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High fat diet induces anti-inflammatory effect in experimental colitis

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The prevalence of ulcerative colitis, one of the inflammatory bowel diseases, has been increasing worldwide. Though fatty diet leads to development of colitis, only little is known about the separate and combined effects of different fat compositions and intermittent fasting, and the effects of preventative dietary changes on experimental colitis. In this study, we investigated the effect of feeding type and frequency on the inflammation ulcerative colitis. Five groups, each comprising 7 male Wistar albino rats, were formed viz. Colitis (as a control), High sucrose diet + Colitis, High sucrose diet + Intermittent fasting + Colitis, High fat diet + Colitis, High fat diet + Intermittent fasting + Colitis. The intermittent fasting group (experimental group) was not fed for 2 days (non-consecutive) in a week (except water), otherwise fed with *ad libitum*. Following the 7-wk feeding application, the rats were treated with intrarectal administration of 4% acetic acid (pH 2.4). After the rats were sacrificed, the levels of interleukin-1β, insulin, C-reactive protein, leptin, tumor necrosis factor-α, interleukin-6, insulin-like growth factor-1 and adiponectin were analyzed from the blood samples. Analyzes of results revealed a statistically significant decrease in interleukin-1β, C-reactive protein, tumor necrosis factor-α, interleukin-6 and adiponectin levels in High sucrose diet + Intermittent fasting + Colitis and High fat diet + Intermittent fasting + Colitis groups (P<0.05). According to these findings, the amount of fat and fatty acid composition in the fatty diet may have a protective effect against the development of colitis. Intermittent fasting further enhances this protective effect by lowering proinflammatory cytokine levels and reducing systemic inflammation in the body.

Keywords: Intermittent fasting, Inflammation, Inflammatory bowel disease (IBD), Ulcerative colitis

Ulcerative colitis is an inflammatory bowel disease (IBD) characterized by chronic inflammation of the gastrointestinal tract (UC). In terms of the prevalence of IBD, developedcountries have been surpassed developing countries[1]. Genetic predisposition as well as environmental and dietary factors play effective role in the onset of the disease[2]. Approximately, 70% of IBD patients use elimination diets during remission[3,4]. Disease-related attacks and colorectal cancer risk are also reduced by suppressing mucosal inflammation in the UC[5].

Consuming sugary foods with high fructose levels is directly related to health problems[6]. Excess calories coming from consumption increase the risk of obesity and associated diseases[7]. There have been many contradictory findings on the role of UC etiology in the various dietary regimens[8]. Non-steroid anti-inflammatory drug use aggravates the UC and makes it reoccur[9].

Adipose tissue is important in insulin resistance[10] and contributes to the systemic inflammation[11]. Proinflammatory cytokines, such as IL-6, CRP and leptin are released from adipose tissue even in the absence of acute injury or inflammation[12]. These elevated cytokines trigger pathophysiological processes resulting in inflammation and immune system disruption[13].

High fat diet causes eventually systemic low-level inflammation[14]. Consumption of saturated fatty acid-

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Abbreviations: ANOVA, one-way analysis of variance; BDNF, brain-derived neurotrophic factor; CD, Crohn's disease; CRP, c-reactive protein; DSS, dextran sulphate sodium; FMDs, fasting-mimicking diets; HFD, High-fat diet; HFD+C, high fat diet + colitis; HFT+IF+C, high fat diet + intermittent fasting + colitis; HSD+C, high sucrose diet + colitis; HSD+IF+C, high sucrose diet + intermittent fasting + colitis; IBD, inflammatory bowel diseases; IGF-1, insulin-like growth factor-1; IL-, interleukin-; ISCs, intestinal stem cells; MCP-1, monocyte chemotactic protein 1; PF, periodic fasting; SD, standard diet; SPSS, Statistical Package for the Social Sciences; TNF-α, tumor necrosis factor-α; UC, ulcerative colitis]

rich foods and fast-food type diets increase the risk of IBD[15,16]. UC and Crohn's Disease (CD) are caused either by inflammation-related cytokines in the intestinal mucosa or by complex inflammatory processes[17]. Increased levels of inflammatory factors, such as TNF-α, IL-1β, IL-6 and IL-8 have been reported in inflammatory colonic tissues of patients[18].

Recent research has focused on the potential therapeutic effects of several dietary treatments, including intermittent fasting, calorie restriction, and protein restriction[19]. There has been an increasing number of studies on the positive effects of intermittent fasting and fasting-mimicking diets in terms of delaying the aging, increasing the quality of life, and preventing the various pathologies due to aging[20]. Although the effects of different diet interventions are investigated, only few studies are available on the protective action of different diets and intermittent fasting against IBD development[21].

Since ulcerative colitis studies usually focus on alleviating the disease's effects, there is a large gap in the field of protective environmental factors against the disease development. Therefore, in this study, we investigated the effects of time restricted feeding on inflammatory markers, which contribute to the development of ulcerative colitis in rats fed a high fat and high-sugar diet, as well as the protective effects of intermittent fasting and feeding type on inflammation in an experimental colitis model in rats.

Materials and Methods

Animals

Animals of the study were purchased from Experimental Animal Units of Van YuzuncuYil University. A total of 42 male Wistar albino rats, grown in standard conditions for 8 to 10 weeks, weighing between 200-250 g were used. The animals were kept under standard humidity, light (12:12 h light-dark) and temperature conditions (23°C) during the experiment and all other conditions were met within the laboratory animal care standards, except experimental diet. All the rats were fed with standard rat feed for a week to ensure homogenization between the groups. The cages had wire mesh floors to prevent coprophagia. Ethical approval was obtained from Van YuzuncuYil University Animal Experiments Local Committee (Approval number: YYU/201509).

Experimental groups

The rats were randomly divided into five groups (7 rats in each group). as follows: Gr. I, Colitis (as a control); Gr,II, High sucrose diet + Colitis (HSD+C); Gr. III, High sucrose diet + Intermittent fasting + Colitis (HSD+IF+C); Gr. IV, High fat diet + Colitis (HFD+C); and Gr. V, High fat diet + Intermittent fasting + Colitis (HFD+IF+C). Animals were weighed before and after the experiment.

Intermittent fasting

Intermittent fasting groups had restricted food for 24 h twice a week (Monday and Thursday) without water restriction and were allowed *ad libitum* food intake on other days.

High sucrose diet

In addition to the standard rat feed, sucrose (300 g/L) was added to the water of the high sucrose diet groups[22].

High fat diet

High fat diet was achieved by melting 25 g of margarine into 100 g of standard rat food and mixing the pellets to ensure that the pellets absorb the oil[23]. High-fat diet was prepared fresh every day. Rat pellet and high fat diet analysis results are given in Table 1.

The composition of margarine per 100 g is as follows; total fat (75 g; saturated fat (43 g), trans fat

Table 1 — Standard rat pellet[†] and high-fat diet analysis (Rate, %)

Nutrient content	Standard rat pellet	High-fat diet
Raw oil	2.8	15.57
Raw protein	23	19.27
Raw cellulose	5	4.59
Raw ash	7.1	6.48
Humidity	12.8	8.11

[[†]Feed and Flour Industry Corporation, Bayramoglu, Erzurum, Turkey]

Table 2 — Fatty acid composition of the margarine

Fatty acid	%
C12:0 Lauric	0.53
C14:0 Myristic	1.02
C16:0 Palmitic	43.81
C16:1Palmiteloic	0.17
C18:0 Stearic	4.73
C18:13Elaidic (C18:1n9t)	0.12
C18:1 Oleic (C18:1 n9c)	37.44
C18:2Linolelaidic (C18:2n9,12t)	0.19
C18:2 Linoleic (C18:2n9,12c)	11.12
C20:0 Arachidic	0.37
C18:3gama-Linolenic (C18:3n6,9,12t)	0.03
C20:1gadoloic-eicosenoate	0.16
C18:3 Linolenic (C18:3n9,12,15c)	0.15
C22:0 Behenic	0.08
C24:0 Lignoceric	0.07
Total	100.00

(< 0.75 g)), cholesterol (0 mg), carbohydrate (0.2 g), protein (0.1 g), vitamin A (600 µg), vitamin D (2.5 µg). The fatty acid composition of margarine added to high-fat diet is given in Table 2.

Experimental application was maintained for 7 weeks. All groups were allowed to consume their respective treatment diets freely during this period. At the end of the period, the animals were fasted for 24 h before sacrificing but their access to water was not restricted during this time.

Experimental colitis

Rats were anesthetized with ketamine (50 mg/kg, and Rompun (10 mg/kg) intramuscular). The rats were brought to 30^{o} Trendelenburg position, and a soft polyethylene catheter of 8 mm external diameter was inserted into the colon at the depth of 8 cm from the anus. The rats in the all groups were intrarectally administered with 1 mL acetic acid (4%, pH 2.4)[24]. In order to prevent the applied liquid substances from escaping, the subjects were lifted from the tail for 30 s and held upside down and then again, they were kept in Trendelenburg position for about 30 min until they recovered from anesthesia. The animals in all the groups were sacrificed by cervical dislocation method under anesthesia by applying ketamine 80 and 10 mg/kg xylazine intraperitoneally 48 h after the administration of acetic acid.

Sample collection and ELISA analysis

Blood samples were taken from the left ventricle of the sacrificed rats' hearts and collected into EDTA tubes. After the tubes were centrifuged at 3000 rpm for 10 min, the plasma samples were stored in −80^{o}C freezer until the analysis. IL-1β, IL-6, TNF-α, insulin, adiponectin, leptin, IGF-1 and CRP assays from blood plasma were analyzed using specific commercial ELISA kits (Hangzhou Eastbiopharm, Zhejiang, China) in accordance with the manufacturer's protocols. In ELISA analysis, Statfax 2600 automatic washer and Statfax 2100 reader were used. The inter and intra assay coefficient of variation for IL-1β, IL-6, TNF-α, insulin, adiponectin, leptin, IGF-1, and CRP were <10, <12%, and sensitivities respectively were 10.23 pg/L, 2.49 ng/L, 2.51 ng/L, 0.05 mIU/L, 0.16 mg/L, 0.05 ng/mL, 1.55 ng/mL and 1.53 pmol/L.

Statistical analysis

Statistical analyses were performed using SPSS (Ver. 22; IBM-SPSS). Measured values were given as mean ± standard error. The significance of the differentiation of the data between the groups was determined by one-way ANOVA. While the goodness-of fit test was performed to see whether there was a normal distribution in each group, Levene's test was used for evaluating homogeneity intergroups. In the analysis of the variance, Bonferroni correction was used for pairwise comparison of the parameters when there were significant differences and homogeneity was achieved. Games-Howell *post-hoc* test was used in cases where homogeneity was not achieved. For the weight differences of the groups, paired samples t-test was used and $P<0.05$ was considered significant.

Results

It was observed that all groups with colitis had different degrees of damage to the colon tissues. Histopathological examinations of the colon samples showed that acetic acid caused severe colitis, whereas the damage remained at minimal levels in groups with intermittent feeding (Data not shown)[25]. The weight changes of all the groups' pre- and post- experiment are given Table 3.

Table 3 — Mean weight changes of the groups' pre- and post- experiment and comparison of blood parameters of all groups (mean ± standard error, $X \pm S_X$)

	Colitis (n=7)	HSD+C (n=7)	HSD+IF+C(n=7)	HFD+C (n=6)	HFD+IF+C (n=5)
Pre-experiment (g)	207.75±17.99	255±12.73	238.75±28.12	285.71±33.85	241.42±17.23
Post-experiment (g)	232.75±22.01*	276.85±15.86*	268.28±38.25	309.66±24.01*	279.83±24.57
IL-1β (pg/L)	1186.63±300.97	1184.63±182.85	725.42±293.07**	338.39±282.76**	184.40±131**
Insulin (mIU/L)	8.22±0.49	7.84±0.60	5.68±1.51**	5.88±0.43**	5.85±0.48**
CRP (ng/mL)	168.95±18.07	158.88±14.27	145.27±9.56	130.93±10.41**	120.49±10.52**
Leptin (ng/mL)	4.46±0.66	5.18±0.49	4.87±0.53	5.11±0.69	5.53±0.71
TNF-α (ng/mL)	196.79±39.82	174.58±44.56	124.75±9.62**	133.93±33.87	105.29±43.80**
IL-6 (ng/L)	155.10±30.33	147.26±27.29	132.43±26.85	110.63±41.04	95.15±20.03**
IGF-1 (ng/mL)	173.63±23.52	173.20±29.84	147.72±24.79	147.38±12.15	188.63±23.35
Adiponectin (mg/L)	17.79±2.98	13.15±3.03	7.63±2.05**	4.10±1.99**	2.64±0.93**

[HSD+C: High Sucrose Diet + Colitis, HSD+IF+C: High Sucrose Diet + Intermittent Fasting + Colitis, HFD+C: High Fat Diet + Colitis, HFD+IF+C: High Fat Diet + Intermittent Fasting + Colitis, IL-1β: Interleukin-1β, CRP: C-reactive protein, TNF-α: Tumor Necrosis Factor-α, IL-6: Interleukin-6, IGF-1: Insulin-like Growth Factor-1. *The difference between pre-experiment and post-experiment is significant (P <0.05). **The difference is statistically significant compared to the colitis group (P <0.05)]

Statistically significant increase (P <0.05) was observed in the weight changes pre- and post-experiment in all the groups, except Gr. II & V (HSD+IF+C and HFD+IF+C). Statistical comparison of dietary groups regarding blood parameters are given in Table 4.

After the application, before the blood samples were drawn, one animal from Gr. IV(HFD+C) and two animals from Gr. V(HFD+IF+C) died under anesthesia during the sacrificing process. Therefore, the initial number of animals has changed in the blood parameters analysis. The changes of some of the blood parameters of all groups after the application are given in Table 3 and Fig. 1.

When the blood parameters were evaluated, IL-1β, insulin and adiponectin levels in Gr. III, IV & V were found to be significantly lower than the other groups (P <0.05) (Table 3). CRP values of Gr. IV& V (HFD+C and HFD+IF+C) were found to be significantly lower than GR. I(colitis group) (P <0.05). Leptin showed an increase in all the groups compared to colitis groups. Compared to the colitis group, TNF-α values of Gr. III & V (HSD+IF+C and HFD+IF+C) were significantly lower (P <0.05). IL-6 values of only Gr. V (HFD+IF+C) were statistically lower compared to the colitis group (P <0.05).

Table 4 — Statistical comparison of dietary groups in terms of blood parameters

Blood parameters	HSD+C HSD+ IF+C	HSD+C HFD+C	HSD+C HFD+ IF+C	HSD+ IF+CHF D+C	HSD+IF+ C HFD+ IF+C	HFD+C HFD+ IF+C
IL-1β (pg/L)	*	*	*	-	*	-
Insulin (mIU/L	-	*	*	-	-	-
CRP (ng/mL)	-	*	*	-	*	-
Leptin (ng/mL)	-	-	-	-	-	-
TNF-α (ng/mL	-	-	-	-	-	-
IL-6 (ng/L)	-	-	-	-	-	-
IGF-1 (ng/mL)	-	-	-	-	-	-
Adiponectin (mg/L)	*	*	*	-	*	-

[HSD+C: High Sucrose Diet + Colitis, HSD+IF+C: High Sucrose Diet + Intermittent Fasting + Colitis, HFD+C: High Fat Diet + Colitis, HFD+IF+C: High Fat Diet + Intermittent Fasting + Colitis, IL-1β: Interleukin-1β, CRP: C-reactive protein, TNF-α: Tumor Necrosis Factor-α, IL-6: Interleukin-6, IGF-1: Insulin-like Growth Factor-1.*difference between groups is statistically significant (P <0.05)]

Discussion

Nutritional factors serve not only as risk and protective factors but also as an effective and variable cause in IBD development. There are several mechanisms to explain the relationship between IBD and dietary differences. These mechanisms include the direct effect of dietary antigens, changes in intestinal permeability and auto inflammatory response of mucosa due to changes in microbiota[26]. In a study of the opinions of IBD patients about the role of diet, most of the patients reported that dietary factors play an important role in the onset of the disease (15.6%) or relapse of the disease (57.8%)[3]. Depending on the initial symptoms or increased disease activity before the diagnosis, patients may change their dietary habits, in which diet would have significant impact on the disease progression.

A study revealed that high levels of mono-disaccharide and total fat intake increased the risk of occurrence of IBD in both forms[27]. Although diet as a risk factor in CD and UC has been extensively reviewed in the past, there is still a large gap in this

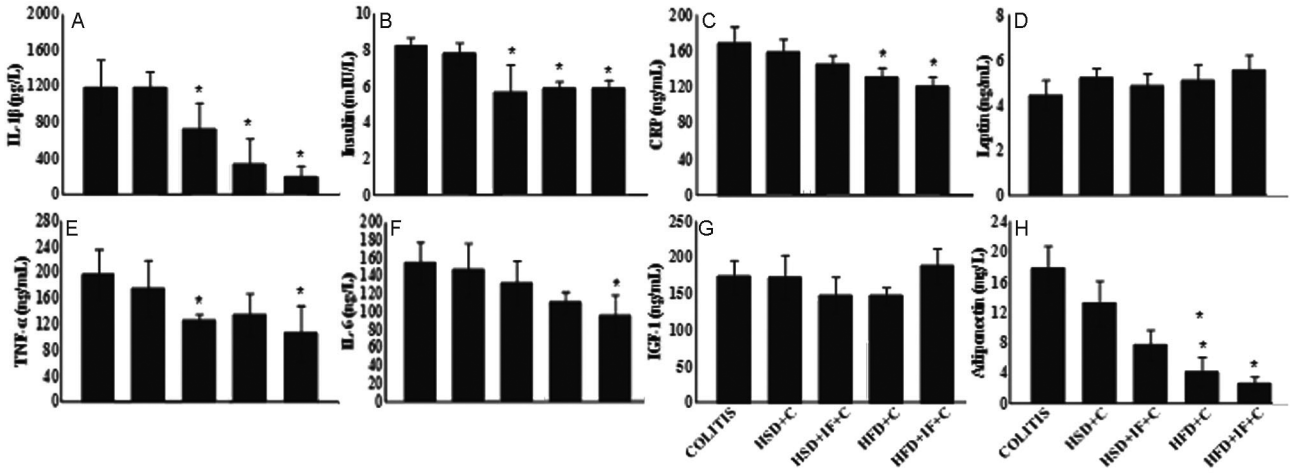

Fig. 1 — Plasma IL-1β, insulin, CRP, leptin, TNF-α, IL-6, IGF-1, and adiponectin values of all groups. [Gr. I (Colitis); Gr. II (High sucrose diet + Colitis); Gr. III (High sucrose diet + Intermittent fasting + Colitis); Gr. IV(High fat diet + Colitis); and Gr. V (High fat diet + Intermittent fasting + Colitis). IL-1β: Interleukin-1β, CRP: C-reactive protein, TNF-α: Tumor Necrosis Factor-α, IL-6: Interleukin-6, IGF-1: Insulin-like growth factor-1. *The difference is statistically significant compared to the colitis group (P <0.05)]

area due to limitations in retrospective data collection and difficulties in remembering diet histories[28].

In the present study, plasma IL-1β, insulin, CRP, Leptin, TNF-α, IL-6, IGF-1 and Adiponectin levels were not statistically significant (P >0.05) in HSD+C group compared to the colitis group.

High fat diet (HFD) prolongs and exacerbates the inflammatory symptoms of chronic UC. In an experimentally generated DSS-colitis model, colon analyzes showed mild inflammation in the DSS colitis group, which became more severe when HFD was performed[29] showed that dietary fat consumption dramatically reshapes the intestinal microflora and triggers the onset of colitis.

In mice with genetic predisposition to colitis, a high fat diet (60% of calories from fat) has been associated with more severe clinical and histopathological inflammation and increased inflammatory markers[30]. It has been shown that obesity, which may trigger inflammation and is an indicator of chronic low-grade inflammation, can be modulated by restricting energy or nutrient intake, even if high fat diet is maintained[31].

A recent study revealed that macroscopic and microscopic colitis in sedentary standard diet (SD) mice caused a significant decrease in colon blood flow whereas increased colonic tissue weight and plasma levels of TNF-α, IL-6 and IL-13. In sedentary HFD-fed mice, severe colon lesions, increased colonic tissue weight and significantly increased plasma TNF-α, IL-6, IL-1β and leptin levels were observed. Simultaneously, a significant decrease in plasma irisin and adiponectin levels was observed when SD and HFD groups were compared. However, exercise significantly reduced macroscopic and microscopic colitis, increased colonic blood flow, decreased plasma TNF-α, IL-6, MCP-1, IL-1β and leptin levels in rats fed HFD, while significantly increasing plasma irisin and plasma adiponectin levels. From these results, it is suggested that experimental colitis caused a decrease in the colonic microcirculation and an increase in proinflammatory secretions in plasma and mesenteric adipose tissue, whereas the HFD exacerbated this situation in mice while voluntary physical activity increased the irisin and plasma adiponectin levels and showed protective effect by reducing the severity of colon damage in mice[32].

In the present study, plasma IL-1β, insulin, CRP and adiponectin levels were found to be significantly decreased (P <0.05) compared to the colitis group in the HFD+C group, but it led to a non-significant increase in leptin levels. Reductions in TNF-α, IL-6 and IGF-1 levels were also observed, but these were not statistically significant (P >0.05). It is believed that this reduction in inflammation parameters in Gr. IV (HFD+C) may be partly due to the fat content (15%) and type (unsaturated fat ratio) of the high fat diet given to this group, in part, to the impact of the supplemental vitamin D in the diet. Therefore, it can be suggested that comparatively high fat diet could be a prominent protective dietary intervention against inflammation depending on the amount and composition of the fatty acid as happened in the present study. Similar studies also report anti-inflammatory actions of the some PUFAs and MUFAs like oleic acid[33,34]. In addition, vitamin D supplement may have played a role partly in reducing inflammation[35], even though that is not proven by measuring blood vitamin D levels.

IBD is widely distributed in Northern Europe and North America but less common in the Asia Pacific region, except for Australia. The incidence of IBD is increasing rapidly in many parts of the world, including Asia, and this increase is often seen in more industrialized countries[36]. Thus, diet has become one of the more prominent environmental factors in connection with the industrialization.

The common health benefits of dietary restriction have been recognized for centuries and have been consistently shown to prolong life in various mammals. Short term fasting (1-3 days) improves insulin sensitivity, reduces inflammation markers and expression of insulin/IGF-1, protects rodents against both liver and kidney ischemia reperfusion-induced damage and it also increases the expression of cell protective genes[37].

Inflammatory markers like CRP, TNF-, leptin, adiponectin, and brain-derived neurotrophic factor (BDNF) have reportedly shown a considerable improvement as a result of intermittent fasting[38]. Earlier studies have observed that Ramadan fasting is significantly associated with low concentrations of inflammatory markers viz. IL-6, CRP and TNF-α[39,40].

In this study, a reduction in IL-1β, TNF-α, CRP and IL-6 was observed in both groups III & V

(HSD+IF+C and HFD+IF+C) compared to the colitis group. While the decrease in IL-1β and TNF-α was statistically significant, the decrease in CRP and IL-6 was not significant. According to these results, although high-fat and high sucrose diet applications were maintained, it can be said that only 2-day intermittent fasting application in a week may have an anti-inflammatory effect by further reducing the levels of systemic inflammation markers in the organism.

Proper nutrition can facilitate the recovery stages during flare-ups and significantly improves the comfort and quality of life in individuals affected by IBD. However, there is no single diet suitable for all IBD patients. Depending on the course of the disease, past surgical procedures, and the type of pharmacotherapy used, specific dietary recommendations should be developed for each patient. For the above reasons, dietary recommendations should be considered as a pharmacotherapy supplement in IBD[41,42].

Conclusion

In this study, the protective effects of intermittent fasting and high-fat or high sucrose diet combination on inflammation have been observed in experimental colitis model in rats. The amount of fat and fatty acid composition in the fatty diet can have a protective effect against the development of colitis. Intermittent fasting further enhanced this protective effect. This is the first study to demonstrate that the protective effectiveness of dietary intervention against colitis is increased much more with intermittent fasting. It is thought that intermittent diets that are administered without any pharmacological intervention or as a supplement to pharmacological applications could be beneficial both by delaying the occurrence of diseases and contributing to the healing process with various effects in the affected individuals. As a conclusion, intermittent fasting could be a novel promising dietary intervention for an additional protective measure against colitis, particularly in the societies where the Western type of diet is prevalent.

Conflict of interest

Authors declare no competing interests.

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