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Research article

Ameliorative effects of inulin on non alcoholic fatty liver disease associated with type 2 diabetes mellitus in obese women

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Key words: Inulin, NAFLD, Obesity, Liver fat index, Irisin, Liver enzymes.

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Abstract

Objectives: This study investigated the effects of inulin at the level of 3 grams twice daily for 4 weeks in alleviating the complications associated with NAFLD. Also, we want to evaluate the role of serum irisin in NAFLD. **Subjects and methods:** Six grams of inulin fructans were given daily for each of the fifty obese type 2 diabetic female patients with NAFLD for a period of four weeks. Parameters estimated pre and post administration of inulin: fasting serum glucose, fasting serum insulin, fasting serum liver aminotransferases (AST, ALT) & Gamma glutamyltransferase (γ-GT) and serum irisin. HOMA Insulin Resistance (IR), AST/ALT ratio and Fatty Liver Index (FLI) were calculated. **Results:** Administration of inulin induced a significant reduction infasting serum glucose, insulin, insulin resistance, lipid profile (Cholesterol & triglycerides), aminotransferase enzymes (AST & ALT) and Fatty Liver Index (FLI). Otherwise, serum HDL-cholesterol and serum irisin levels showed a significant increase after inulin intake. Serum irisin negatively correlated with diabetes mellitus parameters, Total cholesterol, triglycerides and liver enzymes aminotransferases (AST & ALT), but correlated directly with HDL-C. **Conclusions:** Inulin fructans, improve liver function so may reduce the risk NAFLD associated with insulin resistance. Inulin seems to be a valuable add on therapy for hepatic steatosis amelioration. Irisin is considered as a new biochemical marker for diagnosis of NAFLD and might have an essential role in preventing the hepatic steatosis and attenuating its progression to steatohepatitis.

Introduction

Non-alcoholic fatty liver disease (NAFLD), the most common chronic liver disorder is a condition characterized by the accumulation of fat within the liver. NAFLD development is strongly associated with type II diabetes, obesity, and other features of the metabolic syndrome such as hypertension, central obesity, insulin resistance, apoptosis, and altered cytokine and adipokine pathways [1]. Most NAFLD patients revealed benign aspects called steatosis known as lipid aggregation in the liver. However, this disease can proceed into more serious situations as non-alcoholic steatohepatitis, cirrhosis, fibrosis and even hepatocellular carcinoma [2]. Clinically NAFLD does not have apparent symptoms, and it is frequently diagnosed coincidentally when

abnormalities of liver enzyme levels are detected. In several studies on patients with NAFLD, high levels of aminotransferases liver enzymes along with diabetes mellitus have been considered as independent predictors of moderate to severe fibrosis [3]. The ratio AST to ALT is frequently considered in medicine as an independent indicator for predicting existence of advanced hepatic fibrosis and also has been used as an aspect of various panels, as the NAFLD Fibrosis Score [4]. Serum Gamma-glutamyltransferase (γ-GT) is frequently increased in patients with NAFLD, and it has been revealed to be associated with increased the risk of mortality [5].

Irisin, recently discovered as an exercise-mediated myokine, adjusts energy metabolism via inducing browning of white adipose tissue (WAT) and thus liberates chemical energy in the form of heat [6]. This mechanism suggest that irisin, through the improvement of obesity and its associated chronic inflammatory state, may have a hypothetical protective role in fatty liver disease, type 2 diabetes mellitus (T2DM), osteoporosis as well as obesity-related cancer prevention in and cardiovascular disease [7].

The fatty liver index (FLI) implicates markers of obesity as body mass index (BMI) and waist circumference (WC), dyslipidemia (triglycerides (TG), and liver damage Gamma-glutamyltransferase (γ-GT). It strongly relates with objective markers of fatty liver disease and predicts most cases of NAFLD. FLI has been considered to be a valuable agent to detect the existence of NAFLD, as it offers quite harmony with the histological criteria as well as imaging for NAFLD [8].

Accumulated evidence indicated that the gut microbiota is implicated in the pathophysiology of obesity and its-related complications as nonalcoholic fatty liver disease (NAFLD), type 2 diabetes mellitus (T2DM) and insulin resistance [9].

The gut microbiota is involved with the host's metabolism and seems to have an essential role in the pathogenesis of NAFLD via several mechanisms, such as regulation of energy homeostasis by activation of the denovo synthesis of triglycerides in the liver, increasing the fermentation of carbohydrates to short chain fatty acids (SCFAs) and bacteria-derived endotoxins (e.g.lipopolysaccharides) [10].

No efficient therapy has been suggested for NAFLD. However, management strategies, such as lifestyle modifications, have shown to be efficient. Due to the challenge of physical activity for a long time and weight loss, changing the dietary ingredients may be an essential approach [11].

Clinical therapeutic options are still very scarce with respect to safety, effectiveness, and patient compliance. As a result, the intricate relationship between gut microbiota and NAFLD opens up a new window for seeking effective and safe therapies on NAFLD by restoring gut homeostasis of NAFLD patients in various ways and management strategies, such as life style modifications, have proven to be efficient [11].

Prebiotics are known as a group of indigestible carbohydrates that can adjust the activity and composition of the gut microbiota, so, they exert a beneficial impact on the host health [12]. According to a few studies, adding prebiotics, such as inulin, to a diet, leads to an increment proliferation of Bifidobacterium and Lactobacillus in the intestine and the amelioration of liver function in diseases as NAFLD [13].

Thus, the present study aimed to appreciate the effects of inulin fructans at the level of 6g/day for a period of four weeks in alleviating various biochemical markers associated with NAFLD. Also to evaluate the role of serum irisin in ameliorating NAFLD.

Subjects and methods

Subjects

Fifty type 2 diabetic Egyptian females aged 45 to 65 years; were selected from the clinics of the governorate hospitals. No diet restrictions were requested from the patients during the study other than their usual diet as they are diabetics. Their selection was according to the following criteria:

Inclusion criteria

Females, type 2 diabetics, obese or overweight, hypertensive or not, having higher serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST).

The detection method for fatty liver disease was an ultrasound of the liver and bile ducts and liver aminotransferases enzymes tests.

Exclusion criteria

Patients were free of any acute or chronic disease which might affect the metabolic status of the patient such as:

- Acute or chronic bacterial infection like skin infection or ulcers or carbuncles or infected foot or gangrene.
- Any endocrine gland disorder such as suprarenal or thyroid.
- Cancer lesion in any organ.
- Under hormonal therapy or contraceptive pills.
- Organ decompensation: Heart, kidney or lung.

Ethical committee approval

This work has been approved by the Egyptian National Research (NRC) ethical committee. Certificate number 15011.

Consent

Each patient was asked to sign a written consent for her agreement to be enrolled in the study.

Methods

Each patient ingested 6 grams/day of inulin-fructans type prebiotic, 3 grams in the morning and 3 grams in the evening for 4 weeks. Inulin orally intake by the patients was added on therapy to their conventional daily treatment of their diabetic state.

Inulin specifications

Inulin A.R (C6H10O5) N ALPHA-CHEMIKA Mumbai. 400002 (INDIA) An ISO: 9001: 2000 Certified companies.

Each patient was subjected for the following investigations before and after inulin ingestion:

Anthropometric measurements

1. Body Mass Index (BMI) weight in kilograms over height in meters squared (weight in Kg/height in m^2).
2. Waist circumference (WC) measurement to the region between the lower ribs and the iliac crest to the level of the umbilicus.

Laboratory measurements

1. **Fasting serum glucose:** This was estimated by an enzymatic colorimetric method. The principal is enzymatic oxidation of glucose by glucose oxidase enzyme, according to Passing and Bablok, 1983 [14]. Kit used from Egyptian Company for biotechnology (S.A.E.) Obour City Industrial Area. Block 20008 piece 19A Cairo. Egypt.
2. **Fasting serum insulin:** This was estimated quantitatively using an enzyme immunoassay method according to National Committee for Clinical Laboratory Standards [15]. Manufacturer of the kit used: immunospect corporation 7018 Owensmouth Ave. Suit 103 Canoga Park, CA, 91303.
3. **Insulin Resistance (IR):** was assessed using homeostasis model assessment (HOMA) from fasting serum insulin level and fasting serumglucose according to Mathiews *et al.*, 1985 **[**16]. The equation: insulin resistance (HOMA-IR) = fasting glucose (mg/dl) x fasting insulin (m I.U./ml)/ 405.
4. **Lipid profile:** Cholesterol, high density lipoprotein cholesterol (HDL-C) and triglycerides (TG) levels in serum were measured according to the method of Allain *et al.*, 1974 [17], Lopez-Virella 1977 [18] and Glicket *et al.*, 1986 [19] respectively by standard commercial colorimetric enzymatic assays (BioMerieux, Marcy l'Etoile, France; Roche Diagnostics, Basel, Switzerland).
5. **Determination of serum level of irisin**: The levels of irisin (myokine) in the samples were determined using Sandwich-ELISA. ELISA Kit used for the determination of serum irisin (Bioneovan Company, Ltd. No. 18, Keyuan Road, DaXing Industry Zone, Beijing, China) according to the instructions given by the manufacturer**.**
6. **Fasting serum liver enzymes:**

a) Serum aspartate aminotransferase **(AST)** was estimated quantitatively using colorimetric method after Reitman *et al.* 1957 [20]. Kit used from Randox Laboratories Limited 55 Diamond Road, Crumlin, Country Antrim BT29 4QY, UK.

b) Serum Alanine Aminotransferase **(ALT)** was estimated quantitatively using colorimetric method after Reitman *et al.*, 1957 [20]. Kit used from Randox Laboratories Limited 55 Diamond Road, Crumlin, Country Antrim BT29 4QY UK.

c) Serum Gamma Glutanyl Transferase **(γ-GT)** was estimated quantitatively using spectrophotometerical method according to Gendler *et al.*, 1984 [21] Kit used reactive GPL, Barcelona, Spain Industria 113, Nau J 08420 Canovelles-Barcelona.

d) Ratio of AST/ALT calculated.

Estimation of Fatty Liver Index (FLI)

This was estimated according to the equation of Bedoigni *et al.* 2006 [22]. The equation used four parameters: Waist Circumference (WC), Body Mass Index (BMI), serum triglycerides (TG) and serum gamma glutamyl transferase (γ-GT).

Statistical Analysis

Dataanalysis was done using the statistical package for the social science SPSS software version 17 on a personal computer. All numeric variables were expressed as a mean ± SD (standard deviation). To compare means, the independent-sample T test was used. Pearson's correlation coefficient was obtained whereas 'p'value**<**0.01 and P value<0.050 were considered as statistically significant.

Results and discussion

Nonalcoholic hepatic steatosis is mainly characterized by intracellular total cholesterol (TC) and triglycerides (TG) accumulation, due to an imbalance between decreased lipid disposal and increased lipid availability, mainly through de novo lipogenesis or higher circulating lipid uptake and reduces free fatty acid (FFA) oxidation [23]. This has been suggested as the first hit in the pathogenesis of NAFLD.

High levels of plasma total cholesterol, triglycerides and saturated fatty acids would share to metabolic syndrome-correlated inflammation and the secretion of pro-inflammatory cytokines, leading to oxidative stress which results from the excessive reactive oxygen species (ROS) produced. This has been suggested as the second hit in the pathogenesis of NAFLD [24].

Multiple mechanisms are included as oxidative stress, insulin resistance (IR), and also the modification of gut microbiota enhance the evolution of NAFLD by mediating processes of insulin resistance, inflammation, choline metabolism, and bile acids [25].

Prebiotics (such as inulin fructans) are indigestible food ingredients induce valuable effects, as they selectively enhance the growth and/or activity of "good" and inhibit the "bad" bacteriahabitant in the colon. Thus, they can be known as a fermented ingredient that permits alterations in the activity and/or composition in the gastrointestinal microflora conferring improvements upon host health [25].

Inulin fructans change endotoxin translocation and the integrity of the gut barrier in favor of host health increased the gut trophic hormone and glucagon-like peptide- 2(GLP-2), which can regulate endotoxin translocation through modifications of epithelial tight junctions. Steatosis itself increases the liver susceptibility to injury from endotoxins [10].

In our study, we detected that oral administration of 6g/day inulin for 4 weeks induced a significant reduction in the serum levels of fasting glucose, total cholesterol, triglycerides and improvement of insulin sensitivity and insulin resistance; on the other hand, it increased the levels of HDL-C significantly (Table1, Figure 1 & 2).

In agreement with our data Zhang *et al.*, 2018 [26] indicated the same results in diabetic rats and Ning *et al.*, 2017 [28] recorded that a daily dose of 10g chicory inulin significantly improved glucose, liver function and blood pressure in female patients with T2DM. Therefore, they concluded that chicory inulin possesses a potential value as an antidiabetic supplement, is primarily related to an increase in glucagon-like peptide-1 (GLP-1). GLP-1 promotes pancreas β cell proliferation, insulin secretion, controls glycogen synthesis in muscle cells, and enhances satiety [27]. Chicory inulin is also considered as a prebiotic because of its ability to stimulate the proliferation of beneficial microorganisms in the gut, and this property may potentially improve insulin resistance in obese NAFLD patients with T2DM [28].

Table 1. Serum levels of diabetes mellitus parameters, lipid profile, liver enzymes and irisin in pre and post-inulin administration groups.

Group Parameter	Pre-inulin (n=50) Mean ± SD	Post-inulin (n=50) Mean ± SD	P-value
Fasting glucose mg/dl	191 ± 18.26	147 ± 13.28	<0.01
Fasting insulin (µIU)	11.17± 4.69	6.02 ± 3.48	<0.01
Insulin Resistence (IR)	12.2 ± 6.71	7.8 ± 4.23	<0.01
Cholesterol (mg/dl)	234 ± 46.51	190.1± 36.93	<0.01
HDL –C (mg/dl)	76.8 ± 32.70	90.5 ± 34.21	<0.05
Triglycerides (mg/dl)	241 ± 93.42	191± 84.33	<0.01
Aspartate aminotransferase AST (IU/L)	24.8 ± 2.86	18.1± 4.13	<0.01
Alanine aminotransferase ALT (IU/L)	23.8 ± 4.09	16.2 ± 3.36	<0.01
AST/ALT	1.2 ± 0.27	1.07± 0.26	NS
Gamma glutamyl transferase γ-GT (IU/L)	17.3 ± 6.83	16.8 ± 8.11	NS
Irisin (ng/ml)	20.1± 2.61	28.2 ± 2.81	<0.01

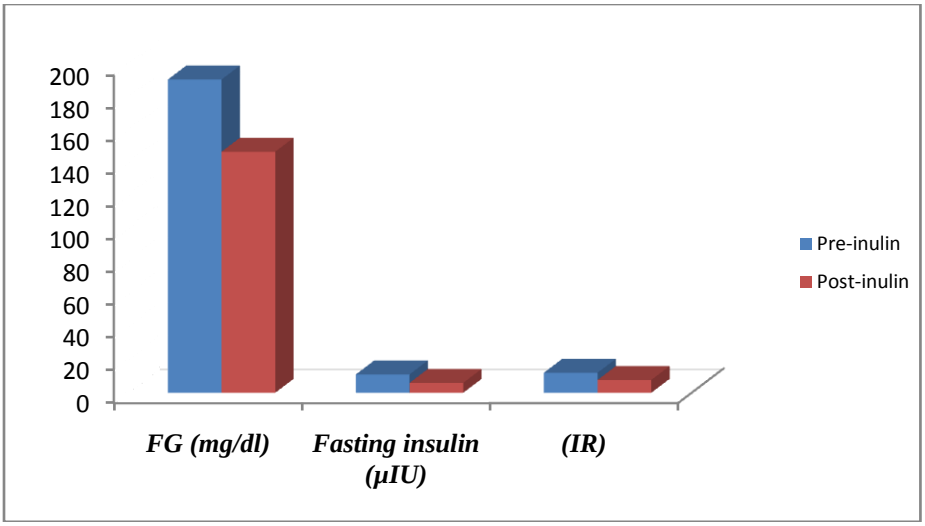


Figure 1. Comparison between mean values of serum fasting glucose, fasting insulin and insulin resistance in the studied groups.

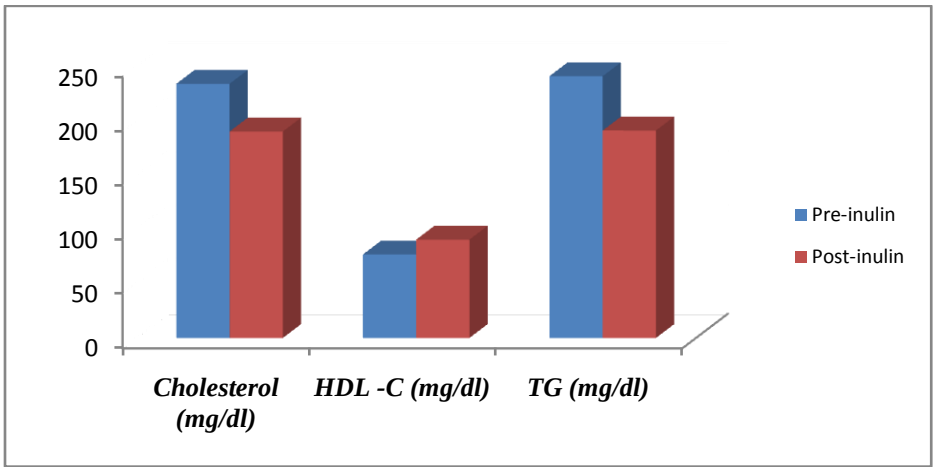


Figure 2. Comparison between mean values of serum cholesterol, HDL-C and triglycerides in the studied groups.

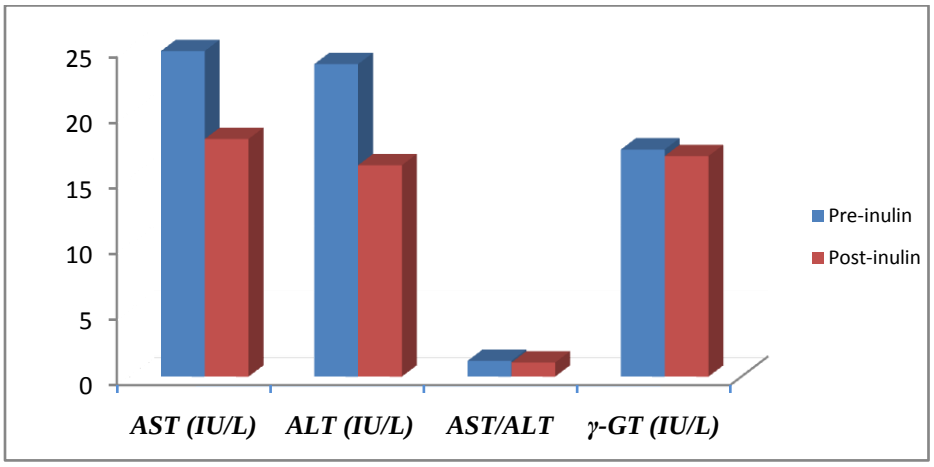


Figure 3. Comparison between mean values of serum liver enzymes: AST, ALT, ratio AST/ALT and γ-GT in the studied groups.

In 2017, Chen *et al.*, [29] indicated that adding chicory inulin promoted glucose uptake in muscle cells and hepatocytes in a dose-dependent manner without affecting the viability of these cells, suggesting that chicory inulin may reduce blood glucose levels by improving glycometabolism in hepatocytes and muscles, improve insulin sensitivity and restore both insulin signaling and glucose homeostasis in T2DM patients with NAFLD. Lipid transport and metabolism are key processes in the recognizing of NAFLD as steatosisemerges as a result of deregulation of fatty acids uptake and input by the liver [30]. In this way, in consistence with Correia-Sá *et al.*, 2013 [31] and Chang *et al.*, 2014 [32] we concluded that inulin fructans are able to modulate lipid metabolism as it reduce plasma triglyceride levels or limit its accumulation in the liver, preventing steatosis and liver damage.

Moreover, we observed a strong hypolipidemic effect of chicory inulin in NAFL diabetic obese patients, as it reduces significantly both serum levels of total cholesterol and triglycerides. These results agree with a previous study showing that chicory inulin improved lipid metabolism by adjusting the expression of acetyl-CoA carboxylase and the activities of xanthine oxidase and fatty acid synthase [28].

One suggested mechanism is via suppression of cholesterol synthesis. The second proposed serum cholesterol lowering mechanism is through inhibition of the activity of hepatic fatty acid synthase (FAS) [33]. Pachikian *et al.* 2013 [34] proposed that supplement of fructo oligosccharide (FOS), (inulin-like fructans with prebiotic properties) reduced accumulation of hepatic triglyceride in NAFLD model by enhancing production of GLP-1, reducing accumulation of cholesterol in liver, through inhibition of SREBP-2 (sterol-regulatory-element-binding protein isoform 2) and altering composition of gut microbiota [35].

In this study we revealed that inulin administration significantly decreased ALT & AST levels, whereas induce a much greater improvement, although non-significant, in ratio AST/ALT and γ-GT. These results are in agreement with Ning *et al.*, 2017 [28] and Aller *et al.*, 2011 [36] who found that supplementation of the prebiotic inulin for 3 months decreased AST and ALT serum levels in the patients with NAFLD (Table 1, Figure 3).

Reductions in serum AST and ALT concentrations in our study suggest the liver protective role of enriched chicory inulin in diabetic NAFLD patients. Previous studies confirmed that even mild decrease in serum concentrations of AST and ALT are in significant relation with reduction in liver fat content and improvement in insulin resistance. Reduction in concentration of serum AST was in parallel of modulation of histological parameters in liver, lobular inflammation and scores for steatosis in diabetic patients with non-alcoholic fatty liver disease [37]. The ratio of AST/ALT is usually less than 1 in patients who have either no or minimal fibrosis, although this ratio may be greater than 1 with the evolution of cirrhosis [5].

Our results revealed a significant increase in serum irisin levels post administration of inulin, which considered as an essential key factor in improvement of NAFLD (Table 1, Figure 4).

Some investigators reported that serum irisin levels were decrease in NAFLD and reduced gradually with increment the severity of liver disease [38]. Increased serum irisin after inulin treatment supports glucose uptake by skeletal muscles modify lipid metabolism and hepatic glucose, having an ameliorative effect on hyperglycemia and hyperlipidemia caused by metabolic syndrome and obesity, thus acting as an insulin sensitizing hormone. It is considered that irisin impacts tissues and organs implicated in type 2 diabetes mellitus, such as the pancreas and liver, by decreasing IR, although the mechanisms by which it modulates the function of pancreatic islets are still unknown [39].

In consistent with our results, Waluga *et al.*, 2019 [40] recorded a significant opposite correlation between serum irisin, and fasting serum glucose, insulin, HOMA-IR, total cholesterol and TG (Figure 6, 7, 8, 9 and 10). Otherwise, we recorded a significant positive correlation between serum irisin level and HDL in diabetic patients with NAFLD (Figure 11).

Recent studies detected a negative correlation between plasma irisin level and atherogenic lipid profile (total cholesterol and TG), also a gradual decrease of irisin level has been shown in parallel with increase in the intrahepatic content of triglyceride [41]. The mechanism by which irisin inhibits accumulation of hepatic triglyceride is by stimulating the signaling pathway of PPARa (Peroxisome Proliferator-Activated Receptor alpha), a key regulator of lipid metabolism that regulates fat oxidation among a thermogenesis mechanism**.**

Furthermore, PPARa also upregulates expression of FGF21 (Fibroblast Growth Factor 21), which has been detected to suppress the transcription of SREBP-1c (Sterol Regulatory Element Binding Protein) master regulators of fatty acid synthetase and lipogenesis in hepatocytes [42]. In addition, a positive correlation between irisin and HDL-C could protect against risk of atherosclerosis through anti-inflammatory effect and its inhibitory impact on cholesterol transport. Therefore, these findings strongly indicated that irisin could play an essential role in lipid metabolism and hence in the prevention of hepatic steatosis [39].

Our study revealed that low serum irisin level was negatively associated with increased in serum levels of ALT and AST (Figure: 12 & 13). This is in accordance with Zhang, *et al.*, 2013 [38] who suggested that irisin could behave as a protective factor against fatty liver diseases.

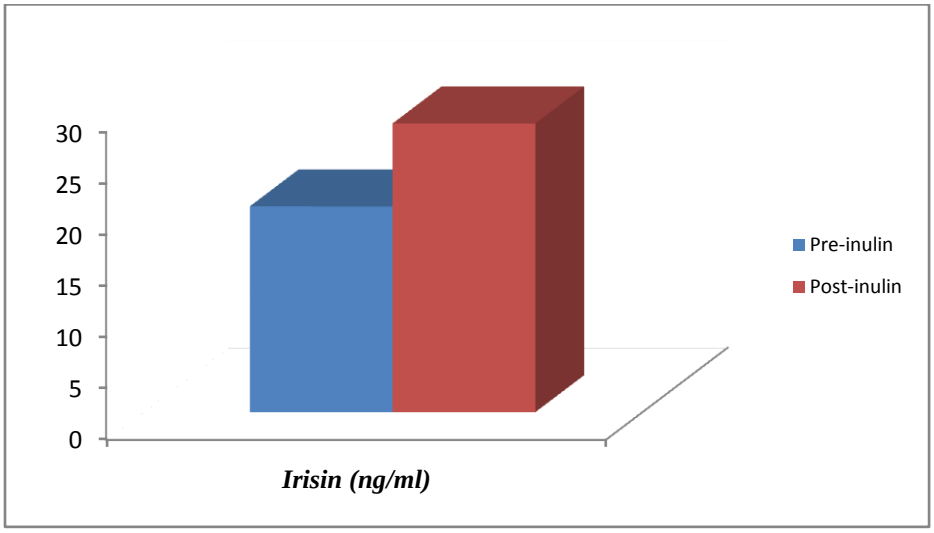


Figure 4. Comparison between mean values of irisin in the studied groups.

It is apparent from this study that reduced serum irisin level was associated with increase the risk of NAFLD. Therefore, this adipokine can be considered as a possible metabolic mediator in the context of NAFLD.

Serum irisin might have a principle role in preventing the hepatic steatosis through a mechanism inhibiting lipid accumulation in liver, and alleviating its progression to steatohepatitis by adjusting the expression of inflammatory cytokines [39].

Fatty liver index (FLI) is a simple, noninvasive and efficient predictor for diagnosis of liver steatosis. Also, it has a strong positive correlation with liver fibrosis, so perhaps it can indicate liver fibrosis too [44]. The FLI ranges from 0 to 100; Bedogni *et al* ruled out fatty liver disease by an FLI <30.

We noticed in our study, a significant decline in the values of fatty liver index (FLI) after inulin administration as compared with its level pre- inulin intake (Table 2, Figure 5). According to Bedogni's formula of liver fat index, and due to the short period of inulin intake, we could not find any valuable decrease in both the waist circumference and body mass index (BMI) after inulin intake, whereas fasting serum gamma glutamyl transferase enzyme (γ-GT) level decreased non significantly, the decrease was numerically appreciable, otherwise Triglycerides show a significant decrease after administration of inulin (table 2). In fact triglycerides are independent predictors of liver fat accumulations in patients with NAFLD [22, 43]. FLI highly correlates with objective measures of fatty liver disease and predicts most cases of NAFLD [44].

Table 2. Fatty Liver index and its parameters.

Group Parameter	Pre-inulin (n=50)	Post-inulin (n=50)	P-value
	Mean ± SD	Mean ± SD	
Fatty Liver Index (FLI)	30.6± 19.1	20.3 ±16.5	<0.01
Waist Circumference WC (cm)	123.3±10.8	121.4 ±12.7	NS
Body Mass index BMI (kg/m²)	36.1± 6.2	35.1 ± 4.8	NS
Gamma glutamyl transferaseγ-GT (IU/L)	17.3 ± 6.83	16.8 ± 8.11	NS
Triglycerides (mg/dL)	241 ± 93.42	191± 84.33	<0. 01

"P" value < 0.01 was considered as statistically significant.
"NS" was considered as statistically non –significant.

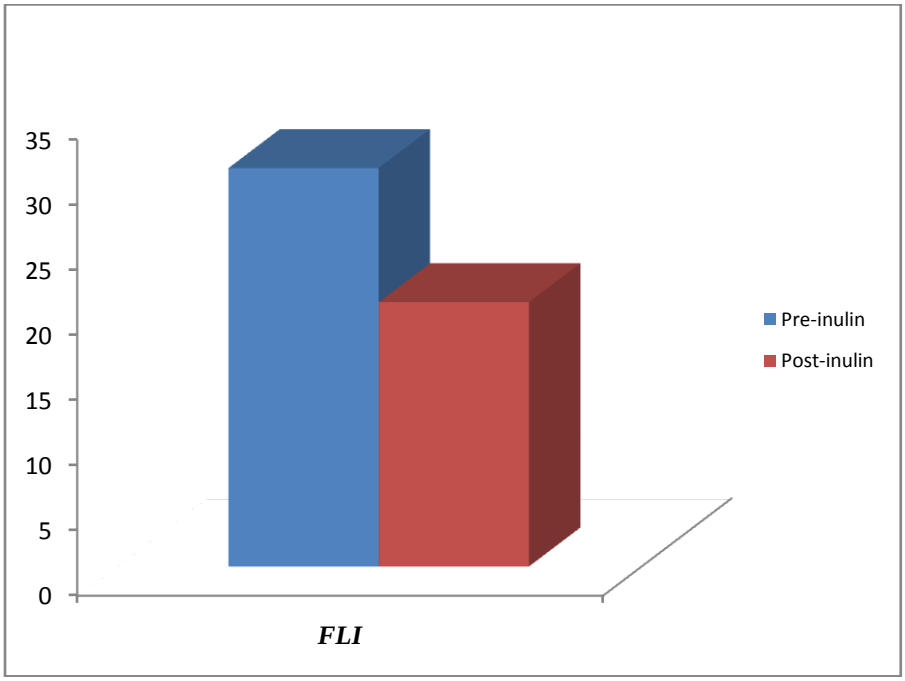


Figure 5. Comparison between mean values of Fatty Liver Index (FLI) in the studied groups.

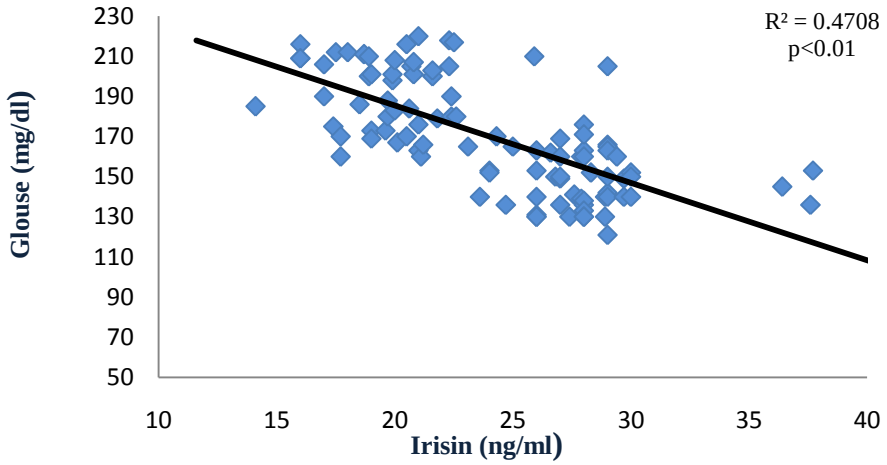


Figure 6. correlation coefficient between Serum Irisin & Glouse.

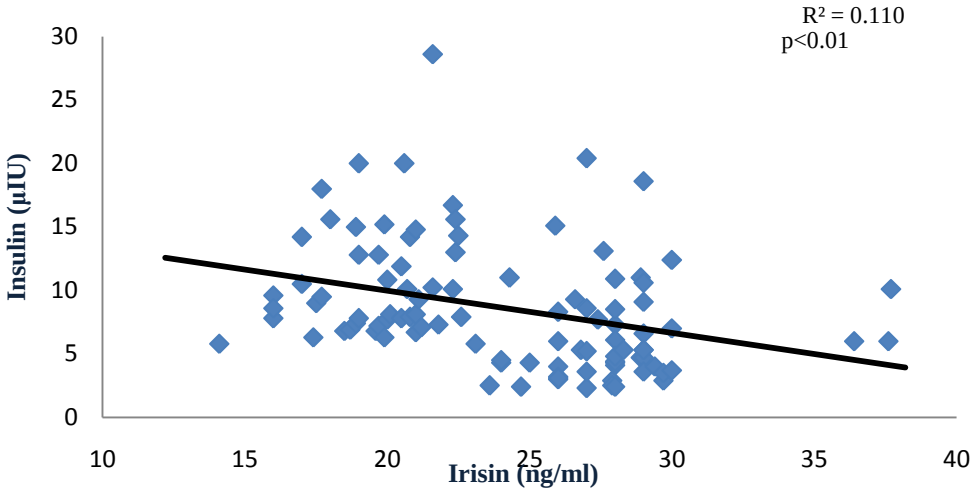


Figure 7. Correlation coefficient between Serum Irisin & Insulin.

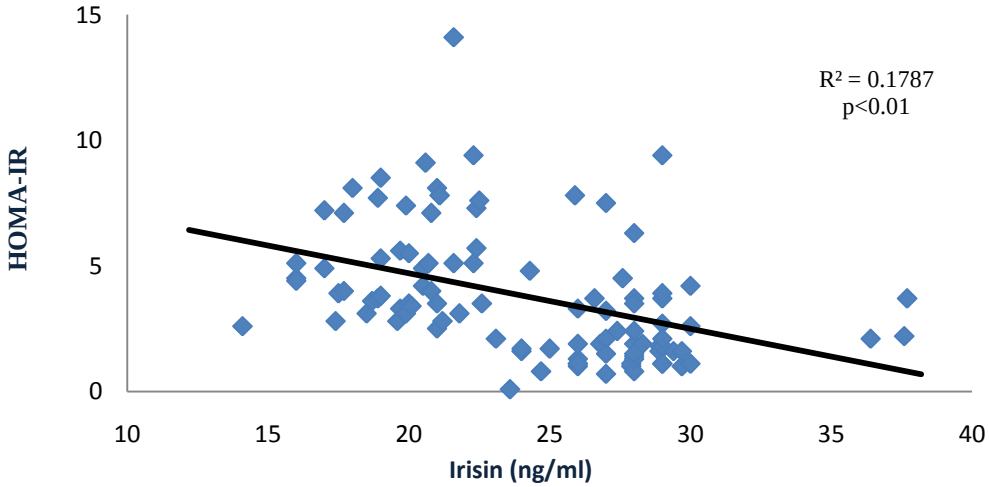


Figure 8. correlation coefficient between Serum Irisin & IR.

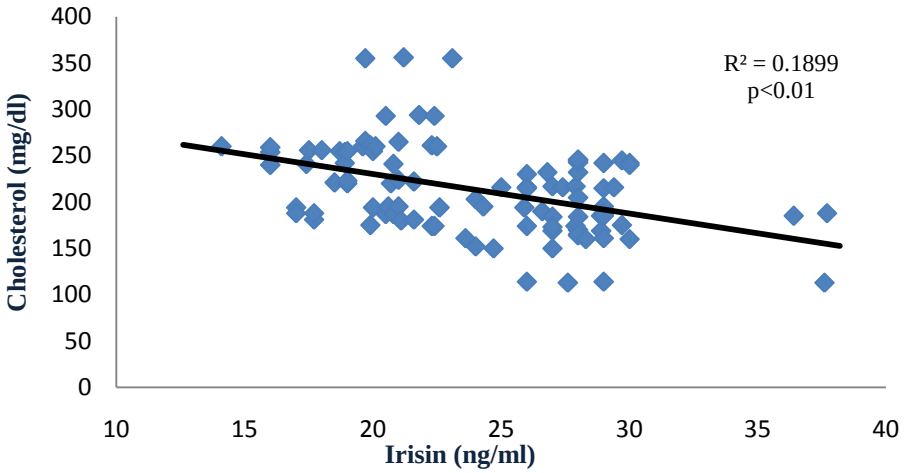


Figure 9. Correlation Coefficient between Serum Irisin & Cholesterol.

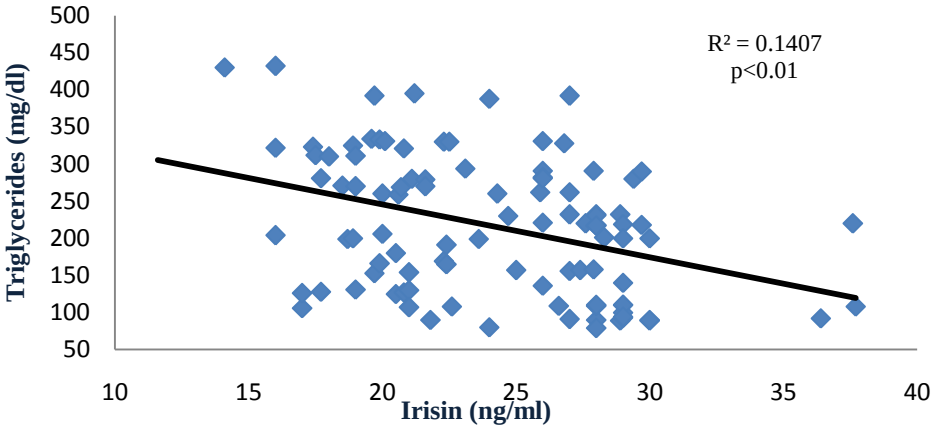


Figure 10. Correlation coefficient between Serum Irisin & Triglycerides.

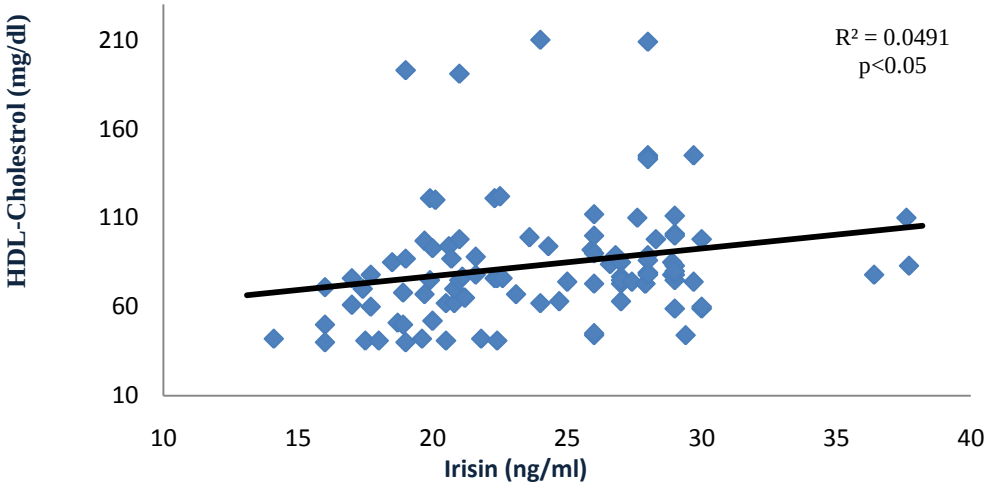


Figure 11. Correlation coefficient between Serum Irisin &HDL-C.

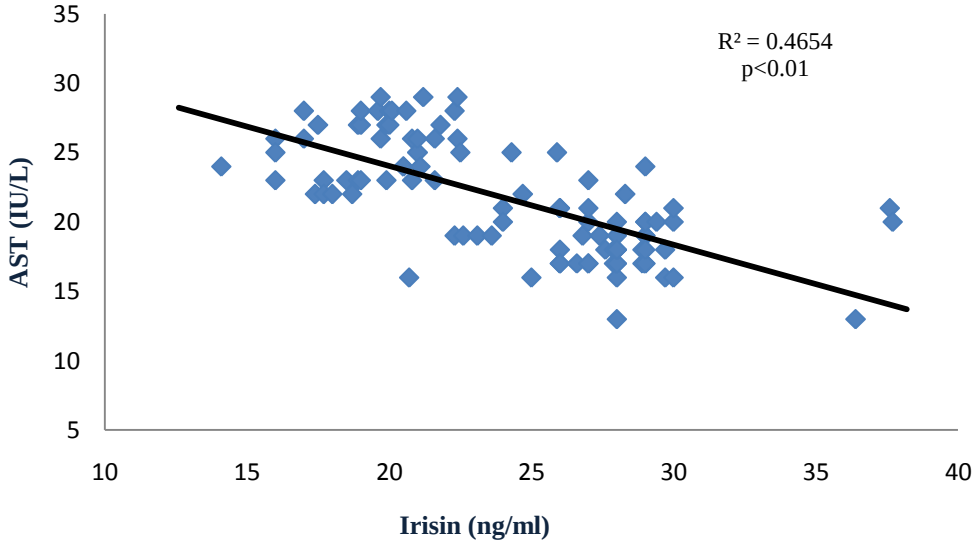


Figure 12. correlation coefficient between Serum Irisin & AST.

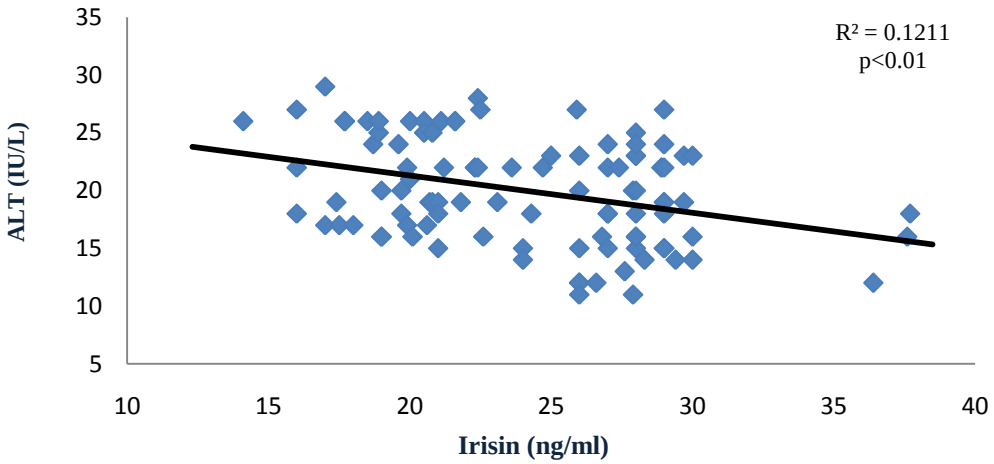


Figure 13. Correlation coefficient between Serum Irisin & ALT.

Conclusion

Our study suggested that inulin fructans have antidiabetic, lipid-lowering, and hepatoprotective effects in obese diabetic NAFL patients. Moreover, inulin may play an important role in the amelioration of hepatic diseases especially NAFLD.

Serum irisin is considered as a new essential biochemical marker for detection of NAFLD and might have a beneficial role in preventing the hepatic steatosis and attenuating its progression to steatohepatitis.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgement

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