EVALUATION OF FECAL ACTIVIN-A AS A NOVEL BIOMARKER FOR EARLY DIAGNOSIS OF ULCERATIVE COLITIS USING EXPERIMENTAL MURINE ANIMAL MODEL

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ABSTRACT

The present study was undertaken to evaluate fecal activin-A, in comparison with the currently used calprotectin, as a potential biomarker for early detection of ulcerative colitis (UC). Rats were divided into 4 groups (5 rats each). These included the acute UC group, where rats received 3% dextran sodium sulphate (DSS) for six consecutive days, and the chronic UC group, where rats received 3% DSS for three cycles (each cycle composed of 3 days of treatment and 12 days off). Control groups included animals that received tap water for six days and kept it as a negative control for short-term treatment and those received tap water for 45 days and served as a negative control for long-term treatment. Fecal samples were collected from all animal groups at the end of the study. Activin A and calprotectin levels were measured in collected fecal samples using a commercial ELISA kit for rat Calprotectin and rat Activin-A. The results revealed significant increases in fecal activin-A, and fecal calprotectin in chronic UC and a significant increase in fecal activin-A in acute colitis. It could be concluded that fecal activin-A is a useful biomarker for both acute and chronic UC. However, fecal calprotectin can be used as an indicator for chronic UC.

Keywords: Activin-A, Calprotectin, Dextran sodium sulphate, Rats, Ulcerative colitis.

INTRODUCTION

The digestive tract is exposed continuously to abundant bacteria and toxins that originated from food and environment, which make it vulnerable to disease.

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Ulcerative colitis (UC) is a recurrent inflammatory disease of the colon, and its elaborative cause remains elusive. Otherwise, interaction of genetic and environmental factors seems to play a crucial predisposing role. These factors initiate changes in normal intestinal microflora and immune-based alteration in mucosal sensitivity to intestinal antigens. (Akiho *et al.,* 2015, Wallace *et al.,* 2014, Randhawa *et al.,* 2014). UC is one of the inflammatory diseases that affect the intestinal tract (Xavier and Podolsky, 2007) disturbing the immune response, causing imbalance in cytokines release and resulting

in the formation of ulcers in the mucosa that associated with abdominal pain, and diarrhea with mucus, pus, or blood (Libby *et al.,* 2010, Fries and Comunale, 2011). If left untreated, UC may lead to peritonitis or colorectal cancer (Johnson *et al.,* 2020).

Early and precise diagnosis of UC is important for the treatment and control of the disease. many laboratory biomarkers can aid in disease assessment (Aghdaei *et al.,* 2018, Kadijani *et al.,* 2018, Baranipour *et al.,* 2018, Iskandar and Ciorba, 2012, Pardi and Sandborn, 2005). Fecal biomarkers of gastrointestinal tract (GIT) inflammation include fecal activin-A and calprotectin. Fecal activin-A is one of the Transforming Growth Factor-β superfamily, it has been discovered to be a mediator in acute and chronic inflammatory diseases such as sepsis and inflammatory bowel disease. Activin-A exhibited effective pro-inflammatory actions such as the release of cytokines, synthesis of nitric oxide, and generation of eicosanoids (Hedger *et al.,* 2011). It has been reported to play a role in damaging inflammatory responses (Dignass *et al.,* 2000). Research data suggest that activin-A plays a role in the pathogenesis of ulcerative colitis and Crohn's disease (Hübner *et al.,* 1997). It is released early during systemic inflammatory episodes and accompanies cytokines in blood circulation (Phillips *et al.,* 2001). Remarkably, the secretion of activin-A by monocyte is exerted upon contact with antigen-specific T cells (Abe *et al.,* 2002)

Fecal calprotectin is routinely used to assess inflammatory diseases of the GIT (Van Rheenen *et al.,* 2010). It plays an important role in the activation of phagocyte NADPH oxidase. Calprotectin binds to the cytosolic arachidonic acid in the presence of calcium and transfers it to the NADPH oxidase complex in the neutrophil plasma membrane (Kerkhoff *et al.,* 2005). The release of calprotectin could result in weakens the contact between cells and modify the permeability of the endothelium, thus leading to leukocyte eruption (Viemann *et al.,* 2005).

This study aimed to find convenient assessments for early diagnosis of ulcerative colitis (Falvey *et al.,* 2015). To achieve this goal, this study focused on the simultaneous measurement of both activin-A and calprotectin levels in the feces of rats with early and late stages of ulcerative colitis. For this purpose, the murine animal model of the early stage of UC represented by the acute model and late-stage UC represented by the chronic model were implemented in the current study.

MATERIALS AND METHODS

1. Animals
A total of 20 Wistar albino female rats (3-4 months old; weight, 200±20 g) had been obtained from the experimental animal house, Department of Pathology, Faculty of Veterinary Medicine, Assiut University. Rats were randomly divided into 4 groups; each animal was kept in a separate cage. Rats were maintained in an environment with a 12/12 - light/dark cycle at 21.0±2.0˚C room temperature and 60.0±5.0% humidity. Rats were kept for 2 weeks to be acclimatized to the new environment and were fed a standard rat pellet diet and tap water, with 12 h fasting employed prior to the experiment.

2. Experimental protocol.
The experiment was performed at the experimental animal house of the Forensic Medicine Department in the Faculty of Veterinary Medicine at Assiut University, Egypt. Dealing with the experimental animals, collection of samples and euthanasia were done according to the regulations for animal care and welfare postulated with the Ethical committee at the Faculty of Veterinary Medicine, Assiut University, Egypt.

Rats were randomly divided into 4 groups; each group was composed of five animals and kept in separate cages. Group I was designated as an acute UC model group, Group II was designated as a chronic UC

model group, while Group III, IV were kept as negative control groups for the study.

3. Induction of ulcerative colitis models.

Ulcerative colitis was induced using 3% dextran sodium sulphate as previously described (Roy *et al.,* 2020 (Arda-Pirincci and Aykol-Celik, 2020) with some modifications. Briefly, the acute model of UC was induced using 3% DSS that was added to drinking water for six successive days. The chronic model of UC was induced with 3% DSS for three cycles. Each cycle consisted of 3 days of tap water containing 3% DDS followed by 12 days of tap water without DDS. The two negative control groups received tap water without treatment for 6 days and 45 days, respectively.

4. Collection of samples

At the end of the experiment (six days for the acute UC model and 45 days for the chronic UC model), rats of all groups were fasted overnight and subsequently were euthanized under complete anesthesia. The whole colon from the rectum to caecum was resected gently, fecal content was emptied into plastic cups, and the fecal samples (0.5 g) were diluted with 2 ml PBS (0.1 M, pH 7.2). This is a qualitative dilution only, which must allow the pipetting of fecal suspensions. any debris was discarded by centrifugation at 1500 rpm for 2 minutes then the supernatant was stored at -20°C till used. Fecal levels of

activin-A and calprotectin were measured in the supernatant by using a commercial ELISA kit for rat Calprotectin and rat Activin-A (Sino Gene Clon Biotech Co., Ltd). The results were expressed as ng/ml of supernatant.

5. Statistical analysis

Data were expressed as Mean ± SD, Statistical analysis was conducted using SPSS 13.0 for Windows (SPSS, Chicago, USA). The difference in fecal activin-A and calprotectin levels were compared using one-way ANOVA followed by least significant difference (LSD) post-hoc analysis ($p<0.05$).

RESULTS

3.1. Clinical findings

Gross examination of GIT revealed no apparent inflammatory signs in the acute group as well as in the control groups. Nevertheless, some inflammatory signs were apparent in the colons of chronic group animals as compared to those of the control group (Fig. 1). Physical examination of the fecal matter revealed the observation of no apparent changes in the acute model of induced UC. However, the fecal matter of the chronic group showed changes in consistency with increased moistening and one rat showed bloody feces (Fig. 2)**.**
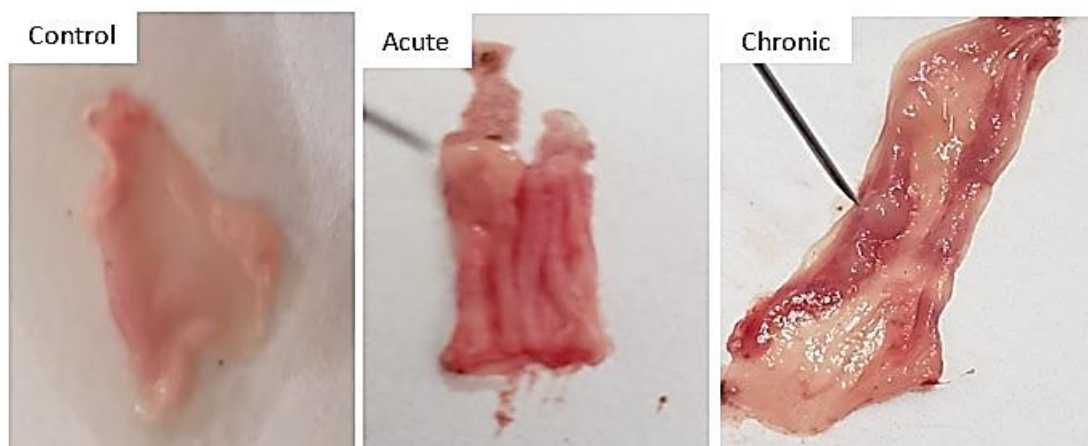
Figure 1: Goss examination of GIT (Colon) in different rat groups. Control and acute show no apparent inflammatory changes while chronic shows congestion, erosion and other signs of inflammation.
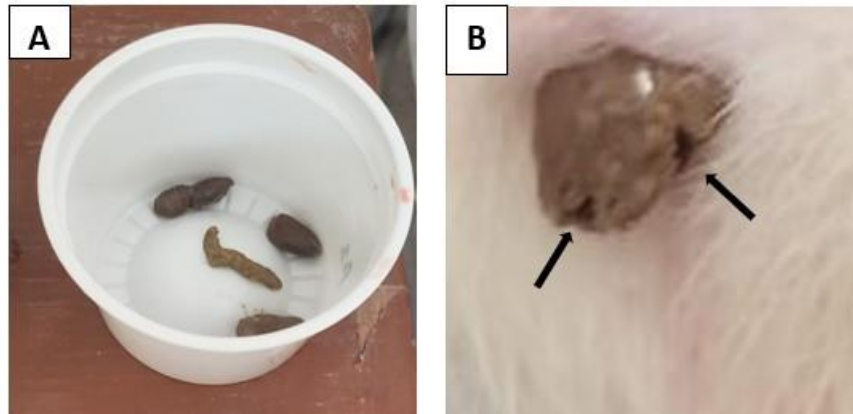
Figure 2: Gross examination of fecal matter. **A)** Normal feces of control rat. **B)** Bloody feces in chronic UC in rat.

2. Fecal levels of Activin-A and Calprotectin

There was a significant increase in fecal activin-A level in both acute (*P value* =0.04) and chronic (*P value* =0.000) groups compared to the control group (74.32±17.85 pg/ml). Also, fecal activin-A level in the chronic group (210.74±37.62 pg/ml) showed a significant increase (*P value* =0.02) compared to the acute group (124.78±44.432 pg/ml).

Fecal calprotectin showed significant increases in chronic colitis (167.30±22.745 ng/ml) compared to the acute (117.00±27.31 ng/ml) (*P value* =0.006) and control (89.82±22.16 ng/ml) (*P value* =0.000) groups, while there was no significant difference between acute colitis and control (*P value* =0.101) groups (Table 1).

Table 1: Fecal Activin and Calprotectin in acute and chronic colitis.

	Control	Acute group	Chronic group
Fecal Activin-A (pg/ml)	74.32±17.85[a]	124.78±44.432[b]	210.74±37.62[c]
Fecal Calprotectin (ng/ml)	89.82±22.16[a]	117.00±27.31[a]	167.30±22.745[b]

Data are expressed as Mean±SD
Values followed by a different superscript letter are significant at P<0.05.

DISCUSSION

Ulcerative colitis is considered an important public health problem, which could lead to peritonitis and increase the risk of progression to colorectal cancer if left untreated (Johnson *et al.,* 2020). In the present study, the inflammation wasn't apparent grossly in the colon of rats in acute UC. However, rats that belonged to the chronic UC group had congestion and erosion in the colon, the same was reported by Awaad *et al.* (2018).

In this study, fecal Activin-A and calprotectin were measured as a marker of mucosal inflammation as an attempt to determine their clinical utility in early diagnosis of ulcerative colitis (acute and chronic ulcerative colitis). Fecal activin-A level was significantly increased in both the acute and chronic UC, these findings were in harmony with Okada *et al.* (2020) who evaluated the clinical utility of rat – calprotectin as a biomarker for ulcerative colitis. The authors concluded that calprotectin would be superior to other inflammatory markers as a useful biomarker for UC and as a novel indicator for its histological severity.

In the current study, the level of fecal activin-A, and fecal calprotectin were significantly increased in chronic ulcerative colitis, these results are supported by the apparent inflammation in the colon and by the presence of bloody feces in some rats of the chronic group. The results agree with Okada *et al.* (2015) who reported that fecal calprotectin level in rats was significantly higher in UC than in the control group as early as two days after the start of the experiment and reached the highest level after ten days (60 folds than control). Fecal calprotectin concentration in humans is considered a highly reliable and reproducible indicator of ulcerative colitis (Limburg *et al.,* 2000, Krzesiek and Iwańczak, 2010, Kolho *et al.,* 2016, Lehmann *et al.,* 2015, Hanai *et al.,* 2004, Foell *et al.,* 2009, Røseth *et al.,* 1997, Zamani *et al.,* 2013, Patel *et al.,* 2017). Several literatures demonstrated that expression of activin-A increased in various inflammatory lesions (Phillips *et al.,* 2001, Hedger *et al.,* 2011), including ulcerative colitis (Hübner *et al.,* 1997), (Sonoyama *et al.,* 2000), Dignass *et al.,* 2002, Zhang *et al.,* 2009).

CONCLUSION

Fecal Activin-A can be used as a biomarker for both acute and chronic forms of ulcerative colitis. Fecal calprotectin is an indicator for chronic colitis.

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التقييم التجريبي لإستخدام أكتيفين- أ في البراز كمؤشر حيوي جديد للتشخيص المبكر لإصابات القولون التقرحي بإستخدام نموذج فئران التجارب

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أجريت هذه الدراسة لتقييم أكتفين-أ في البراز بالمقارنة مع الكالبروتكتين كمؤشر حيوي محتمل للكشف المبكر عن التهاب القولون التقرحي، وقد تم تقسيم الفئران المستخدمة في الدراسة إلى ٤ مجموعات وكانت كل مجموعه تحتوي على ٥ فئران. وتلقت مجموعة التهاب القولون التقرحي الحاد ديكستران كبريتات الصوديوم ٣% لمدة ٦ أيام متتالية، كما تلقت مجموعه التهاب القولون التقرحي المزمن ديكستران كبريتات الصوديوم ٣% لمدة ٣ دورات (تتكون كل دورة من ٣ أيام علاج و١٢ يوم بدون علاج) لمدة ٤٥ يوم. كما تضمنت المجموعة الضابطة الفئران التي تلقت ماء الصنبور لمدة ٦ ايام وكانت بمثابة مجموعة ضابطة سلبية للعلاج قصير الأمد وتلك التي تلقت ماء الصنبور لمدة ٤٥ يومًا وكانت بمثابة مجموعة ضابطة سلبية للعلاج طويل الأمد. وفي نهاية الدراسة تم تجميع عينات البراز من جميع الفئران في المجموعات المختلفه وذلك لقياس مستويات الاكتفين-أ والكالبروتيكتين فيها بإستخدام المقايسة الامتصاصية المناعية للانزيم المرتبط (ELISA). وقد أظهرت النتائج وجود زيادات معنوية في مستوى أكتفين-أ في البراز في حالتي التهاب القولون التقرحي الحاد والمزمن. ومنه يمكننا القول بإمكانية إستخدام اكتفين-أ في البراز كمؤشر حيوي مفيد في حالات التهاب القولون التقرحي الحاد والمزمن. كما يمكن استخدام الكالبروتكتين في البراز كمؤشر لإلتهاب القولون المزمن.

الكلمات الدالة: اكتفين-أ، كالبروتكتين، براز، إلتهاب القولون