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Effect of Different Doses of Sitagliptin in Treatment of Experimentally Induced Colitis in Mice

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Authors' contributions

This work was carried out in collaboration between all authors. Authors RE, KA and AH designed the study, wrote the protocol, and wrote the first draft of the manuscript. Authors RE and HAA managed the literature searches, analyses of the study performed the spectroscopy analysis. All authors read and approved the final manuscript.

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ABSTRACT

Ulcerative colitis is a chronic, relapsing and progressive inflammatory bowel disease (IBD) characterized by diffused mucosal inflammation of the colon. DPP-IV inhibitors may provide a new treatment strategy for IBD. Thus, the aim of this study is to evaluate effect of different doses of sitagliptin as an early treatment of experimentally induced ulcerative colitis in mice. Sitagliptin was administered after the appearance of signs and symptoms of the disease as an early treatment. Twenty four mice were divided into four groups; control group, non treated DSS-induced colitis group, sitagliptin (20 mg/kg/d)-treated DSS-induced colitis group and sitagliptin (100 mg/kg/d)-treated DSS-induced colitis group. The disease activity index (DAI) was calculated by summarizing the scores for weight loss, stool consistency, hemoccult positivity. The length of colon was measured as an indirect marker of inflammation (rate of colon shortening) for each mouse. Serum tumour necrosis factor- α (TNF-α) was measured. Reduced glutathione, Nitrite, Malondialdehyde

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were measured in Colonic homogenates. Histopathological examination was done and the lesion was scored. Reduced glutathione in colonic homogenates was increased. Histopathological score was improved. It can be concluded that sitagliptin is partially effective for treatment of mice with experimentally induced ulcerative colitis.

Keywords: Sitagliptin; inflammatory bowel disease; tumour necrosis factor- α; inflammation; mice.

1. INTRODUCTION

The inflammatory bowel diseases (IBD), Crohn`s disease (CD) and ulcerative colitis (UC), are immune-mediated disorders resulting in chronic, relapsing inflammation of the gastrointestinal tract. Repeated damage and injury of the intestinal surface are key features of inflammatory bowel disease, and require the constant repair of the epithelium. While no specific etiology has been defined, the complex nature of IBD supports that its origin is likely multi-factorial [1]. Ulcerative colitis is a chronic-relapsing, progressive inflammatory bowel disease characterized by diffuse mucosal inflammation of the colon [2].

Although great advances have been made in the management of the disease a curative therapy does not yet exist [3]. ROS and NOS, as well as pro-inflammatory cytokines have a long-standing implication in both the aetiology and the progression of UC [4]. A disturbance of the anti-inflammatory cytokine profile in favour of pro-inflammatory cytokine overproduction leads to disease states, such as that observed in IBD (*Xavier* et al. 2007) overexpression of cytokines such as TNF-α, interferon-γ (IFN-γ), interleukin-1β (IL-1β), IL-12 as well as IL-6 were found in patients with IBD [5]. The increased expression of TNF-α has been demonstrated by several studies in intestinal biopsies, both in CD patients and in those with UC versus healthy controls; in addition, mucosal biopsies from affected areas showed significantly higher levels than those of mucosal biopsies from macroscopically unaffected areas. Finally, serum levels of TNF-α correlate with clinical and laboratory indices of disease activity such as the erythrocyte-sedimentation rate (ESR), C-reactive protein (CRP), and disease activity index (DAI) [6].

Glucagon-like peptide (GLP)-1 and (GLP)-2 are both secreted from enter endocrine L-cells and are rapidly degraded by dipeptidyl peptidase IV [7]. Dipeptidyl peptidase IV(DPP-IV) inhibitors, which are among the newest drugs for the treatment of type 2 diabetes mellitus, are expected to prolong the half-life of GLP-2 as well as GLP-1, thus resulting in the promotion of epithelial cell proliferation and regeneration [8]. As GLP-2 have several actions on the intestine like the promotion of epithelial proliferation and the inhibition of epithelial apoptosis. GLP-2 has been identified as a pharmacological target in treatment for IBD [9]. Furthermore, DPP IV has an important role in the recruitment of immune cells, especially T cells. These data indicate that inhibition of DPP IV and enzymes with DPP IV-like activity may provide a new treatment strategy for IBD [10].

Thus, the aim of this study is to evaluate effect of different doses of sitagliptin as an early treatment of experimentally induced ulcerative colitis in mice.

2. MATERIALS AND METHODS

2.1 Animals

Twenty four female C57BL/6 mice were purchased from (Tudor Bilharz Institute, Cairo, Egypt). This work was done at Mansoura Experimental Research Center (MERC), Faculty of Medicine, Mansoura University. Mice were separated into four groups (n = 6/group) and housed under standard conditions (25ºC and 12-h light–dark cycle, 6 mice per 80 cm2 cage) for at least 1 week to acclimate before starting the experiments. Throughout the experiments the mice were fed with standard pellet diet ad labium. All protocols were approved by our local committee of Animal Care and Use.

At day 5 of the experiment all animals receiving 3% dextran sulphate sodium (DSS) showed clear clinical signs of acute colitis. On showing signs, treatments started from day 5 till day 14.

2.2 Induction of DSS Colitis

Acute colitis was induced by administration of 3% (w/v) dextran sulphate sodium (TDB consultancy, Sweden; MW 40,000) which was dissolved in sterile filtered drinking water. The animals had free access to the DSS solution, which was changed every day for 7 days then returned to

drinking plain water at day 8 [11]. DSS-induced colitis is a well established experimental model that mimics many of the features of human ulcerative colitis including diarrhea, bloody feces [12] and colonic shortening [13]. DSS can promote inflammation by many biological pathways including direct cytotoxic effects [14] as well as apoptotic damage of colonic epithelial cells [15].

2.3 Drugs and Chemicals

- ***Dextran sodium sulphate (DSS):*** 3% (w/v) dextran sulphate sodium (purchased from TDB consultancy, Sweden; MW 40,000).

- ***PBS (phosphate buffer solution):*** It was prepared by dissolving the following chemicals into 1000 ml distilled water, used for washing the blood and in tissue homogenization.

Sodium dibasic phosphate	2.17 gm
Potassium dihydrogen phosphate	0.2 gm
Sodium Chloride	7.1 gm

- ***Sitagliptin (januvia®)*** was obtained from MERCK in form of 100 mg tablets.

2.4 Animal Grouping and Experimental Design

Mice were divided into the following groups (6 mice in each group):

2.4.1 Group 1 (control group)

The animals received plain filtered water.

2.4.2 Group 2; non treated DSS-induced colitis group

The animals had free access to the DSS solution, which was changed every day for 7 days then returned to plain water drinking at day 8 [16].

2.4.3 Group 3; sitagliptin (20 mg/kg/d)-treated, DSS-induced colitis group

DSS-induced colitis mice were treated with sitagliptin orally once daily (20 mg/kg/d) starting from day 5 to day 14. Tablets were suspended in 0.5% methyl-cellulose solution as vehicle [17].

2.4.4 Group 4; sitagliptin (100 mg/kg/day)-treated, DSS-induced colitis group

DSS-induced colitis mice were treated with sitagliptin orally once daily (100 mg/kg/day) starting from day 5 to day 14. Tablets were suspended in 0.5% methyl-cellulose solution as vehicle [18].

For scoring colitis activity, weight changes were recorded daily throughout the experiment. Fecal samples of each animal were visually inspected for signs of diarrhea and rectal bleedings. The disease activity index (DAI) was calculated by summarizing the scores for weight loss, stool consistency, hemoccult positivity (detected by Benzidine test) or gross bleedings (Table 1).

DAI value is the combined score of weight loss, stool consistency, and bleeding divided by 3[19].

At day 14; after the end of each group treatment protocol, animals were anaesthetized by thiopental, dissected and postmortem blood was collected by cardiac puncture; then allowed to stand for clotting, centrifuged and serum was separated.

The entire colon was removed, gently flushed with cold PBS to remove contents and blood clots, placed on an ice-cold plate, cleaned of fat and mesentery and dried between two filter papers then weighed. Each colon was gently stretched; the length of colon was measured from the colo-cecal junction to the anus as indirect marker of inflammation (rate of colon shortening) for each mouse.

2.5 Preparation of Colonic Homogenates

Immediately after sacrificing the mice, colons were excised and washed twice with PBS, dried between two filter papers then homogenized in 5 ml PBS per gram tissue, centrifuged at 4000 r.p.m for 15 minutes. Supernatant was removed, divided into aliquots and frozen at - 80ºC until assayed.

2.6 Histopathological Examination

Colon segments were fixed in 10% formalin solution for 24-h.

Table 1. Scoring of disease activity index

Score	Weight loss (%)	Stool consistency	Occult/gross bleeding
0	None	Normal	Normal
1	1-5%		
2	5–10%	Loose stools	Occult bleeding
3	10–15%		
4	>15%	diarrhea	Gross bleeding

Paraffin wax tissue blocks were prepared for sectioning by sledge microtome at 4 µm thickness. The obtained tissue sections were collected deparaffinized on glass slides. Slides were H & E stained, and scored according to the criteria listed in Table 2. Individual scores and the sum of all scores were calculated [20].

2.7 Biochemical Assay

1-determination of TNF-α concentration in mouse serum as an inflammatory marker (Mouse TNFα ELISA Kit, Boster immunoleader): According to Brenner et al. [21].

2-oxidative stress markers

A. **Colorimetric determination of colonic homogenates reduced glutathione (GSH)** according to Beutler et al. [22].

B. **Colorimetric determination of colonic homogenates Nitrite** according to Montgomer and Dymock, [23].

C. **Colorimetric determination of colonic homogenates lipid peroxide (Malondialdehyde)** according to Ohkawa et al. [24].

2.8 Analytical Statistics

In the statistical comparison between the different groups, the significance of difference was tested using one of the following tests:

1. ANOVA (analysis of variance): Used to compare between more than two groups of numerical (parametric) data followed by post-hoc tukey for multiple comparisons.
2. Kruskal-Wallis test: Used to compare between more than two groups of numerical (non- parametric) data.

A *P* value <0.05 was considered statistically significant in all analyses.

3. RESULTS

3.1 Effect of Sitagliptin on DAI

DAI is a useful index for the degree of colitis. Mice receiving DSS showed a significant increase in DAI compared to the control group ($p < 0.01$). Administration of sitagliptin (20 mg/kg/d) and (100 mg/kg/d) reduced the percentage of DAI by 8% and 16% respectively, compared to the DSS control group (Fig. 1). No death was observed among the experimental animal groups.

3.2 Effect of Sitagliptin on Colonic Length

DSS treatment led to highly significant shortening in colon length of mice (6.10±0.56) as compared to the control (8.25±0.23) group ($p < 0.001$). Sitagliptin treated groups (20 mg/kg/d and 100 mg/kg/d) showed no significant increase in colon length (6.23±0.30, 6.47±0.46; respectively ($p > 0.05$), compared to DSS-induced colitis (6.10± 0.56) control group (Table 3).

3.3 Effect of Sitagliptin on Inflammatory Markers

DSS-induced a significant increase in serum TNF-α ($p < 0.001$) compared with the normal group. Furthermore, Sitagliptin (20 mg/kg/d) significantly reduced (115.12±20.83) TNF-α level ($p < 0.01$) as compared to non-treated DSS-induced colitis (191.62±58.86) group. However, sitagliptin (100 mg/kg/d) produced a more significant reduction (83.45±28.63) of TNF-α level ($p < 0.001$) as compared to non-treated DSS-induced colitis (191.62±58.86) group (Table 3).

Table 2. Histopathological scores

Grade	Extent of inflammation	Infiltration neutrophils+ Lymphohistio-cytes	Extent of crypt damage	Crypt abscesses	Sub-mucosal oedema	Loss of goblet cells	Reactive epithelial hyperplasia
0	None	None	None	None	None	None	None
1	mucosa	focal	Basal one third	focal	Focal	focal	focal
2	Mucosa+ submucosa	multifocal	Basal two thirds	multifocal	multifocal	multifocal	multifocal
3	Mucosa+submucosa+muscle layer	diffuse	Entire crypt damage		diffuse	diffuse	diffuse
4	Transmural		crypt damage+ ulceration				

Table 3. Effect of different doses of sitagliptin on clinical indices of inflammation and serum TNF alpha in DSS-induced colitis in mice

Groups *(n=6)*	Control group	DSS- induced colitis group	Sitagliptin (20 mg/kg/d) treated group	Sitagliptin (100 mg/kg/d) treated group
Colonic length *(cm)* Mean ±SD	8.25±0.23	6.10±0.56 [A]	6.23±0.30 [C]	6.47±0.46 [C]
Serum TNF alpha(Pg/ml)	30.83±9.91	191.62±58.86 [A]	115.12±20.83 [B]**	83.45±28.63 [B]***

[A], p < 0.001 compared with the normal group; [B], p < 0.001 compared with DSS-induced colitis control group; [C], p > 0.05 compared with DSS-induced colitis control group

Table 4. Effect of different doses of sitagliptin on oxidative stress markers activity in colonic tissue in DSS- induced colitis in mice

Groups *(n=6)*	Control group	DSS- induced colitis group	Sitagliptin (20 mg/kg/d) treated group	Sitagliptin (100 mg/kg/d) treated group
Colonic tissue Nitric oxide (µmol/L)	11.12±5.43	45.75±10.47 [A]	41.50±23.19 [C]	29.90±10.38 [C]
Colonic tissue malondialdehyde (MDA) (nmol/mg)	2.95±0.38	7.63±0.66 [A]	6.03±0.80 [B]**	5.30±0.63 [B]***
Colonic tissue *GSH*	1.57±0.36	0.67±0.19 [A]	1.08±0.26 [C]	1.07±0.27 [C]

*[A], p < 0.001 compared with the normal group; [B] Significantly different from DSS group at *p < 0.05 ** p < 0.01 and *** p < 0.001; [C], Non significantly different p >0.05 as compared to DSS-induced colitis group*

3.4 Effect of Sitagliptin on Oxidative Stress

DSS treatment led to a significant increase in the MDA (7.63±0.66), NO (45.75±10.47) and decreased reduced glutathione (0.67±0.19) levels in the colon ($p < 0.001$) as compared to normal group (2.95±0.38; 11.12±5.43 and 1.57±0.36, respectively), thus indicating that elevated oxidative stress is involved in the DSS-mediated colitis in mice.

Both of doses of sitagliptin non-significantly reduced colonic NO levels and rGSH levels ($p >0.05$) as compared to non-treated DSS-induced colitis group.

Small dose of sitagliptin showed significant reduction of colonic MDA (6.03±0.80) levels ($p< 0.01$) as compared to DSS-induced colitis group. However, sitagliptin (100 mg/kg/d) produced more significant reduction of colonic MDA levels ($p< 0.001$) as compared to DSS-induced colitis group (Table 4).

3.5 Effect of Sitagliptin on Histopatho-logical Lesion

As compared to Fig. 2A (normal histological appearance of the mouse colon), Fig. 2B showing that histological signs of colonic inflammation were: multifocal mucosal infiltrations of predominantly neutrophils and lymphohistocytes (grade 2), diffused sub mucosal oedema (grade 3). The extent of inflammation involved mucosa, submucosa and muscle layer (grade 4). Extent of crypt damage included multiple ulcerations characterised by complete loss of the mucosal epithelium (grade 4).

Fig. 2C showed that treating the DSS-induced colitis group by sitagliptin at dose of (20 mg/kg/d) led to non significant reduction of colonic inflammation, showing multifocal mucosal infiltrations of neutrophils and lymphohistocytes (grade 2). The extent of inflammation involved mucosa, submucosa and muscle layer (grade 3). Crypt damage and ulceration was found (grade 4).

Moreover, Fig. 2D showed that sitagliptin at dose of (100 mg/kg/d) led to reduction of the DSS-induced colitis inflammation, showing focal mucosal infiltrations of neutrophils and lymphohistocytes (grade 1) with lost entire crypts (grade 3). Inflammation extended only to mucosa and submucosa (grade 2). This reduction is statistically non-significant.

The sums of histopathological scores were between 9 and 16 in the non-treated DSS groups. The sums of histopathological scores were between 5 &16 in small dose of sitagliptin-treated group, while those in large dose of sitagliptin-treated group ranged between 5 &12.

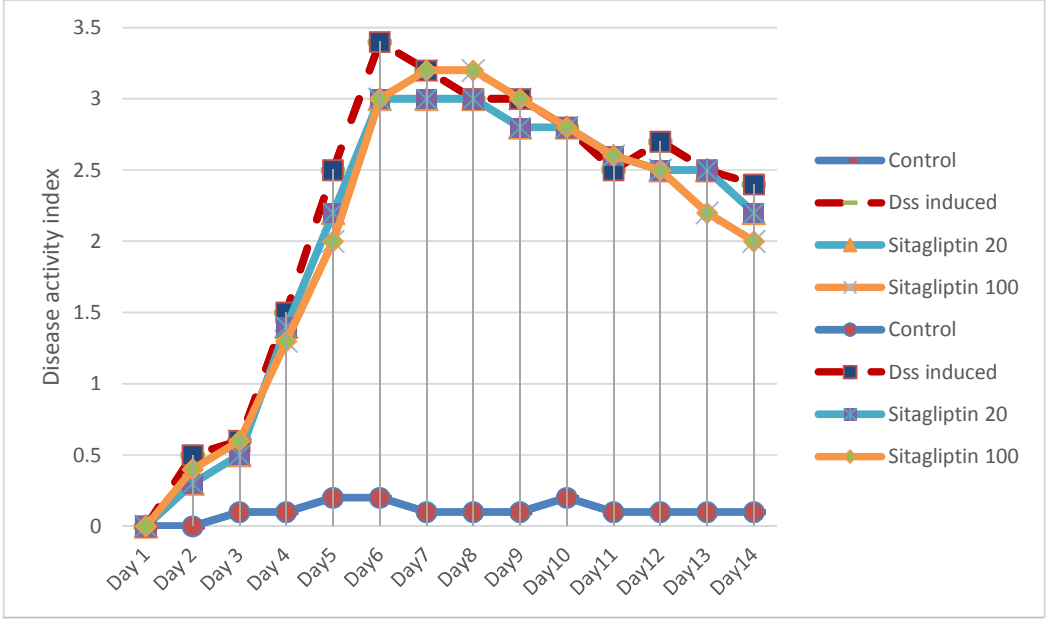

Fig. 1. Effect of different doses of sitagliptin on disease activity index (DAI) in DSS-induced colitis in mice

Table 5. Effect of different doses of sitagliptin on histopathological score in DSS-induced colitis in mice

Groups *(n=6)*	Control group	DSS- induced colitis group	Sitagliptin (20 mg/kg/d) treated group	Sitagliptin (100 mg/kg/d) treated group
Histopathological score	0.00	9.50±8.00-16.00[A]	5.00±4.00-16.00[C]	5.00±4.00-12.00[C]

*Data are presented in form of median and range (Minimum – maximum) and were analyzed by non parametric Kruskal–Wallis test; [A], p < 0.01 compared with the normal group; [B] Significantly different from DSS group at ** p < 0.01 and *** p < 0.001; [C] Non significantly different (p >0.05) as compared to DSS- induced colitis group*

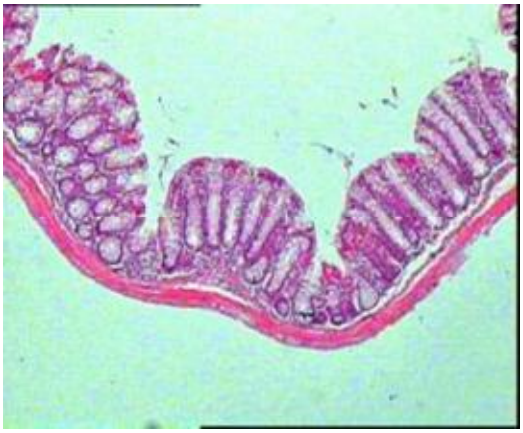

Fig.IIA: Histology of the mouse colon in vehicle control tissues showing normal histological appearance of the mouse colon.

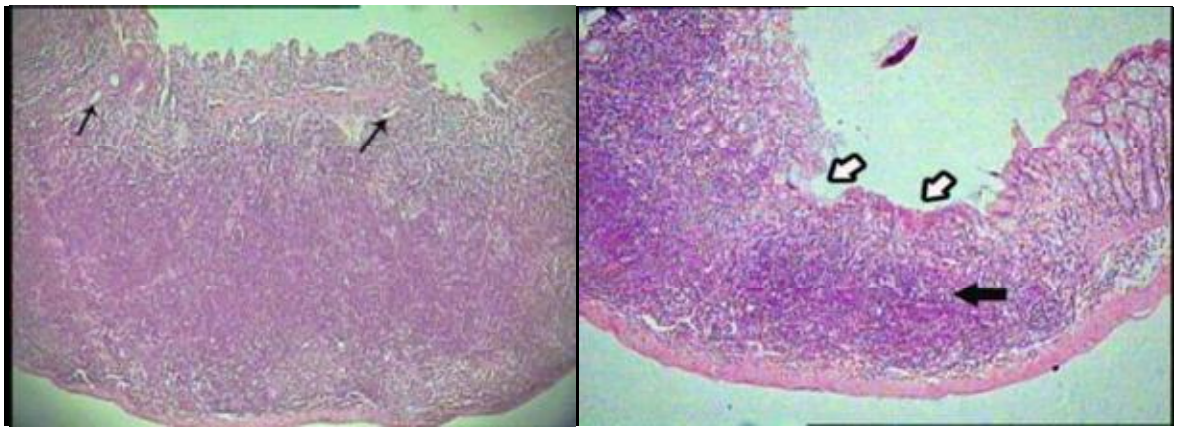

Fig.II B:Histopathological findings of hematoxylin and eosin-stained colon tissue sections from DSS-treated mice

Open arrows show lost entire crypts with ulceration and diffuses loss of goblet cells. Bold black arrow shows diffuse inflammatory infiltrate involved mucosa, submucosa and muscle layer.Thin arrows show submucosal edema.

Fig. 2A. Histology of the mouse colon in vehicle control tissues

4. DISCUSSION

In the present study the DAI shows DSS-induced (administered for 7 days in drinking water) colonic and systemic inflammation in mice (Fig. 1). DSS-induced colitis is a well established experimental model that mimics many of the features of human UC including diarrhea, bloody feces [12] and colonic shortening [13]. These effects of DSS on the colon were explained by the fact that DSS can promote inflammation by many biological pathways including direct cytotoxic effects [14] as well as apoptotic damage of colonic epithelial cells [15].

In the present study, colitis led to a significant increase in the pro-inflammatory markers in the plasma of mice as apparent from increased levels of TNF-α in the plasma of DSS- treated animals as compared to the control animals.

This is in consistent with study of Nishiyama et al. [25] which showed an elevation of the disease activity index score and histological damage score induced by DSS based on the changes in tumor necrosis factor-alpha in plasma. Furthermore, Oz et al. [26] found that inflammatory cytokine levels like TNF-*α* was considerably increased in DSS-induced moderately severe colitis in wild type mice.

In the present study, inflammation in the colon led to the generation of oxidative stress as indicated from a significant increase in the MDA and NO parameters in the colonic tissue as compared to the control group. Similar findings have been previously reported [27,28]. The production and release of ROS species by immune cells appear to play an important role in the pathophysiology of colitis [29]. Increased MDA level in stress condition is responsible for lipid membrane destruction and tissue injury [30]. NO reacts with O2 -produced by activated neutrophils- to form another potent oxidant, peroxynitrite (ONOO).

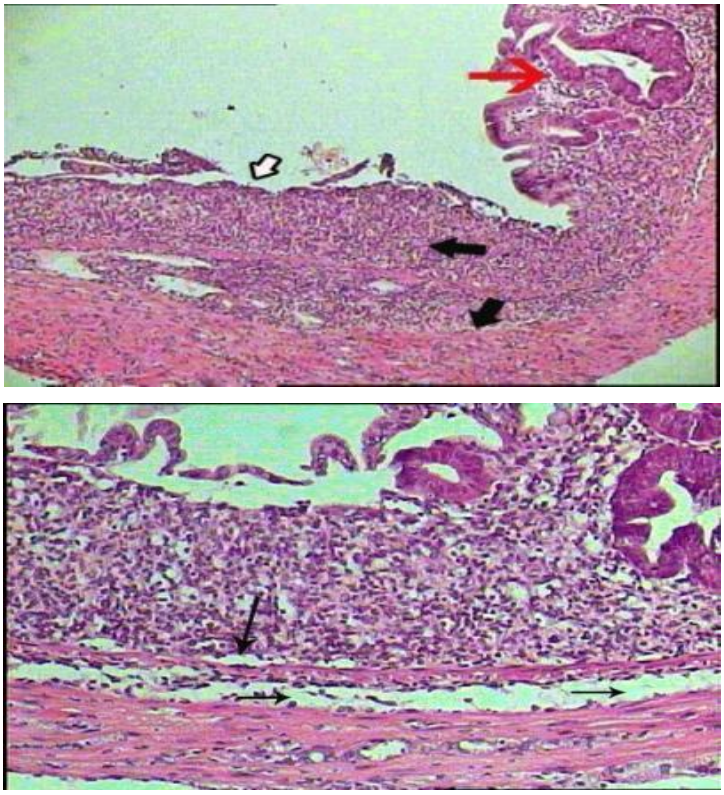

Fig. 2C. Histopathological findings of hematoxylin and eosin-stained colon tissue sections from DSS-induced colitis group treated with sitagliptin 20 mg/kg/d

Open arrow show lost entire crypts with ulceration and diffuses loss of goblet cells. Bold black arrow shows diffuse inflammatory infiltrate involved mucosa, submucosa and muscle layer. Thin arrows show sub mucosal oedema. RED arrow show dysplastic changes

ONOO administration to the colon results in tissue injury [31]. However, inducible nitric oxide synthesase (iNOS)-derived NO stimulates TNF-α production in the middle and distal colon, which promotes the infiltration of neutrophils for example through stimulation of synthesis of intracellular adhesion molecule (ICAM) and P-selectin, therefore leading to colonic tissue damage [32].

Furthermore, in the current study, there was a reduced GSH level in the colonic tissue when compared to the control group. Depletion of GSH is considered a crucial event of colonic damage occurring both in human IBD and in animal models [33]. This depletion could be a consequence of enhanced production of free radicals and could represent a specific disorder due to an impaired colitis activity of GSH synthesizing enzyme [34].

Furthermore, the sums of histopathological scores were between 9 and 16 in the non-treated DSS groups in all studies [20]. Histological signs of colonic inflammation were focal mucosal infiltrations of predominantly neutrophils and lymphohistocytes (grade 2; Fig. 2B), multifocal sub mucosal oedema (grade 2; Fig. 2B). The extent of inflammation affected mucosa, submucosa and muscle layer (grade 3 Fig. 2B).

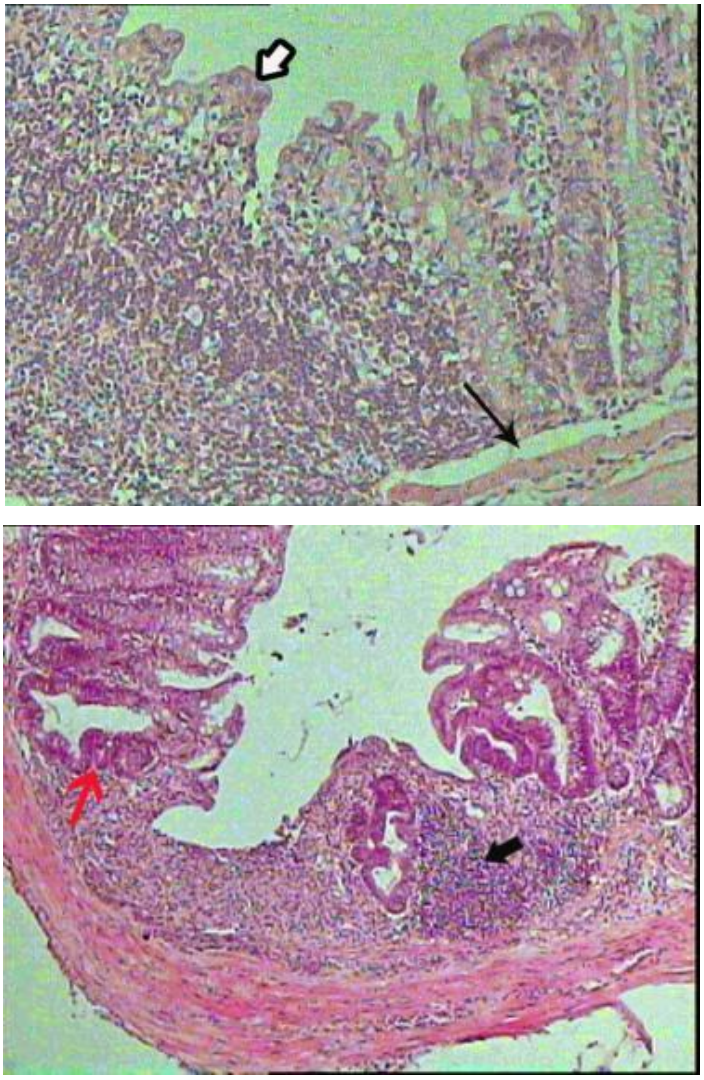

Fig. 2D. Histopathological findings of hematoxylin and eosin-stained colon tissue sections from DSS-induced colitis group treated with sitagliptin 100 mg/kg/d

Open arrow show lost basal two thirds of the crypts. Bold black arrow show focal mucosal infiltrates. Thin arrows show sub mucosal oedema. RED arrow show dysplastic chang

In the present study, sitagliptin in small and large doses reduced serum level of TNF- α in mice with experimentally-induced colitis. Satoh-Asahara et al. [35] concluded that sitagliptin reduces serum levels of inflammatory cytokines such as TNF-α in Japanese type 2 diabetic patients.

This can be explained by the DPP IV/CD26 inhibitors that have been shown to be effective in limiting the activation processes of immunity and to modify the course of disease associated with an imbalanced T cell response, as in IBD [11,18,36] resulting in a decreased secretion of pro-inflammatory cytokines, including tumor necrosis factor (TNF) - *α* and interferon (IFN)-c as well as an increase in the anti-inflammatory cytokine transforming growth factor (TGF)-b [37].

Furthermore, in the present study, sitagliptin in a small dose significantly reduced MDA level. This may in fact support the anti-oxidant effect of sitagliptin [38]. However -in the present study- sitagliptin in large dose produced more pronounced reducing effect on MDA. It has been known that inflammation plays a pivotal role in the generation of oxidative stress [39]. Oxidants play a direct role in the chronic inflammatory process by increasing the number of neutrophils and macrophages that induce a self sustaining phlogogenic loop [40].

Sitagliptin in small dose showed slight effect on infiltration of neutrophils and lymphohistocytes as it showed diffuse inflammatory infiltrate which involved mucosa, submucosa and muscle layer. (Grade 2; Fig. 2C).

However, Sitagliptin in a large dose led to more reduction of DSS-induced colitis inflammation showing focal mucosal infiltrations of neutrophils and lymphohistocytes (grade 1). Inflammation is only extended to mucosa and submucosa (grade 2) with no submucosal oedema (grade 0) and no loss of goblet cells (grades 0-1). Thus, our histopathological scoring revealed that sitagliptin improved histological score particularly with a large dose (Fig. 2D).

Our results indicated that starting sitagliptin treatment on day 5 after diarrhea and bleeding started till sacrifice day in small dose, modify DAI by a percentage of 8% while a large dose of sitagliptin, modify DAI by a percentage by 16% (Fig. 1). Furthermore, sitagliptin suppressed the systemic inflammatory marker: serum TNF-α and partially ameliorated local lesion in the colon as indicated by decreased colonic tissue MDA and improved histopathological grades and scores and restored goblet cells particularly with large dose of sitagliptin. This means that treatment with sitagliptin in the present study is partially effective which can be explained by the short duration of treatment as we started at the 5^{th} day of appearance of signs of systemic inflammation till the end of the study at the 14^{th} day. Moreover, substrates of the DPP-IV inhibitors included not only GLP-1, GLP-2 but also peptides which mediate immunity, e.g. lymphotaxin, monocyte chemo attractant protein and interferon-inducible protein 10. Therefore, inhibition of DPP-IV may result in increased pro-inflammatory chemokines [41]. Moreover, function of cellular DPP IV in growth regulation and cytokine production is mainly regulated by a binding site within the central pore of the enzyme, which interacts with DPP IV inhibitors [42].

5. CONCLUTION

It can be concluded that sitagliptin is partially effective for treatment of mice with experimentally induced ulcerative colitis. The results may reflect that a large dose of Sitagliptin, decreased Malondialdehyde and increased proliferation and regeneration of epithelial cells and has no anti-inflammatory effects.

CONSENT

It is not applicable.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate our local ethics committee with No. MS 437 Faculty of Medicine, Mansoura university.

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To: Sarah El-Shahat who is veterinarian at MERC.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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