Evaluation of acarbose and metformin on physiological parameters in diabetic male rat induced by high supplementation of fructose

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Received: September 2022 Accepted: December 2022

Abstract

Background: Dietary modification is a frequent strategy used in scientific investigations to replicate circumstances related with insulin resistance, obesity, and type 2 diabetes.

Objective: This research intended to find out how a high-fructose diet affected glycemic control, antioxidant status, as well as immunological function in male rats.

Materials and methods: A group of twenty-four male adult rats was divided at random to four even groups, each composed of six animals. The groupings were categorized as the following: The Negative Control Group comprised rats that received a standard saline. Rats in the Positive Control Group were given solution of a high-fructose (60%) in their drinking water. The rats in the third group received 30 (mg/kg) of acarbose via oral administration. The rats in the fourth group were given 15 mg/kg of metformin orally. Blood samples were taken at the end of the month-long trial to analyze a diverse factors associated with glycemic control and antioxidant status.

Results: The results revealed a rise in the glycemic index, Characterized by raised levels of insulin and glucose in the high-fructose treatment group as compared to the control group. However, acarbose treatment has resulted in significant enhancements in glucose regulation, antioxidant status.

Conclusion: This study provides a comprehensive analysis of the hyperglycemic effects of fructose and implies that the oral administration of acarbose may serve as a significant intervention to alleviate these effects.

Keywords: Acarbose, Diabetic Rat, Fructose, Glycemic index

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Introduction

Diabetes mellitus is a serious metabolic illness marked by problems in the metabolism of carbohydrate, protein and lipid (Sartorelli *et al*., 2009; Feillet-Coudray*et al*., 2019). According to estimations, diabetes is responsible for around 11.3% of the rate of total global death annually (Todoric *et al*., 2020). In 2019, about 4.2 million individuals between the ages of (20-79) died from diabetes-related causes (Todoric *et al*., 2020). The elevated number of deaths from diabetes confirms the significance of studying its origins.

Obesity has been linked to an increased risk of developing type 2 diabetes mellitus (T2DM), prompting the World Health Organization to issue several dietary recommendations (Sartorelli *et al*., 2009; Gugliucci, 2017). An increased risk of developing dyslipidemia has been linked to dietary patterns high in both saturated fat and refined carbohydrates (Sakasai-Sakai *et al*., 2019), overweight (Castro *et al*., 2012; Sreeja *et al*., 2014; Shimomura *et al*., 2016), insulin resistance (Takeuchi *et al*., 2017), and heart diseases (Hayyan *et al*., 2016; Winterbourn, 2017). High adherence to a Western diet pattern has also been linked to an increased risk of developing type 2 diabetes, as shown by a large number of cross-sectional studies and meta-analyses (Taati *et al*., 2020). However, it is still unclear which organs diet directly affects and how exactly it plays a role in the onset of type 2 diabetes.

Honey, vegetables, and fruits are all good natural sources of the monosaccharide fructose. Its high sweetness, low cost, palatability, and flavor-enhancing characteristics make it widely used in the food and beverage industries (Sartorelli *et al*., 2009). Conditions like obesity and dyslipidemia are thought to have a causal relationship with oxidative stress and inflammation, both of which have been linked to a high-fat/high-fructose diet (Feillet-Coudray *et al*., 2019; Todoric *et al*., 2020). The formation of harmful Advanced Glycation End-Products has been related to a diet high in fructose (Gugliucci, 2017; Sakasai-Sakai *et al*., 2019) and oxidative stress (Castro *et al*., 2012; Sreeja *et al*., 2014), both of which are associated in the pathogenesis of numerous chronic diseases (Shimomura *et al*., 2016; Takeuchi *et al*., 2017). Acarbose, classified as an alpha-glucosidase inhibitor, is exclusively used for the management and prevention of type 2 diabetes mellitus (Hayyan *et al*., 2016; Winterbourn, 2017). Patients with type 2 diabetes may benefit from reduced oxidative stress and inflammation if insulin therapy is combined with acarbose (Taati *et al*., 2020). There is hope for future combination therapies incorporating acarbose and immunotherapies because of the positive effect it has on intra-tumoral immunity, particularly T cell responses within the tumor microenvironment (Sharifi-Rad *et al*., 2020). Patients with type 2 diabetes in the COVID-19 study who took both acarbose and metformin had a lower risk of dying (Kaludercic and Di Lisa, 2020).

Despite the positive effects of fructose have been studied extensively in vitro, its negative consequences in vivo systems have received comparatively less attention. Fructose's harmful impacts on health are also poorly understood. We hypothesize that acarbose, when administered to rats on a high-fructose (HFr) diet, can improve a number of physiological indices, such as antioxidant status and glycemic index.

Materials and methods

The procedures employed in this study underwent a comprehensive evaluation and received approval from the Scientific Committee in the Faculty of Veterinary Medicine at the University of Basrah. All treatments strictly adhered to ethical standards governing the humane care of animals. A total of twenty-four adult male rats were randomly divided into four equal groups, each consisting of six rats, for duration of one month. The groups and their respective treatments were as follows:

1. Control Group (CC), Animals in this group received no specific treatment.
2. Second Group: Male rats in this group were provided with a high-fructose solution (60%) in their drinking water (Kim *et al*., 2021).
3. Third Group: Rats in this group received high-fructose treatment as in the second group, with the addition of oral administration of acarbose at a dose of 50 mg/kg (Oguma *et al*., 2021).
4. Fourth Group: Rats in this group were treated with an oral dose of 15 mg/kg of metformin (Cheng *et al*., 2022).

Blood samples were obtained using the heart puncture technique before and after the one-month experimental period. Serum samples were then analyzed to measure various parameters, involved the measurement of glycemic index, insulin and glucose concentrations using a glucose and insulin hormone kit obtained from Biosystem/Spine. Additionally, insulin resistance (IR), in accordance with the method outlined by (Ali and Khudair, 2019). Additionally, several biochemical parameters, such as antioxidant stress, lipid profile, interleukin-6, C-reactive protein, calprotectin, liver enzyme levels, and total protein, were assessed.

Statically analysis

The statistical disparities across the experimental groups were assessed through the use of a one-way analysis of variance (ANOVA).

Results

The Impact of Acarbose and Metformin on Weight and Weight Gain of the Body in Male Rats with Diabetes as a result of High Fructose Supplementation.

The results given in Table 1 reveal a statistically significant decrease ($p \leq 0.05$) in both body weight and body weight gain in male rats with diabetes exposed to high fructose supplementation when compared to two other groups: the control group (designated as -ve) and the group

treated with acarbose. Conversely, the results indicate that there was no significant alteration ($p \leq 0.05$) in body weight observed among diabetic male rats treated with acarbose or metformin, when compared to the control group (designated as -ve). On the other hand, the findings demonstrate a statistically significant increase ($p \leq 0.05$) in body weight gain among diabetic rats treated with acarbose and metformin, as compared to the control group (+ ve). Additionally, there is a statistically significant reduction ($p \leq 0.05$) in body weight gain among diabetic rats treated with acarbose and metformin, as compared to the control group (-ve).

Table 1: Impact of Acarbose and Metformin on the weight and weight gain of the body in male rats with diabetes as a result ofhigh fructose feeding. (Mean±SD), (n=6).

Groups	Parameters		
	Body weight (g)		Body Weight Gain(g)
	(0) Days	(30) Days	
Negative control Normal Saline (0.9%NaCl)	218.80±14.15	235.00±17.03a	16.20±2.13a
Positive control Fructose (60%)	208.20±21.05	173.20±29.28b	-35.00±0.04d
Fructose +Acarbose	217.00±16.03	223.20±19.60a	6.20±0.08b
Fructose +Metformine	216.50±30.23	220.20±21.47a	3.70±0.67c
LSD	NS	39.00	10.00

The variable "n" represents the number of animals. Lowercase letters are used to indicate differences between groups. The notation "$p \leq 0.05$" demonstrates a statistically significant difference when compared to the control group.

The impact of acarbose and metformin on the levels of insulin and glucose in male rats with diabetes as a result of high fructose supplementation.

The results obtained from Table 2 indicate a statistically significant increase ($p \leq 0.05$) of glucose concentration in diabetic male rats that were given a high fructose supplementation, In comparison to the untreated control group and an additional treated group. Conversely, the results show no statistically significant notable alteration ($p \leq 0.05$) in serum glucose concentration in diabetic male rats treated with carbose, if compared to the negative control group.

Table 2: Impact of Acarbose and Metformin on Insulin and Glucose Levels in the Serum of Male Rats with Diabetes as a result of High Fructose Supplementation. (Mean±SD), (n=6).

Groups	Parameters	
	Glucose (mg/dl)	Insulin (µL U/ml)
Negative control Normal Saline(0.9%NaCl)	91.01±6.33c	5.80±0.37c
Positive control Fructose (60%)	250.32±8.14a	22.15±0.12a
Fructose +Acarbose	97.22±3.52c	6.41±0.33c
Fructose +Metformine	135.04±3.15b	12.00±1.41b
LSD	35.54	5.20

The variable "n" represents the number of animals. Lowercase letters are used to indicate differences between groups. The notation "$p \leq 0.05$" demonstrates a statistically significant difference when compared to the control group.

The findings of this study demonstrated a statistically significant increase ($p \leq 0.05$) in serum insulin levels in diabetic male rats that were administered a high fructose supplementation, when compared to the negative control group and another treatment group. Conversely, the results indicated a non-significant alteration ($p \leq 0.05$) in serum insulin levels in diabetic male rats treated with acarbose, in comparison to the negative control group.

The impact of acarbose and metformin on the levels of malondialdehyde, superoxide dismutase, and glutathione peroxidasein male rats with diabetes as a result of high fructose supplementation.

The findings derived from Table 3 demonstrate a statistically significant elevation ($p \leq 0.05$) in serum malondialdehyde (MDA) concentrations among diabetic male rats generated by high fructose supplementation in the positive control group, in comparison to the negative control group and other treatment groups. Furthermore, the findings of this study indicate a statistically significant elevation ($p \leq 0.05$) in serum malondialdehyde (MDA) concentrations in male rats with diabetes who were administered acarbose plus metformin, if compared to the negative control group.

Table 3: Impact of Acarbose and Metformin on oxidative stressenzymes'levels, namely: MDA, SOD, and Gpx, in male diabetic rats as a result of high fructose supplementation. (Mean±SD), (n=6).

Groups	Parameters		
	MDA (mg/dl)	SOD (mg/dl)	GPx (mg/dl)
Negative Control Normal Saline (0.9%NaCl)	1.76±0.074c	358.18±9.29a	4.01±0.17b
Positive Control Fructose (60%)	3.59±0.16a	158.72±19.62b	5.10±0.55a
Fructose +Acarbose	3.27 ±0.18b	366.82±15.83a	3.92±0.14b
Fructose +Metformine	3.15±0.12b	164.85±9.01b	4.15±0.04a
LSD	0.31	193.33	0.94

The variable "n" represents the number of animals. Lowercase letters are used to indicate differences between groups. The notation "$p \leq 0.05$" demonstrates a statistically significant difference when compared to the control group.

The results of the study demonstrate a statistically significant decrease ($p \leq 0.05$) in superoxide dismutase (SOD) levels among male rats with diabetes produced by high fructose supplementation, in comparison to both the negative control group and the group receiving acarbose treatment. Nevertheless, the findings indicated that the administration of metformin to male rats with diabetes did not result in a statistically significant alteration ($p \leq 0.05$) in the levels of superoxide dismutase (SOD) in their serum, as compared to the positive control group.

The results of the GlutathionePeroxidase(GPx) analysis revealed a substantial increase ($p \leq 0.05$) in diabetic male rats that were administered high fructose supplementation (+ve), as compared to both the control (-ve) and acarbose-treated groups. In contrast, the findings demonstrated a lack of statistically significant change ($p \leq 0.05$) in serum GPx levels among diabetic male rats administered metformin, as compared to the positive control group (+ve).

The impact of acarbose and metformin on aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and total protein levels in male rats with diabetes as a result of high fructose supplementation.

The results obtained from Table 4 indicate a statistically significant increase ($p \leq 0.05$) in the levels of AST in the serum of male rabbits with diabetes that were induced by high fructose supplementation (positive control) compared to the negative control group. Additionally, the levels of AST in the serum of diabetic male rats treated with acarbose were found to be non-significantly different ($p \leq 0.05$) compared to the negative control group. Similarly, there was no significant change ($p \leq 0.05$) in the levels of AST in the serum of diabetic male rats treated with acarbose and metformin compared to the negative control group.

Table 4: Impact of Acarbose and Metformin on the levels of (AST, ALT, ALP enzymes), and total protein in male rats with diabetes induced by high fructose feeding. (Mean±SD), (n=6).

Groups	Parameters			
	AST (U/L)	**ALT (U/L)**	**ALP (U/L)**	**Total Protein (mg/dl)**
Negative control Normal Saline (0.9%NaCl)	43.00±2.07b	45.00±7.77b	28.83±0.17b	5.65±0.2b
Positive control Fructose (60%)	59.33±18.04a	69.33 ±6.47a	44.10±0.55a	6.80±0.8a
Fructose +Acarbose	28.16±8.77c	42.16±4.79b	25.33±6.53b	6.08±0.4ab
Fructose +Metformine	43.50±6.94b	67.16±9.57a	48.50±5.43a	6.18±0.7ab
LSD	0.31	193.33	0.94	1.12

The variable "n" represents the number of animals. Lowercase letters are used to indicate differences between groups. The notation "$p \leq 0.05$" demonstrates a statistically significant difference when compared to the control group.

The findings from the analysis of alanine aminotransferase (ALT) and alkaline phosphatase (ALP) levels indicated a statistically significant elevation ($p \leq 0.05$) in diabetic male rats that were subjected to a high fructose diet (positive control) compared to the negative control group. Additionally, the results demonstrated that the administration of acarbose to these rats did not lead to a significant alteration in ALT and ALP levels ($p \leq 0.05$). Conversely, the analysis of superoxide dismutase (SOD) levels in the serum of diabetic male rats treated with metformin showed no significant

change ($p \leq 0.05$) when compared to the positive control group.

The findings of the total protein analysis demonstrated a statistically significant elevation ($p \leq 0.05$) in diabetic male rats that were administered a high fructose supplementation (+ve) in comparison to the control group (-ve). Conversely, the results indicated a non-significant alteration ($p \leq 0.05$) in total protein levels in the serum of diabetic male rats treated with acarbose and metformin when compared to the control group (+ve).

The impact of acarbose and metformin on serum lipid profile in male diabetic rats induced by high fructose supplementation

The results obtained from Table 5 indicate a statistically significant increase ($p \leq 0.05$) in the serum total cholesterol levels of male diabetic rats that were induced by high fructose supplementation in the positive control group, when compared to the negative control group and another treatment group. However, there was no statistically significant change ($p \leq 0.05$) in the serum total cholesterol levels of diabetic male rats treated with acarbose or metformin, when compared to the negative control group.

Table 5: Impact of Acarbose and Metformin on Lipid Profile levels in Male Rats with Diabetes as a result of High Supplementation. (Mean±SD), (n=6).

Groups	Parameters				
	Total cholesterol (mg/dl)	**Triglyceride (mg/dl)**	**HDL (mg/dl)**	**LDL (mg/dl)**	**VLDL (mg/dl)**
Negative control Normal Saline (0.9%NaCl)	117.50±13.69b	65.83±19.0	37.83±8.84a	15.16±5.03b	53.33 ±21.60ab
Positive control Fructose (60%)	213.33±51.25a	96.66±35.9	21.00±4.73b	84.66±18.18a	72.16±20.88a
Fructose +Acarbose	131.67±17.51b	67.83±25.3	35.00±13.03a	24.16±8.08b	47.33± 16.02b
Fructose+Metformine	144.17±19.60b	65.66±27.7	32.16±5.81a	26.33±3.82b	51.50±17.61ab
LSD	69.16	NS	11.16	58.33	24.83

The variable "n" represents the number of animals. Lowercase letters are used to indicate differences between groups. The notation "$p \leq 0.05$" demonstrates a statistically significant difference when compared to the control group.

The findings of the triglyceride analysis indicated that there was no statistically significant difference ($p \leq 0.05$) in diabetic male rats who were given a high fructose supplementation (+ve) compared to the control group (-ve). Similarly, there was no significant change ($p \leq 0.05$) in the serum triglyceride levels of diabetic male rats treated with metformin compared to the control group (-ve) and rats treated with acarbose.

The findings from the analysis of high-density lipoprotein (HDL) levels indicated a statistically significant reduction ($p \leq 0.05$) in male rats with diabetes that were exposed to high fructose supplementation (+ve) compared to both the control group (-ve) and another group that received a different treatment. In contrast, the

findings indicated a lack of statistically significant change ($p \leq 0.05$) in high-density lipoprotein (HDL) levels inside the serum of male rats afflicted with diabetes who received treatment with acarbose and metformin, in comparison to the control group (negative).

The results of the investigation on low-density lipoprotein (LDL) revealed a substantial statistical increase ($p \leq 0.05$) in male rats with diabetes that were administered high fructose supplementation (+ve), in comparison to the control group (-ve) and other groups receiving treatment. Furthermore, the findings demonstrated a statistically significant rise ($p \leq 0.05$) in low-density lipoprotein (LDL) concentrations in the blood serum of male rats with diabetes who were administered metformin, as compared to both the control group (referred to as the negative control group) and the group of male rats with diabetes who received acarbose treatment. Nevertheless, the study did not observe a statistically significant alteration ($p \leq 0.05$) in low-density lipoprotein (LDL) levels within the serum of male rats with diabetes who were administered acarbose, when compared to the control group (-ve).

The study's results revealed a statistically significant increase ($p \leq 0.05$) in the levels of very low-density lipoprotein (VLDL) in male rats with diabetes who were administered high fructose supplementation (+ve), when compared to both the control group (-ve) and another group that received an alternative treatment. Additionally, the results indicated a significant increase ($p \leq 0.05$) in VLDL levels in the serum of diabetic male rats treated with metformin, as compared to both the control group (-ve) and the group of diabetic male rats treated with acarbose. However, the results did not show any significant changes ($p \leq 0.05$) in VLDL levels in the serum of diabetic male rats treated with acarbose, as compared to the control group (-ve).

The impact of acarbose and metformin on the levels of calprotectin, interleukin-6, tumour necrosis factor-α, and C-reactive protein in male rats with diabetes as a result of high fructose diet

The study presented in Table 6 demonstrated a statistically significant increase ($p \leq 0.05$) in serum calprotectin (Cal), Tumour Necrosis Factor-α(TNF-α), andInterleukin-6(IL-6) concentrations in the group of male rats with diabetes compared to the control group. Additionally, the results indicated a significant increase ($p \leq 0.05$) in serum calprotectin (Cal) levels in diabetic male rats treated with acarbose at a dose of 50mg/kg and the metformin group, when compared to the negative control group.

The results of this study demonstrate a statistically significant elevation ($p \leq 0.05$) in TNF-α concentrations among male rats with experimentally induced diabetes through high fructose supplementation (+ve) in comparison to the control group (-ve).Nevertheless, upon administering acarbose at a dosage of 50mg/kg to the diabetic rats, a notable reduction in TNF-α levels was observed in comparison to the positive control group. In contrast, the findings indicated that administration of metformin did not result in a statistically significant alteration ($p \geq 0.05$) in the levels of TNF-

α in the serum of male rats as compared to a (+ve) control group.

The results of the IL-6 analysis revealed a statistically significant increase ($p \leq 0.05$) in IL-6 levels in male rats with diabetes produced by high fructose supplementation (+ve) compared to the control group (-ve) and the group treated with acarbose at a dosage of 50mg/kg.In contrast, the findings demonstrated a statistically insignificant change ($p \leq 0.05$) in the levels of IL-6 in the serum of male rats administered with metformin, as compared to the positive control group.

The findings from the C-reactive protein (CRP) analysis demonstrated a statistically significant elevation ($p \leq 0.05$) in diabetic male rats that were induced with high fructose supplementation (+ve) when compared to the control group (-ve) and those treated with acarbose at a dosage of 50mg/kg. Conversely, the results indicated a non-significant alteration ($p \leq 0.05$) in serum interleukin-6 (IL-6) levels in male rats treated with metformin in comparison to the positive control group (+ve).

Table 6: Impact of acarbose and metformin on the concentrations of proinflammatory cytokines in the serum of male rats with diabetes induced by high fructose supplementation. (Mean±SD), (n=6).

Groups	Parameters			
	Cal (µg/mg)	TNF-α (ng/L)	IL-6 (pg/mL)	CRP (Pg/mL)
Negative control Normal Saline (0.9%NaCl)	350.92 ± 10.01b	120.12 ± 36.43c	1.85±0.37d	0.67± 0.004b
Positive control Fructose (60%)	500.34 ± 36.89a	200.60 ± 45.23a	5.56±0.09a	15.28 ±0.79a
Fructose +Acarbose	377.41± 18.41b	160.17±14.21b	2.26±0.27c	0.75± 0.001b
Fructose+Metformine	360.52 ± 4.39b	140.11±30.25b	4.05±0.35b	0.86± 0.003b
LSD	250	35	0.5	12

The variable "n" represents the number of animals. Lowercase letters are used to indicate differences between groups. The notation "$p \leq 0.05$" demonstrates a statistically significant difference when compared to the control group.

Histological examination of pancreas

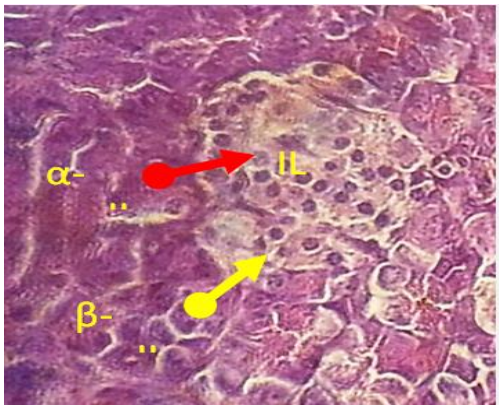

Figure 1: Depicts a segment of the pancreas, with a particular focus on the typical islet of Langerhans (IL) cells. The cells demonstrate cytoplasm that contains granules. β-cells are distinguished by their nuclei, which are both light and huge. On the other hand, α-cells are identified by their nuclei, which are small and black, and are situated near the periphery. Furthermore, the depicted figure showcases typical acini (A) that have been stained utilising the hematoxylin and eosin (H&E) staining procedure. The image was magnified at 400X.

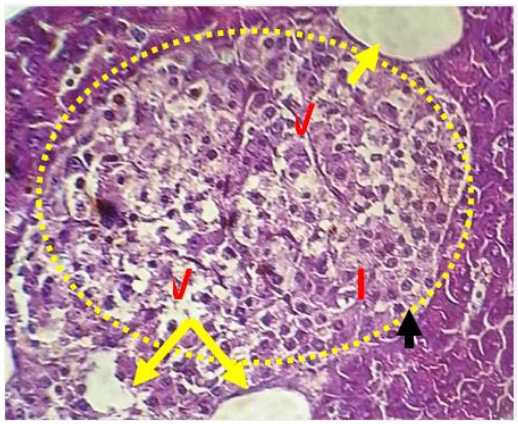

Figure 2: Depicts a cross-sectional perspective of the pancreas exhibiting diabetes (positive control group) induced by a high fructose diet. The histological analysis demonstrated the occurrence of hyperplasia in the β-cells of the islets of Langerhans, concomitant with pyknosis of their nuclei. Furthermore, the presence of degenerate vacuolated (V) islets of Langerhans was identified through the utilisation of hematoxylin and eosin (H&E) staining. The magnification employed for the purpose of observation was set at 400X.

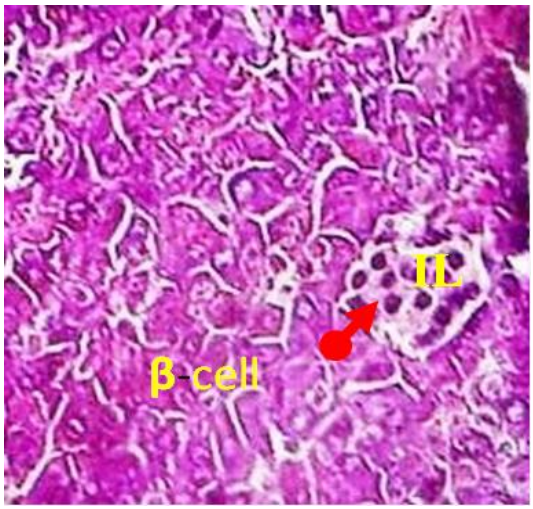

Figure 3: displays a pancreatic slice of rats with diabetes that underwent acarbose therapy. The image displays the islet of Langerhans (IL), which has been subjected to hematoxylin and eosin (H&E) staining method for visualization. The image was magnified at 400X.

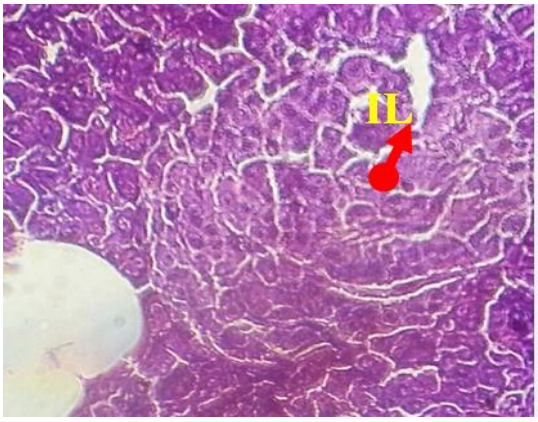

Figure 4: Illustrates a cross-sectional perspective of the pancreas obtained from male rats afflicted with diabetes and afterwards treated with Metformin. The histological analysis demonstrates the existence of an islet of Langerhans (IL) distinguished by the presence of vacuolated cells (V). Furthermore, an increase in the number of β-cells within the islets of Langerhans has been noted, together with condensation of their nuclei. The staining technique employed for visibility is Hematoxylin and Eosin (H&E), at a magnification level of 400X.

Discussion

Acarbose improved the glycemic index of rats fed a high-fructose (HFr) diet, as shown by the results of the present study. Several studies have demonstrated acarbose's hypoglycemic effects (Li *et al*., 2016; Zhang *et al*., 2016; Holman *et al*., 2017; Turbitt *et al*., 2019). In the small intestine, acarbose functions by binding competitively to alpha-glucosidase, preventing the breakdown of oligosaccharides and polysaccharides. Blood sugar control and intestinal glucose uptake are both slowed by this mechanism (Pourkhodadad *et al*., 2016; Li *et al*., 2022; Khudair and Al-Okaily, 2022). Acarbose can cause hypoglycemia by blocking the action of glucosidase and a-amylase when taken with other antidiabetic plant extracts like Artemisia

roxburghiana (Obaid *et al*., 2022). Acarbose inhibits a-amylase and alpha-glucosidase activity, which is why it is able to reduce postprandial hyperglycemia (Zhang *et al*., 2017a; Holmbäck *et al*., 2020). Acarbose's hypoglycemic effects can be explained by the fact that it boosts hepatic glucokinase activity and decreases glycolytic product concentrations (Kumar *et al*., 2022). In addition, acarbose causes weight loss by increasing glucagon-like peptide-1 and blocking the body's ability to absorb carbohydrates (Pishdad *et al*., 2020). Reduced insulin resistance and enhanced glucose control result from its effect on insulin sensitivity, which is mediated by the activation of peroxisome proliferator-activated receptor (PPAR), a novel signaling pathway connected with glucose metabolism and insulin signaling proteins (Ghabi *et al*., 2020). According to Pourkhodadad *et al*., acarbose has antioxidant qualities that reduce oxidative stress because it causes an increase in glutathione (GSH) levels and a drop in MDA levels (Pourkhodadad *et al*., 2016). The etiology of diabetes relies heavily on oxidative stress, which is known to be exacerbated by hyperglycemia. Causes oxidative damage via processes like lipid peroxidation, is leading to heightened insulin resistance and reduced glucose tolerance (Gerstein *et al*., 2020). The effects of hyperglycemia on cells are mediated by multiple routes, one of which is the facilitation of heightened activation of NADPH oxidase. This enzymatic activity upsets the cellular redox state (Attjioui *et al*., 2020). When sorbitol accumulates as a result of changes in protein tyrosine kinase and protein kinase C regulation, the equilibrium between NADH and NAD+, and NADPH and NADP+, is thrown off. Sorbitol (polyol) pathway overactivity is the primary factor in these alterations (Ji *et al*., 2021). Acarbose's hypoglycemic properties may, in turn, account for its antioxidant effects.

The hypoglycemic and antioxidant effects of metformin were the focus of this study in diabetic rats. The results of this study align with previous research endeavors conducted by (Chung *et al*., 2020; Altay, 2022), in which showed that metformin and hydroxytyrosol extract were equally effective in reestablishing normal glucose, insulin, and the HOMA-IR. Hyperglycemia may be reduced by metformin, which increases glucose uptake by peripheral tissues (Wang *et al*., 2018) and inducing insulin secretion from pancreatic cells (Fki *et al*., 2020). Hydroxytyrosol extract, which contains the compound oleuropein, has also been demonstrated to be effective in treating and preventing diabetes-related problems (Scalbert *et al*., 2005).

Rats had their glycemic control compromised and oxidative stress produced when fructose was added to their drinking water. The effects of a high-fructose diet on glucose tolerance and insulin sensitivity have been well-documented (Merra *et al*., 2014), leading to decreased insulin clearance in the liver after eating a lot of

carbohydrates (Borjan *et al*., 2020). Our findings that HFFD is linked to higher levels of fasting glucose can be explained by the fact that it inhibits p-IRS-1 phosphorylation. After being phosphorylated by p-IRS-1, Akt is a downstream molecule that is inhibited by this inhibition. High blood insulin and fasting glucose levels, as well as decreased insulin sensitivity, arise from this suppression of GLUT-4 expression (Çömez *et al*., 2020). It is possible that the body's ability to control processes like gluconeogenesis, glycogenolysis, and glycogen synthesis in the liver could be compromised by excessive fructose intake in addition to the stress placed on the body. These changes might cause insulin resistance in the liver (Lafka *et al*., 2013; Hassanzadeh *et al*., 2014). When pancreatic beta cells are exposed to fructose over the long term, they become more sensitive to glucose's effect on insulin release via extracellular ATP signaling (Veličković *et al*., 2019). Furthermore, in both rodent models and human beings, hyperinsulinemia is a common consequence of high fructose ingestion (Attia *et al*., 2019), It is quite probable that the observed phenomenon can be attributed to the rise of insulin resistance (Li *et al*., 2013). The adverse consequences attributed to fructose consumption have been correlated with heightened levels of reactive oxygen species (ROS) (Zhang *et al*., 2017b). The body's enzymatic as well as non-enzymatic antioxidant levels are reduced by oxidative stress, which is exacerbated by a high-fructose diet (Bartley *et al*., 2019). Fructose consumption is associated with an increase in free radicals, primarily ROS, and oxidative stress due to sustained hyperglycemia, hyperinsulinemia, insulin resistance, and dyslipidemia (Ter Horst *et al*., 2016; Hannou *et al*., 2018). Therefore, it is reasonable to assume that the oxidative stress seen after fructose consumption is mediated by the hyperglycemia it induces. Exposure to fructose consistently resulted in increased blood glucose and insulin concentrations, as well as insulin resistance. Fructose's capacity to cause oxidative stress and produce free radicals is well established (Herman and Samuel, 2016). Oxidative stress is produced as a result, and this can activate mediators of insulin resistance in the signaling cascade, such as uncoupling protein-2, leading to insulin resistance and pancreatic -cell malfunction (Putakala *et al*., 2017; Abolghasemi *et al*., 2020). It is widely hypothesized that these pathways have a role in the adverse impact of fructose on glycemic regulation.

In conclusion, the current study provided evidence that fructose causes hyperglycemia, which can be reduced by taking an acarbose supplement orally.

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