Effect of Inulin on Metabolic Changes Produced By Fructose Rich Diet

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Abstract: Aim of the work: The present study was designed to assess the effect of inulin on metabolic changes produced by fructose rich diet. **Methods:** 45 male albino rats were divided into three groups (each group consisted of 15 rats); first (control) group fed standard commercial chow with tap water for 3 weeks, second (Fructose rich diet, FRD) group fed fructose rich diet in the dose 1.74 g / 100 g body weight per day by nasogastric tube plus standard commercial chow with tap water for 3 weeks and third (inulin treated) group fed fructose rich diet in the same dose and inulin in the dose of 0.174 g / 100 g body weight plus standard commercial chow with tap water for 3 weeks. **Results:** In the FRD group, the high fructose diet produced significant increase in blood level of glucose, insulin, and in insulin resistance. Also, the same group showed significant increase in serum level of total cholesterol, triglycerides (TG) and Low density lipoproteins (LDL) with significant decrease in High density lipoproteins (HDL) as compared to the control group. Inulin supplemented group showed significant decrease in blood levels of glucose, insulin and in insulin resistance. In addition, inulin supplementation caused significant elevation in the serum level of HDL with significant reduction in total cholesterol, TG and LDL serum levels as compared to FRD group. **Conclusion:** This study demonstrated that inulin could play a role in the correction of the metabolic disturbances produced by high fructose diet by improvement of carbohydrate and lipid metabolism.
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1. Introduction:

Fructose rich diet (FRD) can induce metabolic alterations, the most prominent being disturbance of plasma lipid profile[1]. The total sugar and fructose intake increased in the past three decades with evidence that FRD may bear direct effect in epidemics of obesity and related metabolic disorders[2].

Although fructose was proposed as natural substitute for sucrose in diabetic patients, it was found that increased dietary intake of fructose is associated with rise in plasma triglycerides, hepatic steatosis, impaired glucose tolerance, insulin resistance and even high blood pressure[3].

Fructose syrup has become popular sweetener used in soft drinks and many other products of massive daily consumption[4]. Consumption of sweetened beverages accounts for the major portion of fructose intake, the remaining being added sugar[1].

In the diet, fructose is consumed in various amounts as fruits, honey, beverages sweetened with high fructose corn syrup (HFCS) or sucrose [5].

Vartanian et al., (2007) reported that sweetened beverages consumption was associated with increased body weight[6] and increased the risk of developing type 2 diabetes but this effect is essentially linked to body weight changes[7].

In animals, FRD caused development of excess body fat and ectopic lipid deposition in the liver and the muscle which may be linked to development of metabolic syndrome[1].

In another study, the results showed that FRD increases plasma triglycerides (TG) concentration in animals and humans[8]. Fructose by providing large amount of triose-phosphate as precursors for fatty acids (FA) synthesis is highly lipogenic as lipogenesis is stimulated after acute fructose administration contributing to production of both the glycerol and fatty-acyl part of very low density lipoproteins (VLDL)[9].

FRD increases postprandial TG, stimulates secretion of TG-rich chylomicrons and induces lipogenic gene expression in small intestine hence raising the possibility that gut de novo lipogenesis may be factor in fructose induced hypertriglyceridemia[10].

In addition to altering plasma lipid profile, FRD may also modulate intracellular lipid deposition which are called ectopic lipids. Such ectpoic lipid deposition is related to tissue-specific insulin resistance [11].

Hepatic TG accumulation is major mediator of hepatic insulin resistance[12]. The mechanism by which intra-hepatic lipids causes insulin resistance is through diacylglycerol activation of novel protein kinase C (nPKC) and both are associated with lipid-induced insulin resistance in human muscle[13].

FRD leads to development of group of metabolic and cardiovascular alteration among which insulin resistance plays an important role[5]. It increases blood glucose and insulin levels with development of hepatic insulin resistance in healthy men[14].

Moreover, long term consumption of fructose may promote development of diabetes[15]. In rats, long term feeding of moderate amounts of fructose (15% of the diet) resulted in impaired glucose tolerance[16].

FRD may also decrease insulin sensitivity through changes in the microbial gut flora and/or alteration of intestinal permeability[17]. FRD was shown to increase the plasma concentration of endotoxin which activates inflammatory pathways and impairs actions of insulin leading to development of insulin resistance[18].

Inulin-type fructans are present in several fruits and vegetables. The most common dietary sources are wheat, onion, banana and garlic [19]. Inulin and oligofructose (OFS) may improve the function of the immune system [20] and the endocrine functions of the body [21].

In individuals with normal lipid levels, the most consistent observation that inulin-type fructans have no significant effect on lipid levels[22]. In persons with elevated blood lipid levels, the effect of inulin supplementation is conflicting. Some studies reported improvement in lipid levels following inulin intake[23], while others showed no effect of supplementation with inulin on the level of blood lipids especially that of triglycerides[24].

Also, the effects of inulin-type fructans on glucose and insulin are conflicting and dependent on physiological (basal or postprandial) and disease (insulin resistance or obesity) conditions[25].

The present work was designed to study the effect of inulin on the metabolic changes produced by high fructose diet especially that of lipid and carbohydrate metabolism.

2. Material and methods:
2.1. Animal

This study was performed on 45 male Wistar albino rats, weighed 230-250 grams.

The animals were obtained from animal house of the faculty of Medicine, Tanta University. The handling of the animals was carried out in accordance with the ethical guidelines for investigations and approved by the local Ethical Committee for the care and use of laboratory animals. The rats were housed in isolated animal cages and kept under a 12-hour light-dark cycle at room temperature. They had free access to water and food all over the period of the work.

2.2 Experimental design

The rats were classified into three groups:

First group (control group):

This group consisted of 15 rats which were fed standard ad libitum (free access of animal to food and water) commercial chow with tap water for 3 weeks.

Second group (Fructose rich diet group):

This group consisted of 15 rats which were fed fructose rich diet (obtained from Sigma) in the dose 1.74 g / 100 g body weight per day[26] dissolved in 10 ml distilled water given via intra-gastric tube plus standard commercial chow with tap water for three weeks.

Third group (Inulin treated group):

This group consisted of 15 rats which were fed fructose rich diet fructose rich diet in the dose 1.74 g/100 g body weight per day and inulin (obtained from Sigma) in the dose of 0.174 g / 100 g body weight via intra-gastric tube[27] plus standard commercial show with tap water for 3 weeks.

2-3 Blood sampling

At the end of the experimental period, the rats were anaesthetized by intra-peritoneal injection of pentobarbital sodium in dose of 50 mg/Kg body weight[28]. Then, the rats were sacrificed and blood samples were collected and centrifuged at 3000 rpm for 10 minutes and the separated serum was then transferred into clean storage tubes to be tested.

2-4 Biochemical assays

High density lipoproteins (HDL)[29], low density lipoproteins (LDL) [30] and fasting blood glucose[31] were measured by using enzymatic colorimetric method. Total cholesterol was measured by using BioMed cholesterol-LS kits[32] and triglycerides was measured by glycerol phosphate dehydrogenase (GPO) enzymatic method [33]. Insulin level was determined by radioimmunoassay (RIA) using Immulite device (RIA-Immulite, IML2000,IML 2500 insulin) provided by Siemens Medical Solutions Diagnostic. Insulin resistance was calculated using the formula of the Homeostasis Model Assessment (HOMA-IR)[34].

2-5 Statistical analysis:

Data were processed using the Statistical Package for Social Sciences® (SPSS) program v. 20. The results were expressed as mean (M) and standard deviations (SD). Then, the unpaired t test was performed and the differences were considered to be statistically significant if the P values were < 0.05.

3. Results

In the present study, by checking the results of the second (FRD) group, as shown in table (1) and figures (1-3), we can notice that the administration of fructose rich diet in a dose of 1.74 g / 100 g body weight per day dissolved in 10 ml distilled water for 3 weeks resulted in significant increase in the blood level of glucose, insulin , serum triglycerides , total cholesterol , LDL-cholesterol and HOMA-IR as compared the first (control) group.

Also, there was significant reduction in the serum HDL-cholesterol level.

In the third (inulin treated) group, as shown in table (1) and figures (1-3), the administration of inulin in a dose of 0.174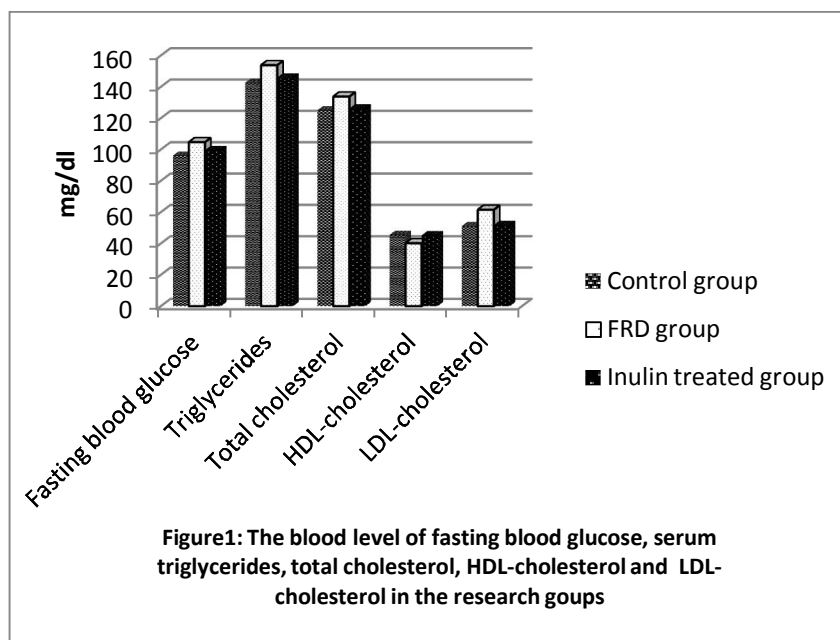 g / 100 g body weight together with FRD produced significant decrease in the blood level of glucose , insulin , serum triglycerides , total cholesterol LDL-cholesterol and HOMA-IR as compared to the (FRD) group. Also, there was significant reduction in the serum HDL-cholesterol level.
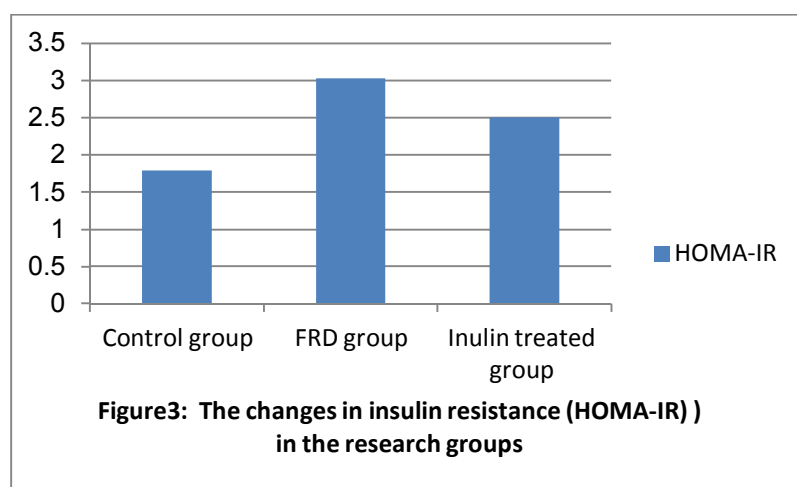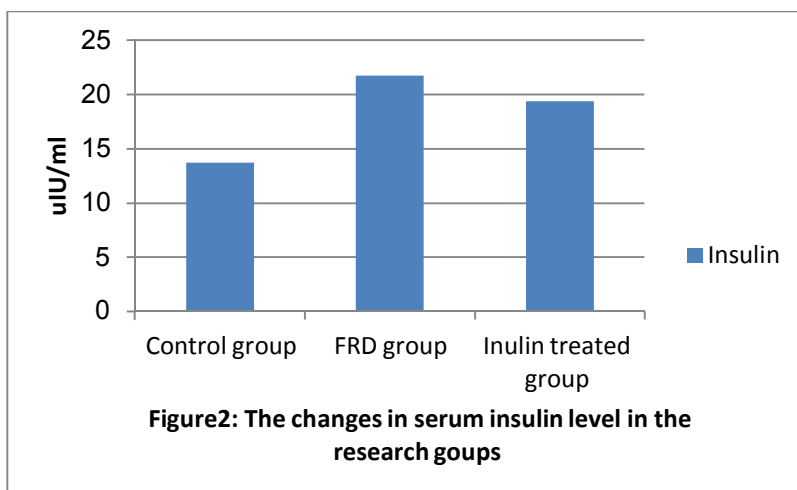
Table (1) : Changes in fasting blood glucose, insulin, serum triglycerides, total cholesterol, HDL- cholesterol, LDL- cholesterol, and insulin resistance (HOMA-IR) in all studied groups.

	Control group	FRD group	Inulin treated group
Glucose (mg/dl)	96.06 ±6.49	104.68±5.14	99.64±3.92
t		$t_1 = 4.03*$	$t_2 = 3.02*$
Insulin (uIU/ml)	13.7±2.02	21.76±1.43	19.37±1.17
t		$t_1 = 12.64*$	$t_2 = 5.03*$
Triglycerides (mg/dl)	142.57±7.45	153.83±10.81	145.98 ± 8.22
t		$t_1 = 3.32*$	$t_2 = 2.24*$
Total cholesterol (mg/dl)	125.02±10.95	133.8 ±13.11	126.24 ±11.50
t		$t_1 = 2.22*$	$t_2 = 2.06*$
HDL-cholesterol (mg/dl)	45.46 ± 6.50	40.16 ± 5.97	45.24 ± 5.45
t		$t_1 = 2.33*$	$t_2 = 2.44*$
LDL-cholesterol (mg/dl)	51.19±3.58	61.53±6.60	51.90 ± 5.32
t		$t_1 = 5.14 *$	$t_2 = 4.23 *$
HOMA-IR	1.79±0.26	3.03±0.18	2.51±0.15
t		$t_1 = 15.50*$	$t_2 = 8.50*$

Results are expressed as mean ± SD *denotes statistical significance ($p < 0.05$).
t_1 difference between **FRD** group Vs **control** group. **t_2** difference between **FRD** group Vs **inulin treated** group

Figure1: The blood level of fasting blood glucose, serum triglycerides, total cholesterol, HDL-cholesterol and LDL-cholesterol in the research goups

Figure2: The changes in serum insulin level in the research goups

Figure3: The changes in insulin resistance (HOMA-IR)) in the research groups

4. Discussion

In developed countries, exaggerated consumption of carbohydrates and lipid produces many metabolic disturbances which are expected to be the most likely cause of rising prevalence of metabolic syndrome and its related diseases [35].

Many prebiotics has been proposed to be able to protect or treat animals with metabolic syndrome[36]. The present study was designed to assess the effect of inulin on the metabolic changes produced by the intake of fructose rich diet.

The results of the current study showed that fructose rich diet (FRD) caused significant increase in the blood glucose and insulin levels and insulin resistance. Also, it produced significant increase in serum triglycerides, total cholesterol and LDL-cholesterol with significant reduction of HDL-cholesterol.

The administration of inulin in FRD rats resulted in significant reduction in blood glucose level, insulin level and insulin resistance. As regard lipid profile, it produced a significant decrease in the blood level of serum triglycerides, total cholesterol and LDL-cholesterol associated with significant increase in HDL- cholesterol.

The results of the present work are in accordance with previous researchers who observed that dietary inulin lowered serum glucose level and prevented hyperglycemia induced by fructose[37]. Also, **Byung-Sung (2011),** reported that inulin increases insulin sensitivity and secretion reducing the risk of diabetes[38]. However, **Rozan et al., (2008)** observed that supplementation of rats of both sexes with inulin produced no change in blood glucose level in both male and female rats[39].

As regard lipid metabolism, the results of the present study are similar to those reported by **Rault-Nania et al., (2008)** who observed that inulin caused significant reduction in serum triglycerides level and significant increase in HDL-cholesterol level caused by high fructose diet[40]. Also, **Byung-Sung (2011)**, proved that ingestion of inulin increased serum level

of HDL-cholesterol[38]. **Delzenne and Williams (2002),** reported that inulin improved blood lipid profiles in human [41].

However, no statistically significant differences were observed in total cholesterol or HDL-cholesterol serum levels following supplementation with inulin in another study [42].

The hypolipidemic effect of inulin could be secondary to fermentation of inulin in the colon by the large bowel bacteria. This fermentation involves a variety of metabolic process in the anaerobic breakdown of organic compounds yielding energy from microbial growth and production of short chain fatty acids (SCFAs) such as acetate, propionate and butyrate which are rapidly absorbed into the portal blood [43].

Tarini and Wolever (2010), reported that serum acetate, propionate and butyrate were significantly higher after inulin ingestion [44]. The direct rise in propionate caused by inulin could be the cause of inhibition of cholesterol[27]. Propionate has been shown to induce reduction in the corporation of acetate into cholesterol [23].

The increase in SCFA products can also improve the function of AMP activated protein kinase (AMPK) which is considered as a major cellular fuel and master regulator of the metabolic homeostasis. **Hu et al., (2010)** suggested that AMPK can be activated by SCFA either directly or indirectly [45].

Fructose rich diet induces hyperglycemia which exhibits more oxidative stress[46]. It also induces hyperlipidemia which causes oxidative stress and lipid peroxidation and reactive substances with the accompanying deficient anti-oxidant system [47].

The effect of inulin in improving several metabolic parameters could be explained by its anti-oxidant effect against the proxidant effect of fructose [40].The anti-oxidant effect of inulin may be indirect through the anti-oxidant action of butyrate [47]. which is one of the fermentation products of inulin in the colon [43].

Moreover, the oxidant effect of FRD may be related to the effect of fructose on copper metabolism , as fructose inhibits dietary absorption of copper, leading to severe copper deficiency. This copper deficiency is associated with dramatic decrease of superoxide dismutase and leads to alteration of antioxidant defense systems [48].Ingestion of inulin is accompanied by normalization of copper state and inulin exerts its beneficial effect through metabolic regulation of copper rather than through enhancing copper absorption and this will decrease the oxidative effect produced by FRD [43].

As a result of the anti-oxidant action of inulin, the insulin resistance will be decreased [49]. This will lead to hypoglycemia, and improvement of lipid profile [50] which were similar to the results observed in this work.

Also, it was reported that inulin may decrease the absorption of both glucose and fats. So, it positively affects both glucose and lipids especially TG level[51]. Inulin lowers the synthesis of triglycerides and fatty acids in the liver and decrease their levels in serum. It also decreases the de novo lipogenesis in the liver through the reduction in the activity of lipogenic enzymes [50]. **Delzenne et al., (2002)** reported that the activity of acetyl coenzyme A (coA) carboxylase, fatty acid synthase, malic enzyme, ATP citrate lyase and glucose-6-phosphate dehydrogenase decreased by 50 % in rats receiving inulin [52]. The reduction in the fatty acid synthase indicates a down regulation of lipogenic gene expression mRNA concentration in the liver tissue of inulin fed animals [53]. Also, inulin could be able to reduce serum TG level by extra-hepatic mechanism through stimulating TG catabolism [52], or by enhancing its clearance [23].

The hypocholesterolemic effect of inulin could be due to the increased fecal bile excretion [54]which stimulates liver synthesis of bile acids from cholesterol and reduces serum cholesterol level [23].

Another possible explanation to the effect of inulin on glucose, insulin and lipid profile is altered secretion of GIT hormones induced by the presence and/or fermentation of inulin in the distal colon [55].

Glucagon like peptide-1 (GLP-1) is a gut hormone secreted by the ileal L cells in response to the presence of nutrients in the intestinal lumen and has the ability to suppress hepatic lipogenesis via activation of AMPK pathway. So, GLP-1 can reduce serum triglycerides level accompanied by down regulation of lipogenesis enzymes and parallel regulation of carnitine palmitoyl transferase-1, a key enzyme in fatty acid β-oxidation [56]. When GLP-1 is infused it greatly reduces the increase in serum triglycerides level [57].

GLP-1 is a potent antihyperglycemic hormone inducing glucose-dependent stimulation of insulin secretion while suppressing glucagon secretion. It is also considered to be insulinotropic to augment insulin response when glucose is elevated[58]. It appears to restore the glucose sensitivity of pancreatic β-cells, with the mechanism possibly involving the increased expression of GLUT2 and glucokinase. Also, it is known to inhibit pancreatic β-cell apoptosis and stimulate the proliferation and differentiation of insulin-secreting β-cells.

Inulin causes an increase in glucagon like peptide-1 (GLP-1) in the proximal colon which can modulate glucose and lipid homeostasi[56]. SCFA mainly butyrate and propionate promote pro-glucagon expression in mature intestinal cells that could contribute to increase production of GLP-1 after ingestion of inulin[59].

Inulin can produce its effect on blood glucose level, insulin and lipid profile through its ability to change the blood level of adipocytokines[60].

Adiponectin decreases the blood glucose level by decreasing gluconeogenesis in the liver and increasing the glucose uptake in the skeletal muscles[61]. It also enhances insulin action and protects against insulin resistance as it increases fatty acid oxidation in the liver and skeletal muscles[62]. Moreover, it was reported that the increased blood level of adiponectin was associated with decrease the serum level of total cholesterol, triglycerides and LDL – cholesterol [63].

The increased production of postprandial (SCFAs) induced by the colonic fermentation of inulin reduces the production of ghrelin and this will lower the serum triglycerides level[44].

FRD is an inhibitor of peroxisome proliferator-activated nuclear receptors α (PPAR α) [62]. PPAR α is the master of regulation of insulin and lipids as it decreases triglyceride content in the liver and skeletal muscle, thereby increases in vivo insulin sensitivity, enhances glucose homeostasis[64] and facilitates glucose and lipids uptake by tissues[65]. Inulin counteracts the effect of FRD as it enhances the activation of peroxisome proliferator receptors α (PPAR α) [62].

5. Conclusion:

This study demonstrated that inulin could play a role in the correction of the metabolic disturbances produced by high fructose diet by improvement of carbohydrate and lipid metabolism.

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