Table 2).

In this study, there was no significant difference in the average years of endoscopists' experience between the agreed findings group (12.2 ± 8.9) and the non-agreed findings group (11.9 ± 8.4).

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**Table 1**. Demographic findings of patients and frequency of location and type of endoscopic and pathologic findings

| Variable | No. (%) |
|---|---|
| Gender | |
| Male | 159 (62.1) |
| Female | 97 (37.9) |
| Age group | |
| 18-29 | 22 (8.6) |
| 30-49 | 89 (34.8) |
| 50-69 | 110 (43) |
| >70 | 35 (13.7) |
| Endoscopists' experience (years) | |
| <5 | 98 (38.3) |
| 5-9 | 53 (20.7) |
| 10-19 | 51 (19.9) |
| >20 | 54 (21.1) |
| Endoscopic findings | |
| Esophageal varices | 21 (8.2) |
| Gastric varices | 2 (0.8) |
| Hiatal hernia | 29 (11.3) |
| Cancer | 16 (6.3) |
| Ulcer | 115 (44.9) |
| Erythema & erosion | 136 (53.1) |
| Polyp | 20 (7.8) |
| Atrophy | 3 (1.2) |
| Normal | 13 (5.1) |
| Location of endoscopic findings | |
| Esophagus | 37 (14.5) |
| Fundus | 37 (14.5) |
| Body | 71 (27.7) |
| Incisura, antrum, prepyloric region, pylorus | 147 (57.4) |
| Duodenum | 96 (37.5) |
| Histopathological Findings | |
| Cancer | 20 (7.8) |
| Ulcer | 19 (7.4) |
| Metaplasia | 41 (16) |
| *Helicobacter pylori* | 86 (33.6) |
| Gastritis | 211 (82.4) |
| Polyp | 13 (5.1) |
| Dysplasia | 8 (3.1) |
| Normal | 7 (2.7) |

**Table 2.** The agreement of endoscopy reports with pathology reports based on different components

| Variable | Agreement | | |
|---|---|---|---|
| | Yes, n (%) | No, n (%) | *P* value |
| Gender | | | |
| Male | 115 (72.3) | 44 (27.7) | 0.740 |
| Female | 72 (74.2) | 25 (25.8) | |
| Age group (years) | | | |
| 18-29 | 15 (68.2) | 7 (31.8) | 0.215 |
| 30-49 | 71 (79.8) | 18 (20.2) | |
| 50-69 | 74 (67.3) | 36 (32.7) | |
| >70 | 27 (77.1) | 8 (22.9) | |
| Endoscopists' experience (years) | | | |
| <5 | 72 (73.5) | 26 (26.5) | 0.977 |
| 5-9 | 39 (73.6) | 14 (26.4) | |
| 10-19 | 36 (70.6) | 15 (29.4) | |
| >20 | 40 (74.1) | 14 (25.9) | |
| Endoscopic findings | | | |
| Cancer | 12 (75) | 4 (25) | 0.856 |
| Ulcer | 94 (81.7) | 21 (18.3) | 0.005* |
| Erythema And Erosions | 100 (73.5) | 36 (26.5) | 0.853 |
| Polyp | 13 (65) | 7 (35) | 0.398 |
| Atrophy | 1 (33.3) | 2 (66.7) | 0.178 |
| Normal | 4 (30.8) | 9 (69.2) | 0.001* |
| Location of endoscopic findings | | | |
| Esophagus | 20 (54.1) | 17 (45.9) | 0.005* |
| Fundus | 27 (73) | 10 (27) | 0.991 |
| Body | 57 (80.3) | 14 (19.7) | 0.106 |
| Incisura, antrum, prepyloric region, pylorus | 112 (76.2) | 35 (23.8) | 0.188 |
| Duodenum | 78 (81.3) | 18 (18.7) | 0.022* |
| Total | 187 (73) | 69 (27) | |

*$P$ value<0.05.

Regarding the type of endoscopic findings, the endoscopists' average years of experience were significantly higher in patients diagnosed with erythema and erosive lesions on endoscopy (13.8±9.4) than in patients without these lesions (10.1±7.4) ($P$=0.001).

Regarding the lesion location, the endoscopists' average years of experience were significantly higher in patients diagnosed with fundus lesions on endoscopy (17±10.5) than those without these lesions (11.3±8.1) ($P$=0.003). Similarly, the years of experience were higher in patients diagnosed with lesions in the body of the stomach on endoscopy (14.2±9.3) relative to patients without these lesions (11.3±8.3) ($P$=0.016) (Table 3).

In patients with abnormal findings, the sensitivity and specificity of endoscopy were 96.4% and 57.1%, respectively. Cohen's κ value for the statistical agreement was 0.37, considered low to moderate. In patients with cancer, the sensitivity and specificity of endoscopy were 60% and 98.3%, respectively; a good level of agreement was marked by a κ value of 0.64.

In this study, the highest number of endoscopies was in people 50 to 69 years old. Most guidelines recommend that people with dyspepsia without warning symptoms undergo endoscopy at the age of 60 years.[3] However, in Iran, due to the high prevalence of stomach cancer,[4] endoscopy and biopsy are recommended at a younger age.[5]

In many studies, the most reported pathology was gastritis (75.5%) ,[6] with our study showing that the prevalence of gastritis with and without *Helicobacter*

**Table 3.** Average years of endoscopists' experience according to location and type of endoscopic findings

| Variable | Agreement, Y/N | Years, Mean ± SD | *P* value |
|---|---|---|---|
| **Endoscopic findings** | | | |
| Cancer | Y | 14.2 ± 11.3 | 0.450 |
| | N | 12 ± 8.5 | |
| Ulcer | Y | 11.8 ± 8.4 | 0.592 |
| | N | 12.4 ± 8.9 | |
| Erythema & erosions | Y | 13.8 ± 9.4 | 0.001* |
| | N | 10.1 ± 7.4 | |
| Polyp | Y | 14.2 ± 9.4 | 0.277 |
| | N | 11.9 ± 8.6 | |
| Atrophy | Y | 8.6 ± 5.5 | 0.489 |
| | N | 12.1 ± 8.7 | |
| Normal | Y | 10.1 ± 7.4 | 0.400 |
| | N | 12.2 ± 8.8 | |
| **Location of endoscopic findings** | | | |
| Esophagus | Y | 14.1 ± 10.6 | 0.201 |
| | N | 11.8 ± 8.3 | |
| Fundus | Y | 17 ± 10.5 | 0.003* |
| | N | 11.3 ± 8.1 | |
| Body | Y | 14.2 ± 9.3 | 0.016* |
| | N | 11.3 ± 8.3 | |
| Incisura, antrum, prepyloric region, pylorus | Y | 12.7 ± 8.8 | 0.240 |
| | N | 11.4 ± 8.6 | |
| Duodenum | Y | 11.3 ± 8.5 | 0.285 |
| | N | 12.6 ± 8.8 | |
| Total | Y | 12.2 ± 8.9 | 0.829 |
| | N | 11.9 ± 8.4 | |

*$P$ value < 0.05; Y, Yes; N, No

*pylori* infection was 82.4%. Also, our highest frequency of endoscopic diagnosis was related to mucosal erythema and erosion (53.1%). In other studies,[7,8] the same lesions secondary to *H. pylori* infection or bile reflux have been reported as the most common endoscopic findings.[9]

In this study, the overall agreement of endoscopic diagnoses with the pathology reports was 73%. In some similar studies, the rate of endoscopic diagnosis in agreement with the pathology report was 79.5% in active gastritis[10] and 64.3% in *H. pylori* infection.[11] Of course, it should be mentioned that the optical diagnosis accuracy in colon lesions is much higher than in upper gastrointestinal lesions.[12]

Among the types of endoscopic diagnoses and their agreement with the pathology reports, only in peptic ulcers was there a statistical agreement between the endoscopy report and the diagnosis on pathology. Although it is often assumed that in large lesions such as cancer, there is a reasonable agreement between the endoscopy reports and the pathology reports, this agreement was not found in our study; of course, there was also no such agreement in the study reported by Sun et al.[13] In the study of Watanabe et al, there was a relationship between the endoscopists' experience and the diagnosis of *H. pylori* infection, and the greater the experience of the endoscopist, the greater the diagnostic accuracy.[14] In the study of Bustamante et al, there was a relationship between the endoscopists' experience and the diagnosis of gastric cancer.[15]

In our study, the lowest endoscopy-pathology agreement was in normal endoscopies. Hence, it can be concluded that a histopathological examination is necessary for symptomatic patients with normal endoscopy, irrespective of the endoscopists' experience.

In terms of the location of involvement and agreement between the endoscopy-pathology agreement, there was a significant agreement between the endoscopic diagnosis and the pathology results in duodenal lesions. According to the previous findings of this study about peptic ulcers, it can be concluded that duodenal ulcers have the highest diagnostic accuracy in endoscopy reports. The lowest agreement of endoscopic diagnosis with pathology reports was in esophageal lesions; for this reason, it can be recommended that a biopsy is necessary for all abnormal esophageal lesions.

In our study, regarding the different types of findings, there was a significant relationship between the average years of endoscopists' experience and mucosal erosion and erythema ($P = 0.001$). Although a similar study has not been done about such a relation, this issue is a sign that with increasing experience, the diagnostic accuracy for mucosal surface lesions increases, which shows the importance of experience in medicine.

Our study showed a significant relationship between the average years of endoscopists' experience and lesions of the fundus ($P = 0.003$) and body ($P = 0.016$) of the stomach. Fundus and body lesions may be missed due to the endoscopists' lack of focus or experience,[16] so less experienced gastroenterologists should be given sufficient training on accurately examining the fundus and body of the stomach. In our study, in patients with cancer, the sensitivity rate of endoscopic diagnosis was 60%, and the specificity rate was 98.3%. In the study by Kato et al, the sensitivity was 76.6%, and the specificity was 84.3%.[17]

Although we can rely on the endoscopists' experience to an acceptable extent in diagnosing duodenal ulcers and mucosal surface lesions in the body and fundus of the stomach, endoscopic observations alone are insufficient for the definitive diagnosis of most lesions. This study suggests that all the findings obtained from endoscopy, even by the most experienced endoscopists, should be combined with histopathological analysis to help diagnose GI diseases accurately.

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## Authors' Contribution

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## Competing Interests

The authors declare no conflict of interest related to this work.

## Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Ethical Approval

The study protocol was reviewed and approved by the Ethics Committee of Kerman University of Medical Sciences (IR.KMU.AH.REC.1400.027). We complied with the provisions of the *Declaration* of *Helsinki* in protecting the rights of patients under investigation.

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