The Effects of Flaxseed Supplementation On Circulating Adipokines Concentration in Patients With Ulcerative Colitis

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Research

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Abstract

**Introduction:** Inflammatory bowel disease (IBD) is one of the most common gastrointestinal diseases that can affect people of all ages. Adipokines secreted from adipose tissue have been shown to play an important role in the pathogenesis of ulcerative colitis (UC). The aim of this study was to evaluate the effect of supplementation with your seed on the concentrations of adiponectin, resistin and visfatin in patients with UC.

**Methods:** This trial is an open-labeled randomized controlled trial which conducted among 70 patients with UC. Patients were randomly divided into two groups: axseed and control. Patients in the intervention were received 30 g/day axseed powder for 12 weeks. Anthropometric, nutritional and biochemical factors of patients were evaluated at the beginning and end of the intervention period.

**Results:** Totally, 64 patients (36 men and 28 women) with mean age of 31.12 ± 9.67 included in the final analysis. There wasn't any significant difference between two groups in term of baseline weight and height (P>0.05). After the 12 weeks' intervention, axseed supplementation led to a significant reduction in the resistin (-4.85 ± 1.89 vs. -1.10 ± 2.25, P<0.001) and visfatin concentration (-1.33± 1.14 vs. -0.53 ± 1.63, P=0.018). Moreover, we found a significant increase in the adiponectin levels after the axseed supplementation (3.49 ± 1.29 vs. -0.35 ± 0.96, P<0.001).

**Conclusion:** It has been reported in this study that axseed supplementation could exert beneficial effects on adipokine levels in patients with UC.

**Trial registration:** IRCT registration no. IRCT20180311039043N1

**Introduction**

Crohn's disease (CD) and ulcerative colitis (UC) are inflammatory conditions and include a wide range of inflammatory conditions called inflammatory bowel disease (IBD). In fact, IBD has not been shown to be a simple disease and manifests itself in the form of a systemic inflammation with a variety of clinical manifestations[1, 2]. Chronic inflammation in the intestinal tract of patients with UC may penetrate the surrounding adipose tissue and cause mesenteric hypertrophy of adipose tissue. There has also been evidence of mesenteric adipose tissue in imaging techniques of patients with IBD[3].

Adipose tissue acts as an active component in the secretion of various hormones and in the regulation of the immune system via the secretion of peptides detectable in relevant levels in the systemic circulation, the so-called “adipo(cyto)kines”[4]. These adipocytokines such as leptin, adiponectin, resistin, and visfatin in addition to their role in adipose tissue metabolism, also play an important role in the pathogenesis of various diseases such as UC. Various clinical studies have evaluated the association between adipose tissue changes and its role in the pathophysiology of IBD, especially UC[5, 6]. Resistin is one of the adipokines secreted by adipose tissue and immune cells (mainly produced by PBMC (peripheral blood mononuclear cells) and macrophages) and as a mediator plays an important role in adipose tissue
response to inflammatory factors. Also, expression and serum levels of visfatin are affected by the amount of visceral fat and mesenteric adipose tissue and is involved in the pathogenesis of UC by stimulating leukocytes to produce inflammatory cytokines such as interleukin-6[7, 8].

Flaxseed as a flowering plant containing various active compounds, has been widely used in traditional and modern medicine of different countries. Flaxseed contains active compounds that include a high concentration of alpha linolenic acid (ALA), composing approximately 55% of the total fatty acid content; lignans, a class of phytoestrogen; and dietary fiber (28% by weight), a third of which is soluble fiber[9, 10]. In recent years, various studies have shown that flaxseed has the ability to exert antioxidant and anti-inflammatory effects due to its active ingredients[11, 12]. Rahimlou et al. in a meta-analysis study in 2019 were reported that flaxseed consumption reduces the serum concentration of some inflammatory factors[13].

In addition to these anti-inflammatory and antioxidant effects, various studies have shown that supplementation with flaxseed can regulate the concentration of some adipocytokines. Fukumitsu et al. reported that oral administration of flaxseed active components in animal models caused a significant improvement in the adiponectin gene expression[14]. Moreover, some animal studies have shown that the active compounds in flaxseed such as ALA can act as a ligand for peroxisome proliferator-activated receptor gamma (PPAR-γ), which in turn induces the expression of some anti-inflammatory adipocytokines[15].

Considering the role of adipose tissue and adipokines in the pathogenesis of IBD, we suggest that dietary flaxseed may improve adipokine levels, as an additional mechanism to protect against UC. The purpose of the present study, therefore, is to examine the effects of 12-week dietary supplementation with flaxseed, the richest dietary source of ALA and other active components, on circulating levels of adiponectin, resistin and visfatin.

Material And Methods

Subjects

Participants in this project were selected from patients referred to the gastroenterology and liver diseases clinic in Shahid Beheshti University of Medical Sciences, Tehran, Iran. Potential Participants were screened for UC by a gastroenterologist, and those who met the criteria were included in the study. The criteria for diagnosing UC by gastroenterologist was based on histopathological results in the last three months. As shown in Fig. 1, out of 84 volunteers to participate in this trial, 64 patients met the inclusion criteria. The age range of patients participating in this trial was between 18 and 55 years old and BMI > 20. Patients were excluded from the study if there was evidence of other intestinal diseases, inflammatory diseases, and autoimmune diseases. Other criteria for not including regular consumption of omega-3, flaxseed or any supplements with antioxidant and anti-inflammatory properties during the past month, pregnancy and lactation, sensitivity to flaxseed compounds and the use of anti-inflammatory
drugs using anti-inflammatory drugs (corticosteroids, immune-modulators (such as Azathioprine, 6-mercaptopurine, Methotrexate and Cyclosporine A), and anti-TNF-α medications (such as Adalimumab, Certolizumab pegol and Infliximab)) in the baseline or during the study, and unwilling to participate.

**Study design**

This trial is an open-labeled randomized controlled trial which carried out among the 64 UC patients. Patients participating in this study were randomly divided into two groups receiving axseed and the control group. The duration of intervention in this trial was 12 weeks and the protocol of the project was approved by the ethics Committee of the Shahid Beheshti University of Medical Sciences and carried out in accordance with the Helsinki Declaration (IRCT registration no. IRCT20180311039043N1). Informed consent taken from the participants before the start of the study.

At the beginning of the study, after recording the demographic information of all patients, the patients in the intervention group were asked to consume 30 grams of flaxseed powder daily and the control group was advised to follow their routine medication regimen. The flaxseed was provided from a farm in Khoy, West Azerbaijan province of Iran. Flaxseed powder was analyzed by the School of Pharmacy and the composition of macronutrients and micronutrients per 100 g of powder was as follows: energy: 450 kcal; fat:41 g; ALA:21.5; protein: 20 g; carbohydrate: 29 g and fiber:28 g. The rounded flaxseed (GF) was cleaned, milled and packed (250 g each pack) with a 15 g measure. Subjects in the GF group were asked to use one serving (15 g) of grounded flaxseed mixed in a glass of cold water after breakfast and one serving at the evening with an hour interval of taking medications. Packages were given to the participants at the start, 4th and 8th weeks of the study. Patients were asked not to change their diet or routine medication during the intervention period and to avoid consuming flaxseed containing products. To assess patient compliance, they were asked to return empty packages boxes each time to receive a new package. Patients who did not consume more than 15% of the given flaxseed were excluded from the study.

**Biochemical assessment**

To assess the serum concentration of adipokines, at the beginning and end of the study, 10 cc of blood was taken from all patients after 12 hours of fasting. To separate the serum, 10 cc of the blood samples were centrifuged at room temperature with 3000 rpm for 10 min and the isolated serum was stored at -80°C until the biochemical tests were carried out. Serum concentrations of adiponectin, resistin and visfatin were measured using ELISA kits (EASTBIOPHARM, PRC, and DBC, Canada).

**Dietary intake and physical activity assessment**

Energy, macronutrients and micronutrients intake in all patients at the beginning and end of the study were assessed using three (two consecutive days and a day-off) 24-h food recalls. Then, each food item entered to Nutritionist IV software (1997, First DataBank Inc., San Bruno, CA) and mean intake of energy, micronutrients, and macronutrients were calculated at the baseline and after 12 weeks of the study. Physical activity was assessed using the MET questionnaire.
Anthropometric measurements

At the beginning and end of 12 weeks, the weight and height of patients participating in both groups were assessed using standard equipment. Patients' weight was assessed using Seca device with 100 g precision and patients' height was assessed using Seca stadiometer in a standing position next to the wall and without shoes, with a precision of 0.1 cm. The standard formula was used to calculate the BMI.

Statistical methods

Quantitative and qualitative data were reported as mean (standard deviation) and frequency (%), respectively. Kolmogorov–Smirnov test was used to evaluate the normality of the data. Qualitative variables were compared using the chi-square test. Also, One-way analysis of variance and LSD post-hoc test were used to compare groups in terms of quantitative variables. Also, analysis of covariance (ANCOVA) was used to adjust the effect of confounding variables (dietary intake of energy, protein, fat, polyunsaturated fatty acids, omega 3 polyunsaturated fatty acids, and omega 6 polyunsaturated fatty acids). Moreover, paired sample t-test was used to compare the change of variables over the study period in each group. The P-value < 0.05 was considered as statistically significant. All statistical analyses were performed using SPSS software version 24 (IBM Corp. IBM SPSS Statistics for Windows, Armonk, NY).

Results

Study baseline characteristics

Preliminary information of patients participating in this trial is reported in Table 1. Totally, 64 patients (36 men and 28 women) with mean age of 31.12 ± 9.67 included in the final analysis. The mean diagnosis duration in the intervention group was 5.21 ± 2.45 years vs. 5.00 ± 3.05 years in the control group which wasn't significant differences between two groups (P = 0.73). There wasn't any significant difference between two groups in term of baseline weight and height (P > 0.05).

Compare dietary intakes of the participants

The caloric intake, macronutrients and micronutrients of the flaxseed and control group are shown in Table 2. At the beginning of the study, the mean caloric intake in the intervention group was 2295 ± 281.02 kcal and in the control group was 2226.56 ± 268.27 kcal, but no significant difference was observed between the two groups (P = 0.24). Also, we not found any significant difference between two groups in term of calorie, protein, carbohydrate, total fat, PUFA, omega-3 and omega-6 at the beginning and end of the study (P > 0.05).

Effect of flaxseed on the adipokine parameters

Table 3 compares the mean levels of adiponectin, resistin and visfatin between GF and control groups at the baseline and following 12 weeks of the study. At the beginning of the study, there was no difference
between the two groups in terms of mean serum concentrations of resistin, adiponectin and visfatin (P > 0.05). After the 12 weeks' intervention, flaxseed supplementation led to a significant reduction in the resistin (-4.85 ± 1.89 vs. -1.10 ± 2.25, P < 0.001) and visfatin concentration (-1.33 ± 1.14 vs. -0.53 ± 1.63, P = 0.018). Moreover, we found a significant increase in the adiponectin levels after the flaxseed supplementation (3.49 ± 1.29 vs. -0.35 ± 0.96, P < 0.001). After adjusting the results for confounding variables, there was no difference in the significance of the results.

**Discussion**

The results of present study showed that flaxseed supplementation in patients with UC led to a significant reduction in the resistin and visfatin concentration. Also, we found a significant improvement in the adiponectin level in the intervention group than control.

In recent years, various studies have investigated the role of different adipokines in the pathogenesis of chronic diseases. Adipokines have both pro- and anti-inflammatory effects in IBD patients. Some studies show an increase in leptin concentration in patients with UC despite weight loss, anorexia and enhanced release of TNF-α. Increased leptin concentration is associated with exacerbation of inflammation in patients with UC[16]. Adiponectin as one of the adipokines secreted from adipose tissue has shown anti-inflammatory effects in various studies[17, 18].

We found that adiponectin concentration increased significantly after the flaxseed supplementation. Weigert et al. in a cross sectional study were showed that circulating levels of chemerin and adiponectin are higher in ulcerative colitis[19]. Also, Karmiris et al. [20]described significantly elevated adiponectin levels in UC, whereas Valentini et al.[6] identified reduced adiponectin in the serum of CD and UC patients. Waluga et al., in a study examining the effect of corticosteroid therapy on adipokine concentrations in forty patients with UC, showed that no significant differences in adiponectin concentrations were observed at baseline and end of the study between the two groups[5].

One of the reasons for the difference in the results observed in different studies is the higher concentration of adiponectin in women compared to men and the lack of proper distribution of participants in different studies in terms of sex [21]. Various studies have shown that adiponectin has the ability to exert anti-inflammatory effects by increasing the synthesis of interleukin receptor antagonist and decreasing the dendritic cell release of interferon gamma. Adiponectin also has the ability to induce macrophages to perform more phagocytosis[22, 23].

On the other hand, in line with the results of our study, some findings have indicated an increase in the concentration of adiponectin following supplementation with flaxseed. Haidari et al. were reported an increase in the adiponectin levels after the flaxseed supplementation in women with polycystic ovary syndrome[24]. Also, Sekine et al. showed that ALA-rich flaxseed oil (FSO) oral administration in rats led to a significant increase in the adiponectin levels[25].

However, the results of some studies are contradictory and no significant change in adiponectin concentration was observed following flaxseed supplementation[26, 27]. ALA, the main component of
flaxseed products, acts as a ligand for PPAR-γ, which can increase expression and circulating level of adiponectin[28]. Some researchers have also reported that one of the reasons for the increase in adiponectin concentration after the flaxseed supplementation is weight loss. It has been reported that adiponectin levels and its gene expression increased following weight loss[29]. On the other hand, flaxseed can cause weight loss due to their high fiber content and active ingredients[30]. However, in our study, no significant change was observed in the weight of patients in the intervention group compared to the control group.

Resistin expression in human monocytes was markedly increased by treatment with endotoxin and pro-inflammatory cytokines[31, 32]. Based on the findings of various studies, the serum level of resistin is strongly associated with the concentration of some inflammatory factors[33, 34]. Konrad et al. showed that patients with UC had significantly higher concentration of resistin[35]. Also, Abedimanesh et al. observed that resistin levels was higher in patients with UC compared healthy subjects and correlated with disease activity scores, hs-CRP levels and fat mass[36]. Resistant plays an important role in exacerbating chronic inflammation by inducing nuclear factor-kappa B inflammatory pathways[37]. Bokarewa et al. reported that higher levels of resistin can upregulate IL-6 and TNF-a related genes [38]. Another study revealed that human resistin significantly increase the production and secretion of TNF-a and IL-12 by activation of NF-κB transcription factor[39]. In the present study, we found a significant reduction in the resistin concentration after the flaxseed supplementation. According to our search, no previous study has evaluated the effect of flaxseed on resistin concentration. However, it seems that these positive effects may be due to the high content of ALA in flaxseed.

Another result of the present study was the significant effect of flaxseed supplementation on the concentration of visfatin in patients with UC. Moschen et al. reported that visfatin can increase production and secretion of inflammatory cytokines and may be considered a new pro-inflammatory adipocytokine[40]. Also, it has been reported that visfatin plasma levels and its mRNA expression significantly increased in the patients with UC[6]. Researchers have suggested that visfatin exacerbates IBD through a variety of mechanisms. These mechanisms include effects on peripheral blood mononuclear cells, direct stimulation of pro-inflammatory cytokine production and suppression of neutrophil apoptosis[41, 42]. Moreover, it has been reported that visfatin has also been shown to increase the expression of some genes involved in inflammatory pathways, such as NF-κB p65(RelA) DNA-binding activity in human leukocytes by p38 and MEK-1 [43, 44].

Prior to our study, no study evaluated the effect of flaxseed supplementation on visfatin concentration. However, some studies have shown that omega-3 supplementation significantly reduces serum visfatin concentrations[45, 46].

Our study was the first clinical trial to evaluate the effect of flaxseed supplementation on adipokine levels in patients with UC. However, there were some limitations in the present study that should be considered in analyzing the results. In this study, serum leptin concentration was not assessed. Due to the strong correlation between leptin concentration and the severity of inflammation, evaluation of this factor could
increase the accuracy of the results. On the other hand, measuring the expression of genes related to some inflammatory factors could be helpful. On the other hand, one of the most important limitations of this study was the type of study design, which due to the lack of a suitable placebo, the possibility of double blinding in the study was not provided.

Conclusion

In conclusion, our study showed that flaxseed supplementation led to a significant reduction in the visfatin and resistin concentration and a significant improvement in the adiponectin levels. However, to confirm the present results, further studies with higher sample size and measurement of more adipokines are needed.

Abbreviations

ANCOVA, analysis of covariance; ALA, alpha linolenic acid; CD, Crohn's disease; IBD, Inflammatory bowel disease; NF-Κb, nuclear factor kappa; UC, ulcerative colitis; PPAR-γ, peroxisome proliferator-activated receptor gamma

Declarations

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Availability of data and materials

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

Ethics approval and consent to participate

All procedures in this study were approved by the ethics board committee of Shahid Beheshti University of Medical Sciences.

Consent for publication
All authors agreed to this publication.

**Conflicts of interests**

The authors have no conflicts of interest to declare.

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**References**

1. Kopp A, Buechler C, Neumeier M, Weigert J, Aslanidis C, Schölmerich J, Schäffler A. Innate immunity and adipocyte function: ligand-specific activation of multiple Toll-like receptors modulates cytokine, adipokine, and chemokine secretion in adipocytes. Obesity. 2009;17(4):648–56.

2. Karrasch T, Schaeer A. Adipokines and the role of visceral adipose tissue in inflammatory bowel disease. Annals of Gastroenterology: Quarterly Publication of the Hellenic Society of Gastroenterology. 2016;29(4):424.

3. Zuo L, Ge S, Ge Y, Li J, Zhu B, Zhang Z, Jiang C, Li J, Wang S, Liu M. The adipokine metrnl ameliorates chronic colitis in Il-10−/−mice by attenuating mesenteric adipose tissue lesions during spontaneous colitis. Journal of Crohn's Colitis. 2019;13(7):931–41.

4. Tilg H, Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. Nat Rev Immunol. 2006;6(10):772–83.

5. Waluga M, Hartleb M, Boryczka G, Kukla M, Żwirska-Korczala K. Serum adipokines in inflammatory bowel disease. World journal of gastroenterology: WJG. 2014;20(22):6912.

6. Valentini L, Wirth EK, Schweizer U, Hengstermann S, Schaper L, Koernicke T, Dietz E, Norman K, Buning C, Winklhofer-Roob BM. Circulating adipokines and the protective effects of hyperinsulinemia in inflammatory bowel disease. Nutrition. 2009;25(2):172–81.

7. Ouchi N, Walsh K. Adiponectin as an anti-inflammatory factor. Clinica chimica acta. 2007;380(1–2):24–30.

8. Al-Suhaime EA, Shehzad A. Leptin, resistin and visfatin: the missing link between endocrine metabolic disorders and immunity. European journal of medical research. 2013;18(1):12.
9. Kajla P, Sharma A, Sood DR. Flaxseed—a potential functional food source. J Food Sci Technol. 2015;52(4):1857–71.
10. Touré A, Xueming X. Flaxseed lignans: source, biosynthesis, metabolism, antioxidant activity, bioactive components, and health benefits. Compr Rev Food Sci Food Saf. 2010;9(3):261–9.
11. Parikh M, Maddaford TG, Austria JA, Aliani M, Netticadan T, Pierce GN. Dietary flaxseed as a strategy for improving human health. Nutrients. 2019;11(5):1171.
12. Parikh M, Netticadan T, Pierce GN. Flaxseed: its bioactive components and their cardiovascular benefits. American Journal of Physiology-Heart and Circulatory Physiology 2018.
13. Rahimlou M, Jahromi NB, Hasanyani N, Ahmadi AR. Effects of flaxseed interventions on circulating inflammatory biomarkers: a systematic review and meta-analysis of randomized controlled trials. Advances in Nutrition. 2019;10(6):1108–19.
14. Fukumitsu S, Aida K, Ueno N, Ozawa S, Takahashi Y, Kobori M. Flaxseed lignan attenuates high-fat diet-induced fat accumulation and induces adiponectin expression in mice. Br J Nutr. 2008;100(3):669–76.
15. Maeda N, Takahashi M, Funahashi T, Kihara S, Nishizawa H, Kishida K, Nagaretani H, Matsuda M, Komuro R, Ouchi N, et al. PPARgamma ligands increase expression and plasma concentrations of adiponectin, an adipose-derived protein. Diabetes. 2001;50(9):2094–9.
16. Barbier M, Cherbut C, Aube A, Blottiere H, Galmiche J. Elevated plasma leptin concentrations in early stages of experimental intestinal inflammation in rats. Gut. 1998;43(6):783–90.
17. Fantuzzi G. Adiponectin and inflammation: consensus and controversy. Journal of Allergy Clinical Immunology. 2008;121(2):326–30.
18. Engeli S, Feldpausch M, Gorzelniak K, Hartwig F, Heintze U, Janke J, Möhlig M, Pfeiffer AF, Luft FC, Sharma AM. Association between adiponectin and mediators of inflammation in obese women. Diabetes. 2003;52(4):942–7.
19. Weigert J, Obermeier F, Neumeier M, Wanninger J, Filarsky M, Bauer S, Aslanidis C, Rogler G, Ott C, Schäffler A. Circulating levels of chemerin and adiponectin are higher in ulcerative colitis and chemerin is elevated in Crohn's disease. Inflamm Bowel Dis. 2010;16(4):630–7.
20. Karmiris K, Koutroubakis IE, Xidakis C, Polychronaki M, Voudouri T, Kourousnalis EA. Circulating levels of leptin, adiponectin, resistin, and ghrelin in inflammatory bowel disease. Inflamm Bowel Dis. 2006;12(2):100–5.
21. Pajvani UB, Du X, Combs TP, Berg AH, Rajala MW, Schulthess T, Engel J, Brownlee M, Scherer PE. Structure-function studies of the adipocyte-secreted hormone Acrp30/adiponectin implications for metabolic regulation and bioactivity. J Biol Chem. 2003;278(11):9073–85.
22. Batra A, Zeitz M, Siegmund B. Adipokine signaling in inflammatory bowel disease. Inflamm Bowel Dis. 2009;15(12):1897–905.
23. Wolf AM, Wolf D, Rumpold H, Enrich B, Tilg H. Adiponectin induces the anti-inflammatory cytokines IL-10 and IL-1RA in human leukocytes. Biochem Biophys Res Commun. 2004;323(2):630–5.
24. Haidari F, Banaei-Jahromi N, Zakerkish M, Ahmadi K. The effects of flaxseed supplementation on metabolic status in women with polycystic ovary syndrome: a randomized open-labeled controlled clinical trial. Nutr J. 2020;19(1):8.

25. Sekine S, Sasanuki S, Murano Y, Aoyama T, Takeuchi H. Alpha-linolenic acid-rich flaxseed oil ingestion increases plasma adiponectin level in rats. Int J Vitam Nutr Res. 2008;78(4–5):223–9.

26. Paschos GK, Zampelas A, Panagiotakos DB, Katsiougiannis S, Griffin BA, Votteas V, Skopouli FN. Effects of flaxseed oil supplementation on plasma adiponectin levels in dyslipidemic men. Eur J Nutr. 2007;46(6):315–20.

27. Jalili C, Pezeshki M, Askarpour M, Marx W, Hassani B, Hadi A, Ghaedi E. The effect of flaxseed supplementation on circulating adiponectin and leptin concentration in adults: A systematic review and meta-analysis of randomized controlled trials. Phytotherapy Research 2020.

28. Maeda N, Takahashi M, Funahashi T, Kihara S, Nishizawa H, Kishida K, Nagaretani H, Matsuda M, Komuro R, Ouchi N. PPARγ ligands increase expression and plasma concentrations of adiponectin, an adipose-derived protein. Diabetes. 2001;50(9):2094–9.

29. Ma W, Huang T, Zheng Y, Wang M, Bray GA, Sacks FM, Qi L. Weight-loss diets, adiponectin, and changes in cardiometabolic risk in the 2-year POUNDS Lost Trial. The Journal of Clinical Endocrinology Metabolism. 2016;101(6):2415–22.

30. Mohammadi-Sartang M, Mazloom Z, Raeisi-Dehkordi H, Barati-Boldaji R, Bellissimo N, Totosy de Zepetnek J. The effect of flaxseed supplementation on body weight and body composition: a systematic review and meta-analysis of 45 randomized placebo-controlled trials. Obes Rev. 2017;18(9):1096–107.

31. Kaser S, Kaser A, Sandhofer A, Ebenbichler CF, Tilg H, Patsch JR. Resistin messenger-RNA expression is increased by proinflammatory cytokines in vitro. Biochem Biophys Res Commun. 2003;309(2):286–90.

32. Silswal N, Singh AK, Aruna B, Mukhopadhyay S, Ghosh S, Ehtesham NZ. Human resistin stimulates the pro-inflammatory cytokines TNF-alpha and IL-12 in macrophages by NF-kappaB-dependent pathway. Biochem Biophys Res Commun. 2005;334(4):1092–101.

33. Ramirez JL, Khetani SA, Zahner GJ, Spaulding KA, Schaller MS, Gasper WJ, Hills NK, Schafer AL, Grenon SM. Serum resistin is associated with impaired endothelial function and a higher rate of adverse cardiac events in patients with peripheral artery disease. J Vasc Surg. 2019;69(2):497–506.

34. Park HK, Kwak MK, Kim HJ, Ahima RS. Linking resistin, inflammation, and cardiometabolic diseases. Korean J Intern Med. 2017;32(2):239.

35. Konrad A, Lehrke M, Schachinger V, Seibold F, Stark R, Ochsenkühn T, Parhofer KG, Göke B, Broedl UC. Resistin is an inflammatory marker of inflammatory bowel disease in humans. Eur J Gastroenterol Hepatol. 2007;19(12):1070–4.

36. Abedimanesh N, Motlagh B, Abedimanesh S, Ostadrahimi A, Somi MH, Jafarabadi M, Rezazadeh M. Circulating resistin in ulcerative colitis, relation with anthropometric, body composition and inflammatory parameters. Progress in Nutrition. 2018;20:132–6.
37. Nagaev I, Bokarewa M, Tarkowski A, Smith U. Human resistin is a systemic immune-derived proinflammatory cytokine targeting both leukocytes and adipocytes. PloS one. 2006;1(1):e31.
38. Bokarewa M, Nagaev I, Dahlberg L, Smith U, Tarkowski A. Resistin, an adipokine with potent proinflammatory properties. J Immunol. 2005;174(9):5789–95.
39. Silswal N, Singh AK, Aruna B, Mukhopadhyay S, Ghosh S, Ehtesham NZ. Human resistin stimulates the pro-inflammatory cytokines TNF-α and IL-12 in macrophages by NF-κB-dependent pathway. Biochem Biophys Res Commun. 2005;334(4):1092–101.
40. Moschen AR, Kaser A, Enrich B, Mosheimer B, Theurl M, Niederegger H, Tilg H. Visfatin, an adipocytokine with proinflammatory and immunomodulating properties. J Immunol. 2007;178(3):1748–58.
41. Jia SH, Li Y, Parodo J, Kapus A, Fan L, Rotstein OD, Marshall JC. Pre–B cell colony–enhancing factor inhibits neutrophil apoptosis in experimental inflammation and clinical sepsis. J Clin Investig. 2004;113(9):1318–27.
42. Moschen AR, Geiger S, Gerner R, Tilg H. Pre-B cell colony enhancing factor/NAMPT/visfatin and its role in inflammation-related bone disease. Mutation Research/Fundamental Molecular Mechanisms of Mutagenesis. 2010;690(1–2):95–101.
43. Ghosh S, Karin M: Missing pieces in the NF-κB puzzle. cell 2002, 109(2):S81-S96.
44. Kumar S, Boehm J, Lee JC. p38 MAP kinases: key signalling molecules as therapeutic targets for inflammatory diseases. Nature reviews Drug discovery. 2003;2(9):717–26.
45. Hajianfar H, Hosseinzadeh MJ, Ahmad Bahonar KM, Askari GR, Entezari MH, Keshavarz A, Ansari N. The effect of omega-3 on the serum visfatin concentration in patients with type II diabetes. Journal of research in medical sciences: the official journal of Isfahan University of Medical Sciences. 2011;16(4):490.
46. MJ HA, Hajianfar H, Bahonar A, Mohamad K, Keshavarz S, Entezari M, Gh A. The effect of n-fatty acid (omega 3) on serum visfatin concentration in patients with type2 diabetes. Journal of Jahrom University of Medical Sciences. 2012;10(1):24.

Tables

Table 1. The characteristics of the study participants

Values are means ±SD

Table 2. Dietary intakes of subjects at baseline and post intervention

Values are means 6 SD. SFA: Saturated fatty acids; MUFA: Mono unsaturated fatty acids; PUFA: Polyunsaturated Fatty Acid

Table 3: Means and Standard Deviations of the Outcome Measures
| Variables            | Groups                        | Intervention (n=32) | Control (n=32) | P-value |
|----------------------|-------------------------------|--------------------|---------------|---------|
| Age (year)*          |                               | 30.35 ± 9.90       | 32.10 ± 10.43 | 0.38    |
| Height               |                               | 165.43 ± 12.22     | 163.34 ± 9.23 | 0.68    |
| Weight (kg)          |                               | 65.15 ± 10.80      | 65.89 ± 8.03  |         |
| Sex**                |                               |                    |               |         |
| Male (%)             |                               | 18 (56.3%)         | 19 (59.3%)    | 0.54    |
| Female (%)           |                               | 14 (43.8%)         | 13 (40.6%)    |         |
| BMI(kg/m²)           |                               | 23.69 ± 2.83       | 23.79 ± 2.20  |         |
| Diagnosis duration (years) |                   | 5.21 ± 2.45        | 5.00 ± 3.05   | 0.73    |

FBS, fasting blood sugar; TC, total cholesterol; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TAG, triacylglycerol; HDL, High-density lipoprotein; LDL, Low-density lipoprotein

a Values are expressed as mean ± SD.

b P1 and P2 value, difference compared with the value at the beginning of the study within groups (paired t-test).

c Pt value, mean difference of changes between the two groups (independent t-test).

d Pa value, Based on ANCOVA model regressing change from baseline on the treatment group, baseline value of the outcome, sex, age, MET and energy.

**Figures**
| Variables | Groups | Intervention (n=32) | Control (n=32) | P-value |
|-----------|--------|---------------------|----------------|---------|
| **Energy (kcal)** | | | | |
| Before | 2295 ± 281.02 | 2226.56 ± 268.27 | 0.24 |
| After | 2372.87 ± 259.76 | 2366.97 ± 233.86 | 0.75 |
| P-value | 0.12 | 0.19 | |
| **Carbohydrate (g)** | | | | |
| Before | 326.64 ± 51.18 | 320.65 ± 44.82 | 0.56 |
| After | 334.19 ± 47.85 | 332 ± 45.19 | 0.89 |
| P-value | 0.378 | 0.298 | |
| **Protein (g)** | | | | |
| Before | 70.52 ±18.12 | 70.93 ± 17.93 | 0.29 |
| After | 67.05± 13.46 | 66.19 ± 14.93 | 0.76 |
| P-value | 0.35 | 0.24 | |
| **Fat (g)** | | | | |
| Before | 66.76 ± 14.03 | 63.19 ± 12.95 | 0.35 |
| After | 66.27 ± 13.25 | 63.49 ± 12.63 | 0.85 |
| P-value | 0.79 | 0.82 | |
| **PUFA (g)** | | | | |
| Before | 13.28 ± 2.40 | 13.57 ± 1.94 | 0.56 |
| After | 12.85 ± 2.47 | 13.46 ± 2.02 | 0.45 |
| P-value | 0.18 | 0.83 | |
| **Omega-3 (g)** | | | | |
| Before | 0.65 ± 0.19 | 0.68 ± 0.17 | 0.43 |
| After | 0.66 ± 0.17 | 0.7 ± 0.18 | 0.28 |
| P-value | 0.25 | 0.23 | |
| **Omega-6 (g)** | | | | |
| Before | 1.38 ± 0.52 | 1.58 ± 0.53 | |
| After P-value | 1.48 ± 0.51 | 1.64 ± 0.51 | |
| Variables       | Before Intervention group (n 32) | After Intervention group (n 32) | Before Control group (n 32) | After Control group (n 32) | P Value |
|-----------------|----------------------------------|---------------------------------|----------------------------|----------------------------|---------|
| Resistin        | 20.13 ± 2.51                     | 15.25 ± 1.14                   | 19.33 ± 1.92               | 18.23 ± 2.30               | <0.001  |
|                 |                                  |                                 |                            |                            | 0.01    |
|                 |                                  |                                 |                            |                            | <0.001  |
|                 |                                  |                                 |                            |                            | <0.001  |
| Visfatin        | 16.17 ± 1.87                     | 14.83 ± 1.43                   | 15.82 ± 2.38               | 15.28 ± 2.09               | <0.001  |
|                 |                                  |                                 |                            |                            | 0.07    |
|                 |                                  |                                 |                            |                            | 0.018   |
|                 |                                  |                                 |                            |                            | 0.03    |
| Adiponectin (mg/mL) | 13.65 ± 4.19                 | 17.14 ± 3.65                   | 14.33 ± 4.11               | 13.98 ± 4.22               | 0.002   |
|                 |                                  |                                 |                            |                            | 0.618   |
|                 |                                  |                                 |                            |                            | <0.001  |
|                 |                                  |                                 |                            |                            | <0.001  |
Figure 1

Flow chart of participant’s enrollment in the study