EGYPTIAN ACADEMIC JOURNAL OF

BIOLOGICAL SCIENCES

PHYSIOLOGY & MOLECULARBIOLOGY

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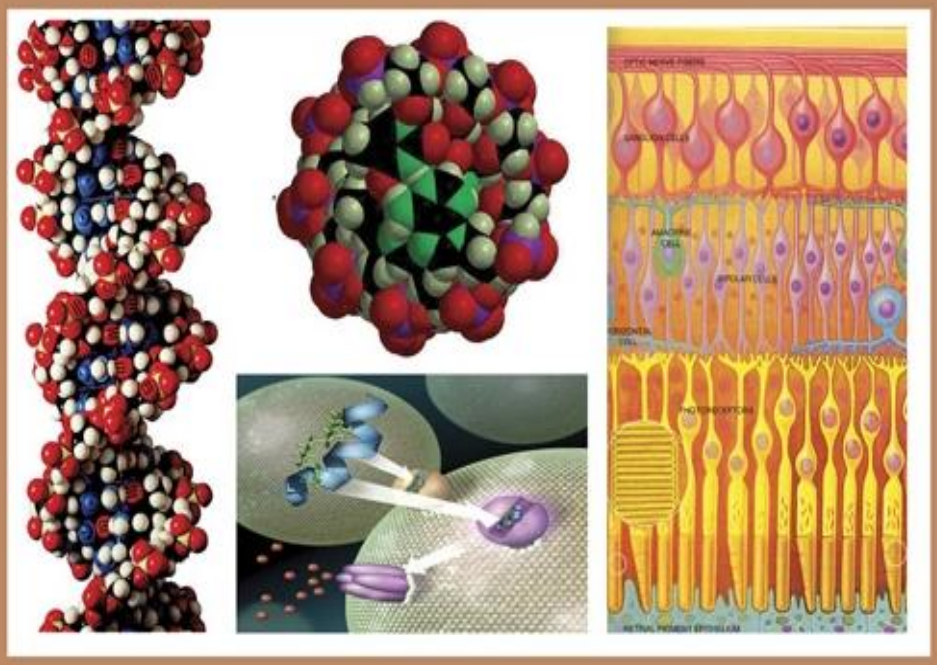

ISSN
2090-0767

WWW.EAJBS.EG.NET

Vol. 14 No. 1 (2022)

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Citation: *Egypt.Acad.J.Biolog.Sci. (C.Physiology and Molecular biology) Vol. 14(1) pp153-163 (2022)*
DOI: 10.21608/EAJBSC.2022.221330

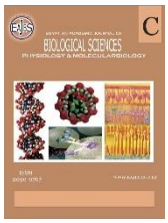
Egypt. Acad. J. Biolog. Sci., 14(1):153-163 (2022)

Egyptian Academic Journal of Biological Sciences

C. Physiology & Molecular Biology

ISSN 2090-0767

www.eajbsc.journals.ekb.eg



Pentraxin-3: A Novel Specific Biomarker for Inflammatory Bowel Disease Diagnosis

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ARTICLE INFO

Article History

Received:1/1/2022

Accepted:20/2/2022

Available:22/2/2022

Keywords:

Inflammatory Bowel Disease (IBD); Pentraxin-3

ABSTRACT

Background and aim*:** Inflammatory bowel disease (IBD); includes Crohn's disease (CD) and ulcerative colitis (UC) is a chronic condition. Endoscopy is the most effective method in the diagnosis of IBD, although it is an invasive, uncomfortable procedure. Pentraxin-3 (PTX-3) is a primary local inflammatory biomarker. This study aims to prove that PTX-3 shows sensitivity and specificity in the diagnosis of IBD as a non-invasive biomarker. ***Subjects and methods: Thirty-six (45 ± 15years) subjects, were divided into Group I (control): 12 healthy volunteers, group II: 12 CD patients and group III: 12 UC patients. Serum levels of PTX-3, antinuclear antibody (ANA) and C-reactive protein (CRP)as well as fecal calprotectin level were assessed at the start of the study and at the end of 8 weeks mesalazine treatment. ***Results:*** Results revealed a significant elevation of both calprotectin and PTX-3 levels in either CD or UC-patients in comparison to the control, with no significant difference between them regarding CRP and ANA levels. After mesalazine therapy, serum PTX-3 level was significantly decreased in both UC and CD patients, while no significant change has been detected in other studied parameters. ***Conclusion:*** PTX-3 can be used as a sensitive, specific, non-invasive inflammatory biomarker for diagnosis and follow-up of IBDs.

INTRODUCTION

Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC) is a chronic, life-long condition that can be treated but not cured. It also affects patients' quality of life and may have a high financial burden (Ponder and Long 2013). They cause chronic inflammation and damage in the gastrointestinal tract which impairs the abilities of affected parts to function properly, leading to symptoms such as persistent diarrhea, abdominal pain, rectal bleeding, weight loss and fatigue (Burgmann et al. 2006). The symptoms of these two illnesses are quite similar, but the areas affected are different. Crohn's disease may affect any part of the gastrointestinal tract (GIT), from the mouth to the anus. Crohn's disease can also affect the entire thickness of the bowel wall (Fakhoury *et al.*, 2014).

Ulcerative colitis is limited to the large intestine (Colon) and the rectum. The inflammation occurs only in the innermost layer of the lining of the intestine (Feuerstein *et al.,* 2019).

Diagnosis depends on the full patient and family history, symptoms and physical examination findings and various investigations which may include: Complete Blood Count (CBC), serum C-Reactive Protein (CRP) (Carter et al. 2004). Other investigations include Magnetic resonance imaging (MRI), computed tomography (CT) and endoscopy which is considered the most effective method in the diagnosis of IBD patients, although it is invasive and an uncomfortable procedure and requires anaesthesia (Lee 2016).

The goals of treatment are to reduce, control the severity of symptoms and prevent flare-ups and complications (e.g. colorectal cancer)(Lamb *et al.,* 2019). Treatment of IBD may include aminosalicylates (5-ASA), antibiotics, corticosteroids, biologic therapies, immunomodulators, and surgery according to disease severity, anatomic location, comorbidities, side effects of drugs and previous response to medication(Carter *et al.,* 2004).

Mesalamine is a nonsteroidal anti-inflammatory drug with a drug class of 5-aminosalicyclic-acid [5-ASA] derivative that has been used for a long time and has a powerful effect in the remedy of IBD. Salazopyrin is the original drug in this category, but mesalazine (5-ASA) is the active mediety drug of this category and is the principal aminosalicylate used in IBD remedies. This drug is useful, well-tolerated and safe for the remedy of ordinary ulcerative colitis or colonic Crohn's disease that applied in most patients who suffer these disorders (Seyedian *et al.,* 2019).

Corticosteroids, used for short periods of time, immunomodulators and anti-TNFα induce remission in resistant IBD patients. We can combine 5-ASA, immunomodulators asnd biological agents together to achieve remission (Wehkamp *et al.,* 2016).

Because there are some limitations, difficulties and conflict in the diagnosis of IBD, the need for a new, specific and reliable biomarker that help in the diagnosis of inflammatory bowel diseases is mandatory.

Pentraxins are a family of inflammatory biomarkers which are classified into short group e.g. C-reactive protein (CRP) and long group e.g. Pentraxin-3 (PTX-3), which is considered the prototype of long pentraxins (Bonacina *et al.,* 2013),(Deban *et al.,* 2009),(Jaillon *et al.,* 2007). PTX-3 is an extrahepatic synthesis inflammatory biomarker, particularly, produced by the innate immune system, which is induced by primary inflammatory mediators such as TNFα and Interleukins-1 (IL-1) compared to CRP which is produced by the liver and stimulated by interleukin-6 (IL-6).(Deban *et al.,* 2009),(Jaillon *et al.,* 2007). PTX-3 is considered to be a primary local inflammatory biomarker (Inoue, Sugiyama, *et al.,* 2007).

In this study, we aim to prove that PTX-3 shows sensitivity, accuracy and specificity in the diagnosis of patients with IBD as a non-invasive inflammatory biomarker.

MATERIALS AND METHODS

Study Design:

The participants in the study were normotensive nondiabetic 36 subjects, free of chronic diseases with normal renal and hepatic functions. They were of the same socio-economic class and were divided into 3 different groups. Group I (control) included 12 healthy volunteer individuals (4 females and 8 males) aged (45 ± 15) years. Group II and group III subjects (12 patients in each group) included mild to moderate IBD patients, their ages (45 ± 12 years). These patients were diagnosed as IBD, treated and followed up in the

endoscopy unit of the Medical Research Institute, Alexandria University. Twelve of them (4 females and 8 males) were diagnosed with Crohn's Disease (group II) and the other twelve (6 females and 6 males) were diagnosed with ulcerative colitis (group III). Criteria for exclusion from these two groups included concomitant other GIT diseases, ileal Crohn's disease and severe IBD.

Diagnosis of CD or UC was based on clinical signs and symptoms and colonoscopy findings. In addition, biochemical parameters were assessed through the withdrawal of 5 ml venous blood from the antecubital vein. Serum was separated and used to assay the levels of Pentraxin-3(Inoue, Sugiyama, *et al.,* 2007), Anti-nuclear antibody (ANA)(Ulvestad 2001), C-reactive protein (CRP)(Gill *et al.,* 1981). Stool samples were also collected to determine Fecal Calprotectin level(Vestergaard *et al.,* 2008).

Treatment of patients in group II & III started immediately after confirming the diagnosis by daily oral administration of Mesalazine "5-aminosalisylic acid" (Salazine 500 mg Capsules-PHAROPHARMA) as the followings: 2 capsules 3 -4 times daily (according to the patients' response) for 8 weeks for induction of remission (Hanauer and Strömberg 2004), (Williams *et al.,* 2011), (Seyedian *et al.,* 2019).

At the end of the 8 weeks treatment period, blood and stool samples were collected from the patients involved in group II & III to assess the same biochemical parameters after induction of remission.

The study has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. The study was approved by the ethics committee of the Medical Research Institute and informed written consent was obtained from each participant, before enrollment.

Biochemical Assays:

1.Determination of Pentraxin-3 was done using RayBiotech, Inc® Human Pentraxin-3 (TSG-14) ELISA Kit, Peachtree Corners Georgia) for quantitative measurement of human PTX3 in serum(Inoue, Sugiyama, et al. 2007).

2.Determination of Antinuclear antibody (ANA) was done using ELISA kit (ORGENTEC Diagnostika GmbH, ORG 600ANA Detect, Germany) by TIM wells and Fully automated ELISA analyzer(Ulvestad 2001).

2.1.C-reactive protein nephelometric quantitative kit (Roche Diagnostics GmbH, USA) is used for the measurement of human CRP in serum samples using BN-prospec- Nephlometer Siemens analyzer(Gill *et al.,* 1981).

2.2.Calprotectin was measured using ELISA kit (Calprest NG &Eurospital, Italy) by TIM wells and a Fully automated ELISA analyzer(Vestergaard et al. 2008).

Statistical Analysis:

Statistical processing of results was done using IBM SPSS software version 20. The results are expressed as mean ± standard error (SE). ANOVA test followed by Post hoc test was used for mean comparison between all groups.

Independent-samples T-test was used for mean comparison between both patients' groups; paired two-tailed t-test was also used. Statistical significance was assumed at a level of P values < 0.05.

Pearson correlation was used to test correlation among the different studied parameters. Statistical significance was assumed at a level of P values < 0.05. ROC curve was used to measure the sensitivity and specificity of different biochemical markers.

RESULTS

Results of the current study revealed a significant elevation of both calprotectin and pentraxin-3 levels in IBD-either CD or UC- patients in comparison to the control group. However; there was no significant difference between patients and control groups as regards CRP and

ANA levels. In addition; serum PTX-3 level was significantly higher (P=0.018) in Chron's disease group than ulcerative colitis' group, while no significant difference between both disease patients' groups regarding all other measured biochemical parameters (Table 1).

Table 1: Comparison between the level of studied biomarkers in Chron's Disease patients, ulcerative colitis patients and healthy subjects before treatment.

	Healthy (n= 12)	Chron's Disease (n= 12)	Ulcerative colitis (n= 12)	F	P-Value
CRP	7.3 ± 2.1	16.7 ± 5.5	10.1 ± 7.9	0.73	0.503
ANA	0.46 ± 0.056	0.62 ± 0.03	0.60 ± 0.1	1.3	0.229
FC	26.8 ± 5.2	448 ± 115[a]	292 ± 53[a]	8.5	0.003*
Pentraxin-3	5.3 ± 0.94	14 ± 1.2[a,b]	10.9 ± 0.4[a]	26.2	0.000*

- F: Fisher test for ANOVA,
- *: Statistically significant at $p \leq 0.05$
- a: Significant difference as compared to the healthy group.
- b: Significant difference as compared to ulcerative colitis group.
- CRP: C-Reactive Protein
- ANA: Anti-nuclear antibody
- FC: Fecal Calprotectin

After mesalazine therapy, serum pentraxin-3 level was significantly (P=0.000) decreased in both UC and CD patients, while no significant change has been detected after treatment as regards all other studied biochemical parameters (Tables 2 &3).

Table 2: Comparison between the level of studied biomarkers before and after mesalazine therapy in Ulcerative colitis patients**.**

	Ulcerative colitis (n= 12)		P-Value
	Before treatment	After treatment	
CRP	10.1 ± 7.9	10.2 ± 7.8	0.733
ANA	0.60 ± 0.1	0.69 ± 0.1	0.349
FC	292 ± 53	250 ± 41	0.062
Pentraxin-3	10.9 ± 0.4	6.8 ± 0.23*	0.000

- *Significant difference between both groups, Statistically significant at $p \leq 0.05$
- CRP: C-Reactive Protein
- ANA: Anti-nuclear antibody
- FC: Fecal Calprotectin

Table 3: Comparison between the level of studied biomarkers before and after mesalazine therapy in Chron's Disease patients

	Chron's Disease (n= 12)		P-Value
	Before treatment	After treatment	
CRP	16.7 ± 5.5	16.0 ± 5.0	0.579
ANA	0.62 ± 0.03	0.66 ± 0.03	0.412
FC	448 ± 115	414 ± 99	0.362
Pentraxin-3	14 ± 1.2	7.1 ± 0.5*	0.000

- *Significant difference between both groups, Statistically significant at $p \leq 0.05$
- CRP: C-Reactive Protein
- ANA: Anti-nuclear antibody
- FC: Fecal Calprotectin.

Statistical Correlations:

- Serum pentraxin values were significantly and positively correlate with fecal calprotectin value in IBD patients (r = 0.476, P= 0.046). However, after aminosalicylate treatment, a significant negative correlation has been found in fecal calprotectin value and serum pentraxin value in IBD patients (r = – 0.728, P= 0.007).
- When dividing patients according to their types of diseases

*A strong significant positive correlation (r= 0.943, P= 0.005) has been found in Ulcerative patients between serum CRP, and ANA test. In addition; after aminosalicylate treatment, there was a significant negative correlation (r = – 0.841, P=0.036) between serum pentraxin value and ANA values.

* Also, after aminosalicylate treatment, a strong significant negative correlation (r= – 0.943, P= 0.005) has been found in Chron's patients between fecal calprotectin value and serum pentraxin levels.

Sensitivity and specificity tests:

Sensitivity and specificity test revealed that although pentraxin-3 and calprotectin are highly sensitive and specific for diagnosis of IBD, but PTX-3 is more sensitive and of higher sensitivity **(Fig.1)**. On the other hand, sensitivity and specificity test revealed that CRP and ANA are not sensitive or specific for diagnosis of IBD **(Fig. 2).**

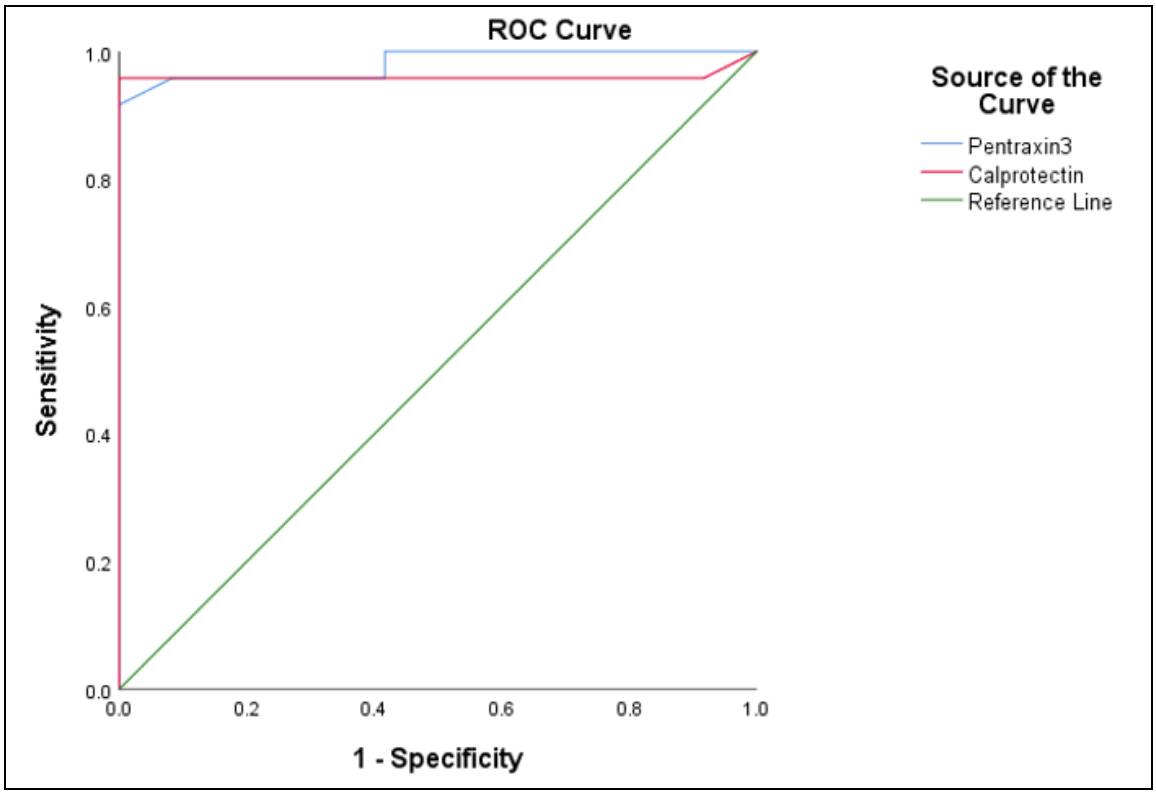

Fig. 1: Receiver Operating Characteristic (ROC) Curve for Pentrixin-3 & Calprotectin

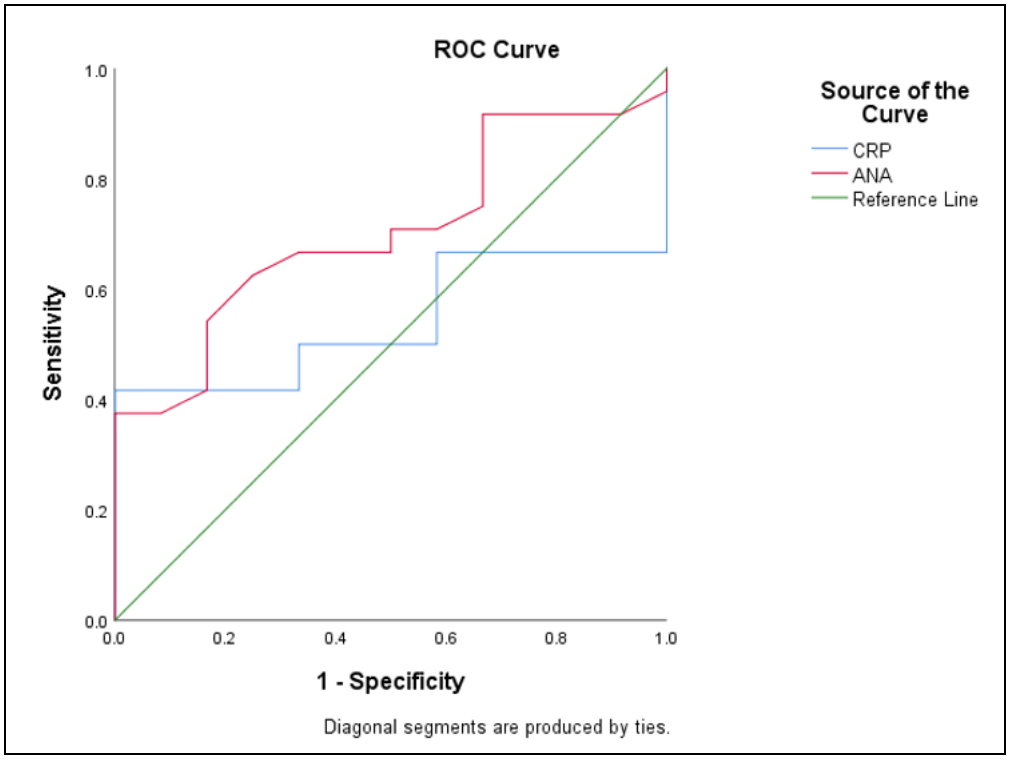

Fig. 2: Receiver Operating Characteristic (ROC) Curve for C-reactive Protein & Anti-Nuclear Antibody.

DISCUSSION

Inflammatory bowel disease (IBD) is a very common gastrointestinal tract inflammatory disorder that may lead to the development of cancer in colon and rectum(Kanneganti 2017). The gastrointestinal tract inflammation in IBD patients is chronic in contrast to acute inflammation which is caused by certain pathogens(Hanauer 2006). In inflammatory conditions PTX-3 level in blood increases and peaks at 6-8 hours, faster than CRP level which peaks at 24-48 hours(Garlanda *et al.*, 2018). PTX-3 has an important regulatory role in inflammation, innate immunity, tissue repair and cancer(Inoue, Kodama, *et al.*, 2012). Increasing plasma PTX-3 levels were noticed in cardiovascular diseases such as heart failure and acute myocardial infarction and many auto-immune diseases as rheumatoid arthritis (Bottazzi, Garlanda, and Teixeira 2019),(Inoue, Kodama, *et al.*, 2012)

Data of our study revealed that there was a significant difference between patients and controls in the mean PTX-3 levels and the mean FC levels compared to the mean levels of CRP and ANA which are inflammatory biomarkers but showed inaccuracy in the identification of mucosal inflammation in GIT. Moreover, a strong relationship was noticed between the serum level of PTX-3 and early stages of inflammation in IBD where the serum levels of PTX-3 were significantly high in patients with mild stages of IBD.

In agreement with our results, previous studies detected a significant positive association between the plasma level of PTX-3 and patients with IBD (Kato et al. 2008). Jaillon S. *et al* and Bottazzi, B. *et al* found also that, PTX-3 positioned in neutrophil granules, is rapidly released upon pro-inflammatory stimuli and reaches the peak much more rapid than CRP (Jaillon *et al.*, 2007),(Bottazzi, Garlanda, Cotena, *et al.*, 2009)

The levels of Fecal Calprotectin (FC) in our study were significantly high in patients with IBD compared to healthy controls but in a patient with mild endoscopic activity, the laboratory results

of FC were negative. Fecal Calprotectin (FC) is an inflammatory biomarker elevated in gastroenteritis and is used as a non-invasive marker in the diagnosis of patients with IBD prior to endoscopy but calprotectin is also released in organic diseases such as celiac disease and diverticular disease and infectious conditions (Konikoff and Denson 2006),(D'Haens et al. 2012). In the study by Lin J-F *et al*, FC shows higher sensitivity in the diagnosis of patients with UC than patients with CD (Lin *et al.*, 2014).

PTX-3 reaches maximal plasma concentration earlier than CRP in many diseases such as hemodialysis-induced inflammation, acute pancreatitis and acute myocardial infarction. etc and PTX-3 is produced at the site of inflammation in previous diseases in contrast to CRP which is a systemic inflammatory biomarker so PTX-3 is more accurate than CRP (Chen et al. 2015),(Fazzini *et al.*, 2001). Chen J. *et al* showed a significant correlation between the level of PTX-3 and mucosal inflammation in CD and demonstrated that PTX-3 is more sensitive than CRP in CD diagnosis(Chen *et al.*, 2015). Kato S. *et al*, also demonstrated that PTX-3 is more reliable than CRP in the diagnosis of IBD because PTX-3 is produced from inflamed cells in GIT in contrast to CRP which is produced from liver (Kato *et al.*, 2008).

On the other hand, Kalyon S. *et al*, showed that PTX-3 or CRP levels are not associated with UC and CD, and the level of PTX-3 was low in patients with IBDs except those with universal colitis (pancolitis), as there was a strong relationship between PTX-3 level of and the degree of inflammation(KALYON *et al.*, 2020).

However, other previous studies (Lochhead e*t al.*, 2016),(Santos-Antunes et al. 2016) augmented our results and proved that CRP and ANA are not sensitive in IBDs diagnosis or in any local inflammation. Moreover; Savchenko AS. *et al*, demonstrated that the serum PTX-3 level is linked to mucosal inflammation in UC thus the serum levels of PTX-3 showed higher sensitivity, accuracy and specificity in the diagnosis of patients with UC (Savchenko *et al.*, 2011).

Conclusion

From the aforementioned data, we can conclude that the novel inflammatory markser PTX-3 can be used as a sensitive, specific, non-invasive biomarker for the diagnosis of IBDs even in the early stages of the disease.

Ethics approval and consent to participate*:* The study was approved by the ethics committee of the medical research institute, Alexandria University and informed written consent was obtained from each participant, before enrollment (Appendix 1. Guiding Principles for Biomedical Research involving participants, 2011).

Data availability statement*:*The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Disclosure statement: Authors declare that they have no conflict of interest

Funding support: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgements

The authors are grateful to Dr. Said A. Ooda, Assistant Prof. of Internal Medicine, Medical Research Institute, Alexandria University, Egypt, for all the facilities he introduced in managing the clinical part of our research.

Prof. Yosra S.R.Elnaggar. Head of International publication and nanotechnology consultation center INCC, faculty of pharmacy, pharos university in Alexandria, Egypt for her guidance during publication of the current manuscript.

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ARABIC SUMMARY

بنتراكسين 3: مؤشر بيولوجى جديد مخصص لتشخيص مرض التهاب الأمعاء

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المقدمة والأهداف: يعد مرض إلتهاب الأمعاء -والذي يشمل كل من داء كرون والتهاب القولون التقرحي- مرض مزمن يستمر مدى الحياة. و يعتبر المنظار التداخلي هو الطريقة الأكثر فاعلية في تشخيص مرضى كرون على الرغم من أنه إجراء مؤلم وغير مريح ويتطلب التخدير. بنتراكسين- 3 هو عبارة عن دليل بيولوجي للالتهاب الموضعي يفرز خارج الكبد .
لذلك في هذه الدراسة، نهدف إلى إثبات أن دليل البنتركسين- 3 فعال ودقيق في تشخيص المرضى الذين يعانون من مرض إلتهاب الأمعاء وبذلك يمكن استخدامه كعلامة بيولوجية على الالتهاب بدون اللجوء للطرق التداخلية العنيفة.
الأشخاص وطرق العمل: شارك في الدراسة عدد 36 فرد تتراوح أعمارهم بين 45 ± 15 سنة. تم تقسيمهم إلى 3 مجموعات مختلفة. وشملت المجموعة الأولى (المجموعة الضابطة)12 متطوع أصحاء. والمجموعة الثانية تكونت من 12 مريض بداء الكرون ، والمجموعة الثالثة تكونت من 12 مريض تم تشخيصهم بداء التهاب القولون التقرحي. وقد تم قياس مستويات البنتركسين-3 و مضاد الجسم النووي، والبروتين التفاعلي في الدم. وكذلك تم قياس مستوى الكالبروتكتين في البراز. تم القياس مرة في بداية الدراسة وأخرى بعد 8 أسابيع من العلاج باستخدام الميسالازين.
النتائج: كشفت عن ارتفاع كبير في كل من مستويات الكالبروتكتين في البراز و البنتركسين-3 في الدم في كل من مرضى كرون والتهاب القولون التقرحي مقارنة مع المجموعة الضابطة، بينما لم يظهر كلا من مضاد الجسم النووي، والبروتين التفاعلي فرق كبير بينهما .
واتضح أنه بعد العلاج باستخدام الميسالازين، انخفض مستوى البنتركسين -3 بشكل كبير في كل من مرضى كرون والتهاب القولون التقرحي في حين أنه لم يكن هناك تغيير ملحوظ كبير في المعايير الأخرى التي تم إجرائها في الدراسة.
الاستنتاج: يمكن أن نستنتج أن البنتركسين- 3 يمكن استخدامه كمؤشر حيوي حساس ودقيق ولا يحتاج لتداخلات عنيفة لتشخيص ومتابعة مرضى إلتهاب الأمعاء في المراحل المبكرة من المرض.

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