Article

HET

Human and Experimental Toxicology
1–11

DOI: 10.1177/0960327120969960
journals.sagepub.com/home/het
SAGE

Effects of TNF-α antagonist infliximab on fructose-induced metabolic syndrome in rats

Yasmine A Abdelhamid[1], Mohammed F Elyamany[2], Muhammad Y Al-Shorbagy[2,3] and Osama A Badary[4]

Abstract

Public health issues have been raised regarding fructose toxicity and its serious metabolic disorders. Deleterious effects of high fructose intake on insulin sensitivity, body weight, lipid homeostasis have been identified. The new millennium has witnessed the emergence of a modern epidemic, the metabolic syndrome (MS), in approximately 25% of the world's adult population. The current study aimed to investigate the effect of the TNF-α antagonist infliximab on fructose-induced MS in rats. Rats were administered fructose (10%) in drinking water for 12 weeks to induce the experimental MS model. infliximab (5 mg/kg) was injected once weekly intraperitoneally starting on the 13th week for 4 weeks. Increase in body weight, blood glucose level, serum triglycerides (TGs), adiponectin level and blood pressure were present in MS rats. They also prompted increases in serum of leptin, TNF-α, and malondialdehyde (MDA) levels. Treatment with infliximab did not affect body weight, hyperglycemia or hypertension, but decreased serum TGs and increased serum HDL-c levels. Infliximab also decreased adiponectin levels. Surprisingly, infliximab increased MDA above its value in the MS group. These results reflect the fact that infliximab affects the manifestations of MS in rats. Though infliximab reduced TGs, increased HDL-c levels, reversed adiponectin resistance occurred by fructose, the drug failed to combat MS-mediated hyperglycemia, hypertension, and elevated MDA above the insult.

Keywords

Infliximab, metabolic syndrome, TNF-α, fructose, triglycerides, adiponectin

Introduction

High intake of fructose in the diet has been documented to induce inflammatory response accompanied by deleterious metabolic consequences including hyperinsulinemia, hyperglycemia, glucose intolerance, hypertriglyceridemia and hypertension.[1–4]

Fructose-fed rats is used as an animal model of MS and is considered to parallel multiple MS noticed in humans.[5]

Prevalence of metabolic syndrome (MS) around the world differs in the range from <10% to 84%, according to the region, environment, sex, age, and race of the population studied, and the definition of the syndrome used. Generally, the International Diabetes Federation (IDF) estimates that one-quarter of the world's adult population has the MS.[6]

Differences in genetic background, diet, levels of physical activity, population age and sex structure, levels of over- and undernutrition, and body habitus all influence the prevalence of both the MS and its components. Regardless of the underlying genetic and environmental influences that mediate the prevalence of the MS, a higher prevalence will certainly result in undesirable consequences such as cardiovascular disease.[7]

[1]Pharmacology Department, Egyptian Drug Authority, Egypt
[2]Pharmacology & Toxicology Department, Faculty of Pharmacy, Cairo University, Giza, Egypt
[3]Pharmacology & Toxicology Department, School of Pharmacy, Newgiza University, Egypt
[4]Clinical Pharmacy Department, Faculty of Pharmacy, British University in Egypt, Cairo, Egypt

Corresponding author:
Yasmine A Abdelhamid, Pharmacology Department, Egyptian Drug Authority, 51 Wezaret Alzeraa Street, Agouza, Giza, Egypt.
Email: jassssy88@gmail.com

There is an association between metabolic syndrome and many inflammatory diseases, Previous studies demonstrated a higher prevalence of MS in patients with Psoriasis[8,9] or ankylosing spondylitis.[10,11] Patients with MS have a higher rate of Crohn's disease-related hospitalization compared to those without MS.[12] The inflammatory cytokine, tumor necrosis factor-alpha (TNF-α) plays an important role in the pathophysiology of these inflammatory disorders and in MS. The central role of TNF-α in inflammation has been demonstrated by the ability of agents that block the action of TNF-α to treat a range of inflammatory conditions, including rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease and psoriasis.[13–15] The effects of TNF-α on lipid and glucose metabolism suggest that TNF-α inhibitors, currently used in the treatment of several inflammatory diseases, may have a role in the reduction in plasma glucose, and in ameliorating lipid profile. Moreover, a lower prevalence of metabolic syndrome has been seen in patients treated with anti-TNF-α agents.[16]

To "neutralize" the proinflammatory action and regulatory role of TNF-α, infliximab is a chimeric anti TNFα monoclonal antibody that was initially approved in the United States in 1998 for the treatment of Crohn's disease and has subsequently been approved for multiple other immunological indications, including rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, and ulcerative colitis.[17] Therefore, the current study aims to investigate the effect of infliximab to affect the manifestations of MS in a model of fructose drinking rats.

Material and methods

Ethics statement

All experiments on laboratory animals were performed in accordance with the protocol approved by Faculty of Pharmacy, Cairo University Research Ethics Committee, Cairo, Egypt. PT number (1642). Every effort was done to minimize the number of animals and their suffering, the animals were cared for in accordance with Guide for the Care and Use of Laboratory Animals

Animals

Adult male Sprague Dawley rats weighing 160–210 g were used in the present study. They were obtained from the breeding colony maintained at the animal house of the National Organization for Drug Control and Research (NODCAR, Cairo, Egypt). Animals had free access to food and water *ad libitum*. They were maintained at 21–24°C and 40–60% relative humidity with 12-h light–dark cycle. Animals were subjected to an adaptation period of 2 weeks in the animal house before experimentation.

Drugs

Unifructose® (Fructose) was purchased from a local pharmacy.

Remicade® (the chimeric monoclonal anti-TNF-α antibody, infliximab) was purchased from a local pharmacy.

Experimental design

The experiment started with 30 rats, of which 10 rats served as normal control and the other 20 received 10% fructose in drinking water for 12 weeks to induce MS.[18] From the MS-induced rats, two groups (group2 and group3) were constructed; each of 10 rats. Group2: Rats received 10% fructose in drinking water for a further 4 weeks (total of 16 weeks), represents MS group. Group3: Rats received 10% fructose in drinking water for further 4 weeks (total of 16 weeks), infliximab administration at a dose of 5 mg/kg, i.p., weekly[19] has been started at the 13th week (treatment group).

Determination of body weight

Bodyweight was measured at the end of the experiment with a digital balance (Sartorius®).

Determination of blood pressure (BP)

BP measurement was done after 3 months of induction of MS and at the end of the experiment by using non-invasive BP measurement technique without any invasive catheterization using non-invasive blood pressure controller NIBP controller, AD instruments, model ml-122. The rat was kept in a warm chamber which provides a comfortable and heated environment necessary to produce peripheral vasodilatation and isolate the animal from external noise, which is critical for accurate BP measurements. A built-in air pump ensures automated cuff inflation/deflation at a constant and even rate. In order to avoid deterioration of the animal's tail after submitting animals to unnecessary high occlusion pressures, the automated

deflation is carried out for each animal and separately, once their own systolic value is reached. The pulse signal level (heart rate) was permanently monitored on the LCD display while an internal pressure transducer was constantly measuring the current pressure applied on the cuff. Measurement of systolic blood pressure was achieved either once the heart pulse disappears or when the first pulse reappears after the occlusion process.[20]

Collection of blood samples and serum separation

After recording the BP, fasted animals were anaesthetized using ether then blood samples were collected from retro-orbital plexus of each animal using a capillary tube in non-heparinized tubes. The serum then was separated by centrifugation for 20 min at 4000 r.p.m. Part of serum samples was directly used for the analysis of liver function, lipid profile and MDA and the other part was stored at -80°C for further analysis of leptin, adiponectin and TNF-α.

Isolation of liver

After blood collection, the liver was carefully excised after cleaning off excess connective tissues and fats then rapidly stored in 10% formalin solution at room temperature for histopathological examination.

Biochemical analyses

Determination of TGs, Glucose, HDL-c, LDL-c, ALT and AST levels.

- Serum TGs was determined according to the method described by Bucolo and David[21] using colorimetric kits (Spectrum, Cairo, Egypt) using a UV-visible spectrophotometer (Jenway Spectrophotometer, England).
- Serum glucose was determined according to the method described by Weissman and Klein and Tietz[22,23] using colorimetric kits (Spectrum, Cairo, Egypt) using a UV-visible spectrophotometer (Jenway Spectrophotometer, England).
- Serum HDL was determined according to the method described by Lopes-Virella et al.[24] using colorimetric kits (Spectrum, Cairo, Egypt) using a UV-visible spectrophotometer (Jenway Spectrophotometer, England).
- Serum LDL was determined according to the method described by Okada et al.[25] using colorimetric kits (Spectrum, Cairo, Egypt) using a UV-visible spectrophotometer (Jenway Spectrophotometer, England).
- Serum ALT and AST was determined according to method described by Reitman and Frankel and Henry et al.[26,27] using colorimetric kits (Spectrum, Cairo, Egypt) using a UV-visible spectrophotometer (Jenway Spectrophotometer, England).

Determination of leptin and adiponectin levels. Serum of leptin and adiponectin levels were measured by sandwich enzyme-linked immunosorbent assay (ELISA) using kits supplied by (WKEA med supplies, Changchun, China) following the manufacturer's instructions with microtiter plate coated with mouse monoclonal antibodies.

Determination of TNF-α level. Serum TNF-α level was measured by sandwich enzyme-linked immunosorbent assay (ELISA) using kits supplied by (CUSA-BIO, Wuhan, China) following the manufacturer's instructions with microtiter plate coated with mouse monoclonal anti-Rat TNF-α antibodies.

Determination of MDA level. Serum MDA level was determined according to method described by Kei[28] using colorimetric kit (Biodiagnostic, Giza, Egypt) using a UV-visible spectrophotometer (Jenway Spectrophotometer, England) following the manufacturer's instructions.

Histopathological examination of liver. Autopsy samples were taken from the liver of rats in different groups and fixed in 10% formol saline for 24 hours. Washing was done in tap water then serial dilutions of alcohol (methyl, ethyl and absolute ethyl) were used for dehydration. Specimens were cleared in xylene and embedded in paraffin at 56 degree in hot air oven for 24 hours. Paraffin bees wax tissue blocks were prepared for sectioning at 4 microns thickness by slide microtome. The obtained tissue sections were collected on glass slides, deparaffinized, stained by hematoxylin&eosin stain for examination through the light electric microscope.[29]

Statistical analysis

Values are represented as mean $\pm$ S.D. Statistical analyses were performed using GraphPad Prism version 6.0. Data were checked for normality using Shapiro–Wilk test. Comparisons between different groups were carried out using One-way ANOVA

Table 1. Effect of infliximab (5 mg/kg/week, ip) on body weight, blood pressure, serum FBG, ALT and AST.

Parameter	Groups		
	Control	MS	INFLX
BW (grams) (Week 0)	183.7 ± 15.69	186.7 ± 14.71	184.4 ± 15.46
BW (grams) (Week 16)	270.1 ± 20.42	344.2 ± 25.97 * (P < 0.0001)	352.3 ± 16.04 * (P < 0.0001)
SBP (mmHg) (Week 16)	116 ± 5.41	142.4 ± 4.37 * (P < 0.0001)	139.6 ± 5.74 * (P < 0.0001)
FBG (mg/dL) (Week 16)	122 ± 6.63	141.9 ± 10.4* (P = 0.0002)	140.6 ± 7.01* (P = 0.0005)
ALT (U/mL) (Week 16)	21 ± 2.14	44.63 ± 4.96 * (P < 0.0001)	41 ± 10.85 * (P < 0.0001)
AST (U/mL) (Week 16)	24.88 ± 1.13	127.9 ± 28.34 * (P < 0.0001)	133.5 ± 16.54 * (P < 0.0001)

Values are expressed as mean ± SD (n = 8–10 rats); statistical comparisons were carried out using One-way ANOVA followed by Tukey's multiple comparisons test. *P < 0.05 VS. control, #P < 0.05 VS. MS. MS, fructose-induced metabolic syndrome rats; INFLX, rats with metabolic syndrome treated with infliximab (5 mg/kg, ip); BW, body weight; SBP, systolic blood pressure; FBG, fasting blood glucose; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

followed by Tukey's multiple comparisons test. Level of significance was set at $p < 0.05$.

Results and discussion

Our study revealed a significant increase in body weight after fructose administration as shown in Table 1. Mechanisms of induction of MS by fructose in previous studies showed that fructose led to significant increase in body weight.[18,30–32] Infliximab treatment didn't show any significant difference in body weight relative to MS group. In a previous study on Male Wistar Kyoto rats and spontaneous hypertensive rats, no changes in body weight were detected during infliximab treatment period, resulting in a similar final body weight among the groups.[33] In humans, long-term treatment with infliximab showed different results. It was reported that 24-weeks treatment with infliximab in number of patients affected with psoriasis showed significant increase in body weight.[34] On the other hand, another 6-months study of infliximab effects on lipid profile of patients with rheumatoid arthritis and ankylosing spondylitis reported no significant change in the body weight during the study.[35]

The current finding that fructose administration in rats significantly increased BP as shown in Table 1 was similar to those reported previously.[18,32,36,37] While infliximab failed to reduce the BP in this model of MS. It reduced the 24-h ambulatory BP in rheumatoid arthritis patients.[38] The effect of TNF-α inhibitors on BP is unclear. Chronic etanercept treatment prevented the development of hypertension in fructose-fed rats[39] but failed to reduce BP in rheumatoid arthritis patients.[40] On the other hand, Anti-TNF antiserum increased mean arterial pressure in an angiotensin II dependent model of hypertension[41] and a recent report has related Anti-TNF therapy with the increased risk of developing hypertension in patients with rheumatoid arthritis.[42] The discrepancy between these reports may result from the presence of a delicate balance between the BP-lowering effect of TNF-a inhibitors[43] and the systemic vasoconstriction effect due to antagonism of the known vasodilator properties of TNF,[44] so the net result is expected to be the sum of both effects.

High fasting plasma glucose level is considered as one of the MS components.[45,46] Fructose administration is a well-known inducer of hyperglycemia in rats.[18,47] The glucose transporter 4 (GLUT4) is a major mediator of glucose removal from the circulation and a key regulator of whole-body glucose homeostasis.[48] Fructose impairs glucose uptake by altering both of insulin-dependent translocation[49] and contraction (exercise)-dependent expression[50] of GLUT4. In this work, fasting hyperglycemia wasn't altered by infliximab administration. Previous work also showed that infliximab treatment didn't affect blood glucose level either in STZ-induced diabetic rats[51] or in male Wistar Kyoto rats and spontaneously hypertensive rats. We did not find previous studies assessing effects of infliximab on blood glucose levels in diabetic

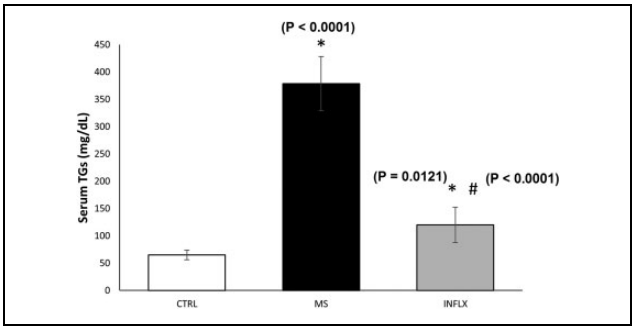

Figure 1. Effect of infliximab (5 mg/kg) on serum triglycerides level in fructose-induced MS in rats. Values are expressed as means of 8–10 rats ± SD; statistical comparisons were carried out using One-way ANOVA followed by Tukey's multiple comparisons test. *: significantly different from control group at P < 0.05. #: significantly different from MS group at P < 0.05.

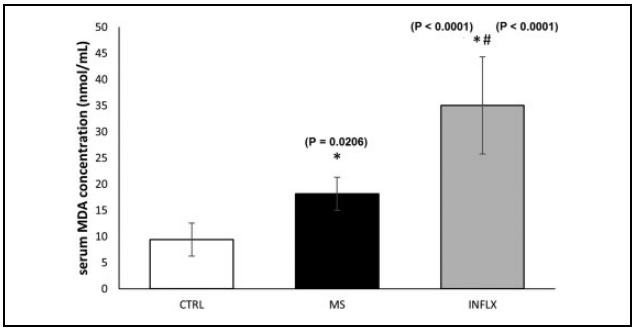

Figure 3. Effect of infliximab (5 mg/kg) on serum MDA level in fructose-induced MS in rats. Values are expressed as means of 8–10 rats ± SD; statistical comparisons were carried out using One-way ANOVA followed by Tukey's multiple comparisons test. *: significantly different from control group at P < 0.05. #: significantly different from MS group at P < 0.05.

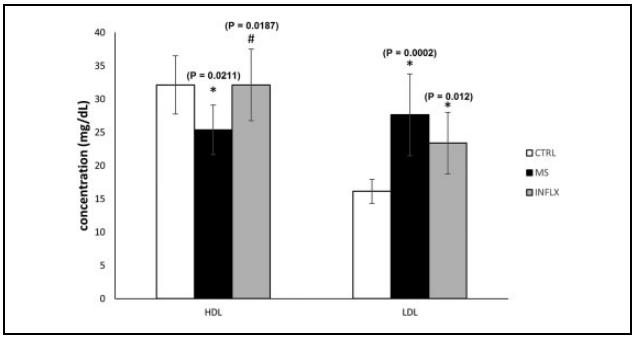

Figure 2. Effect of infliximab (5 mg/kg) on serum HDL-C and LDL-C (B) levels in fructose-induced MS in rats. Values are expressed as means of 8–10 rats ± SD; statistical comparisons were carried out using One-way ANOVA followed by Tukey's multiple comparisons test. *: significantly different from control group at P < 0.05. #: significantly different from MS group at P < 0.05.

patients but in a study of metabolic and vascular effects of another TNF-α blocker etanercept in obese patients with type 2 diabetes, there was no significant change in the blood glucose level after treatment period.[52]

Results of the current study showed that fructose administration was able to induce an increase of serum TGs as shown in Figure 1, an increase in LDL levels while decreasing serum HDL levels as shown in Figure 2. Previous studies also showed the same results regarding TGs levels,[53–55] LDL levels[53,54] and HDL levels.[53,55] In humans, anti-TNF therapy did not interfere with LDL concentrations.[56–58] Indeed, compelling evidence indicates that TNFα blockade may modulate LDL composition rather than LDL level.[59] There was a significant increase in HDL after infliximab treatment in most studies including ours[56,58,60,61] but the underlying mechanism remains unclear.

Infliximab treatment caused a significant reduction in serum TGs, this was in accordance with a previous report which has indicated that infliximab significantly decreased TGs level in patients with active rheumatoid arthritis.[62] In another study on patients with Crohn's disease, TGs level wasn't affected and that was suggested to be due to the initial relatively low level of TGs before treatment initiation.[57] Infliximab significantly reduced steatosis and fibrosis in the liver of rats fed a high-fat diet. The effect of infliximab on steatosis was so remarkable that even upon macroscopic evaluation of the liver it could be noticed.[63] Hepatic SIRT1 upregulation promotes PPARα signaling.[64] SIRT1 transcripts were significantly upregulated in colonic samples taken from Irritable bowel disease (IBD) patients successfully treated with infliximab, whereas no significant change in SIRT1 RNA expression was seen in IBD patients who failed to infliximab therapy.[65] Fenofibrate, TGs lowering drug, is a PPARα activator,[66] hence we suggest that the TGs lowering effect of infliximab may be via the same pathway.

The observation, which needs an extra focus, is that serum MDA level of infliximab treated group is significantly higher than the MS group as shown in Figure 3. Unlike the previous studies which report a significant decrease in serum or tissue MDA level following infliximab treatment,[67–72] the increase in MDA level as a result of infliximab treatment could

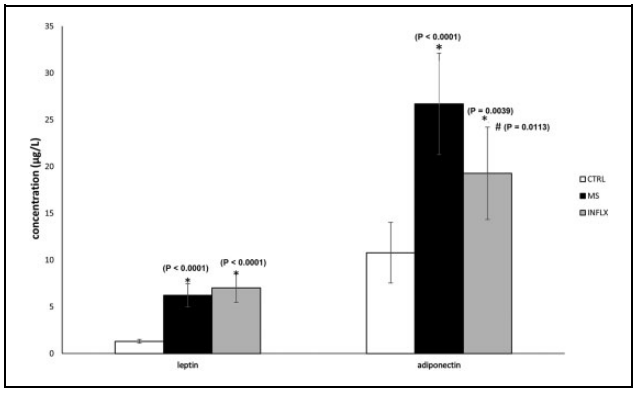

Figure 4. Effect of infliximab (5 mg/kg) on serum leptin and adiponectin levels in fructose-induced MS in rats. Values are expressed as means of 8–10 rats ± SD; statistical comparisons were carried out using One-way ANOVA followed by Tukey's multiple comparisons test. *: significantly different from control group at $P < 0.05$. #: significantly different from MS group at $P < 0.05$.

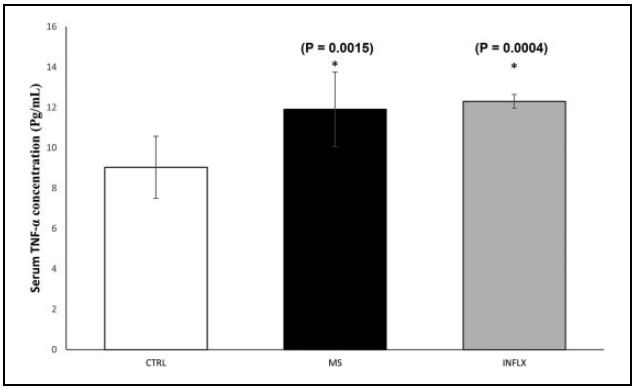

Figure 5. Effect of infliximab (5 mg/kg) on serum TNF-a level in fructose-induced MS in rats. Values are expressed as means of 8–10 rats ± SD; statistical comparisons were carried out using One-way ANOVA followed by Tukey's multiple comparisons test. *: significantly different from control group at $P < 0.05$.

be due to fatty acid oxidation, which in turn increases the free radicals formation. What supports this suggestion is that fenofibrate (approved PPARa activator) also caused a rise in liver MDA level in the same model as the one reported here.[73,74]

There was an observed increase in circulating adiponectin after fructose consumption as shown in Figure 4. The effect of fructose on adiponectin is currently unclear. In one study, adiponectin mRNA levels were found to be low in fructose-fed rats and were increased after the administration of rosiglitazone.[75] In contrast, another study showed an increase in adiponectin levels in rats fed with fructose.[76] Similarly, fructose feeding in cynomolgus monkeys caused an elevation in adiponectin.[77] The increased circulating adiponectin seen with fructose feeding might be a sign of adiponectin resistance, because these animals did not exhibit any of the beneficial effects typically associated with adiponectin, including increased insulin sensitivity and low BP.[78] A recent study has detected that adiponectin resistance in the wild type animals treated with fructose is accompanied by a decrease in the expression of adiponectin receptor 1 (AdipoR1) and adiponectin receptor 2 (AdipoR2) in the liver.[79] Fructose also has been shown to increase fasting plasma leptin concentrations, possibly an indication of leptin resistance.[80]

Infliximab treatment showed no significant effect on serum level of leptin as shown in Figure 4. Infliximab has been previously shown to decrease leptin level in mesenteric adipose tissue of rats with trinitrobenzene sulfonic acid-induced colitis[81] but the effect on circulating leptin wasn't studied on this model. It's worth mentioning that in humans, infliximab caused no significant changes in serum levels of leptin in patients with inflammatory bowel disease[82] and even caused an increase in leptinemia in patients with Crohn's disease.[83] Measuring serum adiponectin level at the end of our experiment has revealed a significant decrease in the circulating adiponectin. In STZ-induced diabetic mice model, infliximab has successfully reversed the downregulated expression of AdipoR1.[84] A reduction of adiponectin levels was also observed in rheumatoid arthritis patients with higher baseline adiponectin levels.[85]

As previously mentioned, infliximab is a TNF-α neutralizing antibody.[86] Many studies have already detected a decrease in TNF-a levels in response to infliximab treatment.[63,87,88] Several studies, including ours, showed that TNF-α levels were not reduced after infliximab treatment, as assessed by enzyme immune assay (EIA) quantification as shown in Figure 5.[81,89] It is imperative to consider that both the TNF-α that was bound to infliximab and the free TNF-α could be detected by EIA analysis and that the high level of TNF-a detected does not correlate with TNF-α activity.[81]

As shown in Table 1, findings of increased ALT and AST activities and the presence of round vacuoles of fatty change indicated by histopathology shown in Figure 6 are markers of hepatic damage occurred after fructose consumption. These results are similar to previous studies showing fructose-induced liver damage in rodents.[90,91]

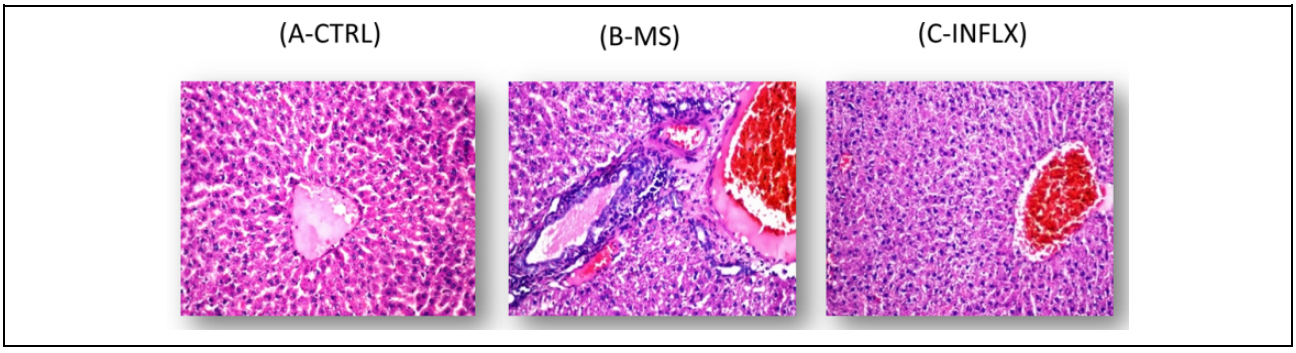

Figure 6. Histological examination of liver stained with (H&E, ×40). Representative liver sections were obtained from control rats (A), MS rats (B) and INFLX rats (C). Liver of rat in normal control group showed normal histological structure of the central vein and surrounding hepatocytes in the parenchyma (A), liver of rat in MS group showed severe congestion in central vein with inflammatory cells infiltration in the portal area mainly surrounding bile ducts (B), liver of rat in INFLX group showed mild congestion in central vein and few fibrosis in the portal vein (H&E, ×40).

Infliximab treatment failed to combat the increase in serum levels of ALT and AST, but ameliorated the congestion around the central hepatic vein and decreased fibroblastic cells proliferation as demonstrated by histopathological examination in Figure 6. Previous reports showed that infliximab could play a hepato-protective role against a wide range of hepatotoxicants such as methotrexate,[92] cisplatin,[93] paracetamol[71] and carbon tetrachloride (CCl4).[89] What is common among those studies is that infliximab treatment was initiated before exposure to the toxicant.

In conclusion, the present study provides evidence that infliximab affects some of the manifestations of MS in rats. Though infliximab reduced TGs, increased HDL-c levels, reversed adiponectin resistance occurred by fructose, the drug failed to combat MS-mediated obesity, hyperglycemia, hypertension, and elevated MDA above the insult. Long-term effects of infliximab on fructose-induced MS model in rats have not been assessed during the current study and needs further investigation.

List of abbreviations

Adipo R1	adiponectin receptor
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
BP	Blood pressure
EIA	enzyme immune assay
ELISA	sandwich enzyme-linked immunosorbent assay
FBG	Fasting blood glucose
GLUT4	glucose transporter 4
HDL	High-density lipoprotein
IBD	Irritable bowel disease
IDF	International Diabetes Federation
LDL	Low-density lipoprotein
MDA	Malonedialdehyde
MS	Metabolic syndrome
NIBP	non-invasive blood pressure controller
STZ	Streptozotocin
TGs	Triglycerides
TNF-α	tumor necrosis factor-alpha

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Yasmine A Abdelhamid https://orcid.org/0000-0002-3507-4961

References

1. Stanhope KL, Schwarz JM, Keim NL, et al. Consuming fructose-sweetened, not glucose-sweetened, beverages increases visceral adiposity and lipids and decreases insulin sensitivity in overweight/obese humans. *J Clin Invest* 2009; 119(5): 1322.
2. Francisqueti FV, Santos KC, Ferron AJ, et al. Fructose: toxic effect on cardiorenal risk factors and redox state. *SAGE Open Med* 2016; 4: 2050312116684294.

3. Tappy L and Mittendorfer B. Fructose toxicity: is the science ready for public health actions? *Curr Opin Clin Nutr Metab Care* 2012; 15(4): 357.
4. Ajala-Lawal R, Aliyu N and Ajiboye T. Betulinic acid improves insulin sensitivity, hyperglycemia, inflammation and oxidative stress in metabolic syndrome rats via PI3K/Akt pathways. *Arch Physiol Biochem* 2020; 126(2): 107–115.
5. Kannappan S, Jayaraman T, Rajasekar P, et al. Cinnamon bark extract improves glucose metabolism and lipid profile in the fructose-fed rat. *Singapore Med J* 2006; 47(10): 858.
6. Kaur J. A comprehensive review on metabolic syndrome. *Cardiol Res Pract* 2014; 2014: 943162.
7. Cameron AJ, Shaw JE and Zimmet PZ. The metabolic syndrome: prevalence in worldwide populations. *Endocrinol Metab Clin North Am* 2004; 33(2): 351–375.
8. Danielsen K, Wilsgaard T, Olsen A, et al. Elevated odds of metabolic syndrome in psoriasis: a population-based study of age and sex differences. *Br J Dermatol* 2015; 172(2): 419–427.
9. Snekvik I, Nilsen T, Romundstad P, et al. Metabolic syndrome and risk of incident psoriasis: prospective data from the HUNT Study, Norway. *Br J Dermatol* 2019; 180(1): 94–99.
10. Aradoini N, Talbi S, Mansouri S, et al. SAT0260 prevalence of metabolic syndrome in patients with ankylosing spondylitis in Morocco: a cross-sectional study of 103 cases. *Ann Rheum Dis 2015*; 74: 752–753.
11. Liu M, Huang Y, Huang Z, et al. Prevalence of metabolic syndrome and its associated factors in Chinese patients with ankylosing spondylitis. *Diabetes Metab Syndr Obes Targets Ther* 2019; 12: 477.
12. Fitzmorris PS, Colantonio LD, Perez ET, et al. Impact of metabolic syndrome on the hospitalization rate of Crohn's disease patients seen at a tertiary care center: a retrospective cohort study. *Digestion* 2015; 91(3): 257–262.
13. Bradley J. TNF-mediated inflammatory disease. *J Pathol* 2008; 214(2): 149–160.
14. Kurizky PS, Galvão LO and Martins GA. Efficacy and safety of biosimilar infliximab CT-P13 in the treatment of psoriasis and psoriatic arthritis: 1-year follow-up. *An Bras Dermatol* 2019; 94(4): 483–484.
15. Zrubka Z, Gulácsi L, Brodszky V, et al. Long-term efficacy and cost-effectiveness of infliximab as first-line treatment in rheumatoid arthritis: systematic review and meta-analysis. *Expert Rev Pharmacoecon Outcomes Res* 2019; 19(5): 537–549.
16. Maruotti N, d'Onofrio F and Cantatore FP. Metabolic syndrome and chronic arthritis: effects of anti-TNF-α therapy. *Clin Exp Med* 2015; 15(4): 433–438.
17. Seitz K and Zhou G. Pharmacokinetic drug-drug interaction potentials for therapeutic monoclonal antibodies: reality check. *J Clin Pharmacol* 2007; 47(9): 1104–1118.
18. Mahmoud AA and Elshazly SM. Ursodeoxycholic acid ameliorates fructose-induced metabolic syndrome in rats. *PLoS One* 2014; 9(9): e106993.
19. Karson A, Demirtaş T, Bayramgürler D, et al. Chronic administration of infliximab (TNF-α inhibitor) decreases depression and anxiety-like behaviour in rat model of chronic mild stress. *Basic Clin Pharmacol Toxicol* 2013; 112(5): 335–340.
20. Ambühl PM, Tissot AC, Fulurija A, et al. A vaccine for hypertension based on virus-like particles: preclinical efficacy and phase I safety and immunogenicity. *J Hypertens* 2007; 25(1): 63–72.
21. Bucolo G and David H. Quantitative determination of serum triglycerides by the use of enzymes. *Clin Chem* 1973; 19(5): 476–482.
22. Weissman M and Klein B. Evaluation of glucose determinations in untreated serum samples. *Clin Chem* 1958; 4(5): 420–422.
23. Tietz NW. *Fundamentals of clinical chemistry*. Philadelphia, PA: Saunders; 1987.
24. Lopes-Virella MF, Stone P, Ellis S, et al. Cholesterol determination in high-density lipoproteins separated by three different methods. *Clin Chem* 1977; 23(5): 882–884.
25. Okada M, Matsui H, Ito Y, et al. Low-density lipoprotein cholesterol can be chemically measured: a new superior method. *J Lab Clin Med* 1998; 132(3): 195–201.
26. Reitman S and Frankel S. A colorimetric method for the determination of serum glutamic oxalacetic and glutamic pyruvic transaminases. *Am J Clin Pathol* 1957; 28(1): 56–63.
27. Henry R, Chiamori M, Golub O, et al. Revised spectrophotometric methods for the determination of glutamate oxaloacetic transaminase, glutamic pyruvate transaminase and lactic acid dehydrogenase. *Am J Clin Pathol* 1960; 34: 381–398.
28. Kei S. Serum lipid peroxide in cerebrovascular disorders determined by a new colorimetric method. *Clin Chim Acta* 1978; 90(1): 37–43.
29. Banchroft J, Stevens A and Turner D.*Theory and practice of histological technique*. 4th edn. New York, London, San Francisco, Tokyo: Churchill Livingstone, 1996.

30. Jürgens H, Haass W, Castañeda TR, et al. Consuming fructose-sweetened beverages increases body adiposity in mice. *Obesity* 2005; 13(7): 1146–1156.
31. Mansour SM, Zaki HF and Ezz-El-Din S. Beneficial effects of co-enzyme Q10 and rosiglitazone in fructose-induced metabolic syndrome in rats. *Bull Fac Pharm Cairo Univ* 2013; 51(1): 13–21.
32. Mamikutty N, Thent ZC, Sapri SR, et al. The establishment of metabolic syndrome model by induction of fructose drinking water in male Wistar rats. *BioMed Res Int* 2014; 2014: 263897.
33. Gazzoto Filho A, Kinote A, Pereira DJ, et al. Infliximab prevents increased systolic blood pressure and upregulates the AKT/eNOS pathway in the aorta of spontaneously hypertensive rats. *Eur J Pharmacol* 2013; 700(1): 201–209.
34. Saraceno R, Schipani C, Mazzotta A, et al. Effect of anti-tumor necrosis factor-α therapies on body mass index in patients with psoriasis. *Pharmacol Res* 2008; 57(4): 290–295.
35. Kiortsis DN, Mavridis AK, Filippatos TD, et al. Effects of infliximab treatment on lipoprotein profile in patients with rheumatoid arthritis and ankylosing spondylitis. *J Rheumatol* 2006; 33(5): 921–923.
36. Dai S and McNeill JH. Fructose-induced hypertension in rats is concentration-and duration-dependent. *J Pharmacol Toxicol Methods* 1995; 33(2): 101–107.
37. Thirunavukkarasu V, Nandhini AA and Anuradha C. Lipoic acid attenuates hypertension and improves insulin sensitivity, kallikrein activity and nitrite levels in high fructose-fed rats. *J Comp Physiol B* 2004; 174(8): 587–592.
38. Yoshida S, Takeuchi T, Kotani T, et al. Infliximab, a TNF-α inhibitor, reduces 24-h ambulatory blood pressure in rheumatoid arthritis patients. *J Hum Hypertens* 2014; 28(3): 165.
39. Tran LT, MacLeod KM and McNeill JH. Chronic etanercept treatment prevents the development of hypertension in fructose-fed rats. *Mol Cell Biochem* 2009; 330(1–2): 219.
40. Van Doornum S, McColl G and Wicks I. Tumour necrosis factor antagonists improve disease activity but not arterial stiffness in rheumatoid arthritis. *Rheumatology* 2005; 44(11): 1428–1432.
41. Ferreri NR, Zhao Y, Takizawa H, et al. Tumor necrosis factor-α-angiotensin interactions and regulation of blood pressure. *J Hypertens* 1997; 15(12): 1481–1484.
42. Zhao Q, Hong D, Zhang Y, et al. Association between anti-TNF therapy for rheumatoid arthritis and hypertension: a meta-analysis of randomized controlled trials. *Medicine* 2015; 94(14): e731.
43. Sandoo A, Panoulas V, Toms T, et al. Anti-TNFα therapy may lead to blood pressure reductions through improved endothelium-dependent microvascular function in patients with rheumatoid arthritis. *J Hum Hypertens* 2011; 25(11): 699.
44. Irace C, Mancuso G, Fiaschi E, et al. Effect of anti TNFalpha therapy on arterial diameter and wall shear stress and HDL cholesterol. *Atherosclerosis* 2004; 177(1): 113–118.
45. Grundy SM, Brewer HB, Cleeman JI, et al. Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation* 2004; 109(3): 433–438.
46. Alberti KGM, Zimmet P and Shaw J. The metabolic syndrome—a new worldwide definition. *Lancet* 2005; 366(9491): 1059–1062.
47. Toop CR and Gentili S. Fructose beverage consumption induces a metabolic syndrome phenotype in the rat: a systematic review and meta-analysis. *Nutrients* 2016; 8(9): 577.
48. Huang S and Czech MP. The GLUT4 glucose transporter. *Cell Metab* 2007; 5(4): 237–252.
49. Li P, Koike T, Qin B, et al. A high-fructose diet impairs Akt and PKCZ phosphorylation and GLUT4 translocation in rat skeletal muscle. *Horm Metab Res* 2008; 40(08): 528–532.
50. Goyaram V, Kohn TA and Ojuka EO. Suppression of the GLUT4 adaptive response to exercise in fructose-fed rats. *Am J Physiol Endocrinol Metabol* 2014; 306(3): E275–E283.
51. Moriwaki Y, Inokuchi T, Yamamoto A, et al. Effect of TNF-α inhibition on urinary albumin excretion in experimental diabetic rats. *Acta Diabet* 2007; 44(4): 215–218.
52. Dominguez H, Storgaard H, Rask-Madsen C, et al. Metabolic and vascular effects of tumor necrosis factor-α blockade with etanercept in obese patients with type 2 diabetes. *J Vasc Res* 2005; 42(6): 517–525.
53. Shahraki MR, Harati M and Shahraki AR. Prevention of high fructose-induced metabolic syndrome in male Wistar rats by aqueous extract of *Tamarindus indica* seed. *Acta Med Iran* 2011; 49(5): 277.
54. Al-Rasheed N, Al-Rasheed N, Bassiouni Y, et al. Potential protective effects of *Nigella sativa* and *Allium sativum* against fructose-induced metabolic syndrome in rats. *J Oleo Sci* 2014; 63(8): 839–848.
55. Prabhakar P, Reeta K, Maulik SK, et al. α-Amyrin attenuates high fructose diet-induced metabolic syndrome in rats. *Appl Physiol Nutr Metab* 2016; 42(1): 23–32.

56. Popa C, Netea MG, Radstake T, et al. Influence of anti-tumour necrosis factor therapy on cardiovascular risk factors in patients with active rheumatoid arthritis. *Ann Rheum Dis* 2005; 64(2): 303–305.
57. Parmentier-Decrucq E, Duhamel A, Ernst O, et al. Effects of infliximab therapy on abdominal fat and metabolic profile in patients with Crohn's disease. *Inflamm Bowel Dis* 2009; 15(10): 1476–1484.
58. O'neill F, Charakida M, Topham E, et al. Anti-inflammatory treatment improves high-density lipoprotein function in rheumatoid arthritis. *Heart* 2017; 103(10): 766–773.
59. Popa C, Netea MG, Van Riel PL, et al. The role of TNF-α in chronic inflammatory conditions, intermediary metabolism, and cardiovascular risk. *J Lipid Res* 2007; 48(4): 751–762.
60. Seriolo B, Paolino S, Sulli A, et al. Effects of anti-TNF-α treatment on lipid profile in patients with active rheumatoid arthritis. *Ann NY Acad Sci* 2006; 1069(1): 414–419.
61. Peters M, Vis M, Van Halm V, et al. Changes in lipid profile during infliximab and corticosteroid treatment in rheumatoid arthritis. *Ann Rheum Dis* 2007; 66(7): 958–961.
62. Popa C, van den Hoogen FH, Radstake TR, et al. Modulation of lipoprotein plasma concentrations during long-term anti-TNF therapy in patients with active rheumatoid arthritis. *Ann Rheum Dis* 2007; 66(11): 1503–1507.
63. Barbuio R, Milanski M, Bertolo MB, et al. Infliximab reverses steatosis and improves insulin signal transduction in liver of rats fed a high-fat diet. *J Endocrinol* 2007; 194(3): 539–550.
64. Purushotham A, Schug TT, Xu Q, et al. Hepatocyte-specific deletion of SIRT1 alters fatty acid metabolism and results in hepatic steatosis and inflammation. *Cell Metab* 2009; 9(4): 327–338.
65. Caruso R, Marafini I, Franzè E, et al. Defective expression of SIRT1 contributes to sustain inflammatory pathways in the gut. *Mucosal Immunol* 2014; 7(6): 1467.
66. Fruchart J-C, Staels B and Duriez P. The role of fibric acids in atherosclerosis. *Curr Atheroscl Rep* 2001; 3(1): 83–92.
67. Triantafillidis JK, Papalois AE, Parasi A, et al. Favorable response to subcutaneous administration of infliximab in rats with experimental colitis. *World J Gastroenterol* 2005; 11(43): 6843.
68. Guven C, Borcek AO, Cemil B, et al. Neuroprotective effects of infliximab in experimental spinal cord ischemic injury. *J Clin Neurosci* 2010; 17(12): 1563–1567.
69. Güzel A, Günaydin M, Güzel A, et al. Infliximab attenuates activated charcoal and polyethylene glycol aspiration-induced lung injury in rats. *Exp Lung Res* 2012; 38(3): 147–156.
70. Tasdemir C, Tasdemir S, Vardi N, et al. Protective effect of infliximab on ischemia/reperfusion-induced damage in rat kidney. *Ren Fail* 2012; 34(9): 1144–1149.
71. Ferah I, Halici Z, Bayir Y, et al. The role of infliximab on paracetamol-induced hepatotoxicity in rats. *Immunopharmacol Immunotoxicol* 2013; 35(3): 373–381.
72. Kurt A, Tumkaya L, Turut H, et al. Protective effects of infliximab on lung injury induced by methotrexate. *Arch Bronconeumol* 2015; 51(11): 551–557.
73. El-Haleim EAA, Bahgat AK and Saleh S. Effects of combined PPAR-γ and PPAR-α agonist therapy on fructose induced NASH in rats: modulation of gene expression. *Eur J Pharmacol* 2016; 773: 59–70.
74. El-Haleim EAA, Bahgat AK and Saleh S. Resveratrol and fenofibrate ameliorate fructose-induced nonalcoholic steatohepatitis by modulation of genes expression. *World J Gastroenterol* 2016; 22(10): 2931.
75. Sharabi Y, Oron-Herman M, Kamari Y, et al. Effect of PPAR-γ agonist on adiponectin levels in the metabolic syndrome: lessons from the high fructose fed rat model. *Am J Hypertens* 2007; 20(2): 206–210.
76. Kamari Y, Grossman E, Oron-Herman M, et al. Metabolic stress with a high carbohydrate diet increases adiponectin levels. *Horm Metab Res* 2007; 39(05): 384–388.
77. Suzuki M, Yamamoto D, Suzuki T, et al. Effect of fructose-rich high-fat diet on glucose sensitivity and atherosclerosis in nonhuman primate. *Methods Find Exp Clin Pharmacol* 2006; 28(9): 609–618.
78. Shimamoto K and Ura N. Mechanisms of insulin resistance in hypertensive rats. *Clin Exp Hypertens* 2006; 28(6): 543–552.
79. Marek G, Pannu V, Shanmugham P, et al. Adiponectin resistance and proinflammatory changes in the visceral adipose tissue induced by fructose consumption via ketohexokinase-dependent pathway. *Diabetes* 2015; 64(2): 508–518.
80. Miller A and Adeli K. Dietary fructose and the metabolic syndrome. *Curr Opin Gastroenterol* 2008; 24(2): 204–209.
81. Clemente TRL, dos Santos AN, Sturaro JN, et al. Infliximab modifies mesenteric adipose tissue

alterations and intestinal inflammation in rats with TNBS-induced colitis. *Scand J Gastroenterol* 2012; 47(8–9): 943–950.
82. Karmiris K, Koutroubakis IE, Xidakis C, et al. The effect of infliximab on circulating levels of leptin, adiponectin and resistin in patients with inflammatory bowel disease. *Eur J Gastroenterol Hepatol* 2007; 19(9): 789–794.
83. Franchimont D, Roland S, Gustot T, et al. Impact of infliximab on serum leptin levels in patients with Crohn's disease. *J Clin Endocrinol Metab* 2005; 90(6): 3510–3516.
84. Nacci C, Leo V, De Benedictis L, et al. Infliximab therapy restores adiponectin expression in perivascular adipose tissue and improves endothelial nitric oxide-mediated vasodilation in mice with type 1 diabetes. *Vasc Pharmacol* 2016; 87: 83–91.
85. Derdemezis CS, Filippatos TD, Voulgari PV, et al. Effects of a 6-month infliximab treatment on plasma levels of leptin and adiponectin in patients with rheumatoid arthritis. *Fund Clin Pharmacol* 2009; 23(5): 595–600.
86. Kirman I, Whelan RL and Nielsen OH. Infliximab: mechanism of action beyond TNF-α neutralization in inflammatory bowel disease. *Eur J Gastroenterol Hepatol* 2004; 16(7): 639–641.
87. Cai Y, Cao Y-X, Lu S-M, et al. Infliximab alleviates inflammation and ex vivo airway hyperreactivity in asthmatic E3 rats. *Int Immunol* 2011; 23(7): 443–451.
88. Yalcin M, Akarsu M, Celik A, et al. A comparison of the effects of infliximab, adalimumab, and pentoxifylline on rats with non-alcoholic steatohepatitis. *Turk J Gastroenterol* 2014; 25(Suppl 1): 167–175.
89. Bahcecioglu IH, Koca SS, Poyrazoglu OK, et al. Hepatoprotective effect of infliximab, an anti-TNF-α agent, on carbon tetrachloride-induced hepatic fibrosis. *Inflammation* 2008; 31(4): 215.
90. Spruss A, Kanuri G, Wagnerberger S, et al. Toll-like receptor 4 is involved in the development of fructose-induced hepatic steatosis in mice. *Hepatology* 2009; 50(4): 1094–1104.
91. Bagul PK, Middela H, Matapally S, et al. Attenuation of insulin resistance, metabolic syndrome and hepatic oxidative stress by resveratrol in fructose-fed rats. *Pharmacol Res* 2012; 66(3): 260–268.
92. Cure E, Kirbas A, Tumkaya L, et al. Protective effect of infliximab on methotrexate-induced liver injury in rats: unexpected drug interaction. *J Cancer Res Ther* 2015; 11(1): 164.
93. Cüre MC, Cüre E, Kalkan Y, et al. Infliximab modulates cisplatin-induced hepatotoxicity in rats. *Balkan Med J* 2016; 33(5): 504.