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Original Article

Effect of Dietary Zinc Supplementation on Type 2 Diabetes Mellitus in Adult Male Albino Rats

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ABSTRACT

Background: Diabetes mellitus [DM] is one of the most prevalent and dangerous diseases affecting public health worldwide. Frequent urine causes the body to lose zinc through hyperzincuria, hypozincemia, and reduced absorption, which results in zinc [Zn] insufficiency.

Objective: The aim of this work was to study effect of dietary zinc administration on type 2 DM induced by alloxan in adult male albino rats fed on the high fructose diet [HFD].

Materials and Methods: The study included 32 adult male albino rats, divided into four equal groups: Group 1 [Control] received 1 ml normal saline/day by gavaging, Group 2 [Zn group] received 100 mg/kg/day Zn by gavaging, group 3 [diabetic], where diabetes was induced by alloxan as well as high fructose diet [HFD], Group 4 [diabetic with Zn supplement], where diabetic rats received 100 mg/kg/day Zn by gavaging. At the end of the experiment, rats were sacrificed, blood samples were obtained to measure fasting blood glucose [FBG], insulin level, glycated hemoglobin [HbAlc], homeostasis Model Assessment for Insulin resistance [HOM-IR], liver enzymes [Alanine transaminase [ALT], Aspartate transaminase [AST]], lipid profile, oxidative stress markers [Malonhydialdehyde [MDA], total antioxidant capacity [TAC], catalase [CAT] activity, Glutathione Peroxidase activity [GPX]] and serum creatinine. Histopathological study of liver and pancreatic tissues were performed.

Results: Alloxan injection led to a significant increase of blood glucose, HbA1c, cholesterol, TG and LDL levels, liver enzymes and MDA while insulin, HDL, catalase and GPX levels were significantly decreased significantly compared to the control and ZN-supplemented groups. ZN supplementation led to a significant improvement of all laboratory parameters. The results were supported by the results of histological examinations.

Conclusion: The study clarifies the beneficial effect of Zinc supplementation in diabetic rats as Zn improved the state of hyperglycemia, oxidative stress, dyslipidemia and liver dysfunction induced by DM.

Keywords: Zinc; Diabetes Mellitus; Oxidative Stress; High Fructose Diet; Albino Rats.

INTRODUCTION

Type 2 diabetes mellitus [T2DM] is one of the most common metabolic illnesses worldwide. It is primarily due to a combination of two primary factors: the inability of the tissues to respond to insulin and the compromised ability of the pancreatic β-cells to release insulin [1-3].

Oxidative stress brought on by hyperglycemia can cause damage to liver tissue and disrupt the metabolism of proteins, carbohydrates, and fats, which in turn increases oxidative stress and sets off the inflammatory cascade [4-6]. An important factor in the etiology and development of diabetes is oxidative stress. Many attempts have been made to use dietary antioxidant supplements, including vitamin C and vitamin E, to enhance the health of diabetic patients due to the link between oxidative stress and the disease [7-9].

The allosteric shift of the insulin hexamer from the R to the T form involves zinc. Beta-cells release it along with insulin, and it might have other purposes [10].

Zinc [Zn] is a trace element, which is the second most abundant element in human after iron. It has many physiological role [regulatory, structural and catalytic] and shared in the structure of more than 2500 proteins [e.g., enzymes and genetic transcriptional factors] [11].

It is an essential element for the proper function of the human body. For instance, it can improve the function of chondrocytes and osteoblast and reduce the activity of osteoclast at the same time. Thus playing a crucial role in bone homeostasis [12,13].

In addition, it plays a role in the support of immune system. Thus, guard against infections [14].

Besides it has anti-inflammatory and antimicrobial effects. Thus, it can help in prevention of acne, dermatitis and other skin diseases and it is involved in collagen synthesis. Thus mainlining healthy skin [15,16].

Furthermore, previous studies suggested that, zinc metabolism and hyperglycemia are link. Thus, it can improve the glycemic control in diabetic patients [17].

One of the potential reasons of the onset of DM is believed to be zinc deficiency. It preserves the structural stability of insulin and plays a direct role in its production, storage, and secretion. Additionally, in noninsulin-dependent DM, zinc deficiency was reported to exacerbate insulin resistance [18].

The current study aimed to evaluate the impact of dietary zinc supplementation on type 2 diabetes mellitus induced by alloxan.

MATERIALS AND METHODS

Animals:

Thirty-two male adult albino rats were obtained from The Nile Center for Experimental Studies and Researches [Al-Mansoura, Egypt] provided the rats [6-7 weeks old, 150-200 g]. All rats [one per 25 x 30 x 30 cm cage] were kept in facilities that were kept between 27 and 32°C, with a relative humidity of 40–60% and a 12-hour light/dark cycle, all without any pathogens.

To minimize the impact of stress throughout the experiment and to help the rats become accustomed to the process, they were handled on a frequent basis. Before the trial began, all rats were acclimated for two weeks and given unlimited access to filtered water and regular rodent chow. The Al-Azhar University Animal Care Committee gave its approval to every surgery. The "Principles of laboratory animal care" were adhered to, together with any applicable national laws.

Induction of type 2 diabetes mellitus:

A single intraperitoneal injection of newly made alloxan, 120 mg/kg body weight in normal saline, caused type 2 diabetes mellitus [19]. The surviving rats were fasted overnight for three days before their blood glucose levels were assessed. Rats having blood glucose levels greater than 200 mg/dl were classified as diabetic rats and served as study animals. Every other day, fresh fructose drinking water was made using a weight/volume formula [21g of fructose was diluted in 100mL of tap water to create fructose 21% drinking water]. After that, aluminum foil was placed over the bottles to stop fermentation. For eight weeks, the fructose drinking water was given daily [20].

Experimental groups:

After induction of diabetes, the rats were randomly divided into four equal groups as follows:

Group [1] [Control groups]: Rats were gavaged 1 milliliter of normal saline per day.

Group [2] [Zn group] were gavaged with 100 mg/kg/day of zinc.

Group [3] [diabetes]: were given 120 mg/kg of alloxan. Additionally, they were gavaged with 1 milliliter of regular saline every day.

Group 4 [diabetic with Zn supplement]: Alloxan [120 mg/kg] was given to rats to induce diabetes. Additionally, they were gavaged with zinc [100 mg/kg/day] [21]. Rats' body weight was recorded at the start of the trial and subsequently weekly over the experiment period, while food consumption was measured on alternate days.

Blood sampling:

At the end of the experiment, blood samples were taken from the heart using the intracardiac blood collection method while under deep general anesthesia from halothane, following a 12-hour overnight fast. Two aliquots of the spurting blood were taken; one was anticoagulated for the purpose of measuring the glycosylated hemoglobin [HbA1c].

After centrifuging the second aliquot for 15 minutes at 3000 rpm after letting it clot at room temperature, the resulting sera were kept at -20°C [in a -20°C REVCO refrigerator] until they were tested.

Biochemical analysis:

The estimation of Fasting blood glucose [FBG] was performed according the method described by **Huggett and Nixon** [22], while glycosylated hemoglobin was estimated according to the method described by **Nayak and Pattabiraman** [23], and fasting insulin determined by the method described by **Voller *et al.*** [24].

The calculation of Homeostasis Model Assessment for Insulin Resistance [HOMA-IR] was calculated according to the formula: Fasting glucose [mg/dL]X fasting insulin[µU/mL]/405[for SI units: fasting glucose [mMol/L] X fasting insulin [µU/L] / 22.5] [25].

The oxidative stress markers were determined by methods described by **Ohkawa *et al.*** [26] for Malonhydialdehyde [MDA], **Koracevic *et al.*** [27] for estimation of plasma total antioxidant capacity [TAC], **Aebi** [28] for measurement of catalase [CAT] activity, and **Paglia and Valentine** [29] for the measurement of glutathione peroxidase [GPX].

The lipid profile was measured according to **Richmond** [30] **and Fossati and Prencipe** [31]**,** for estimation of total cholesterol, triglycerides, high density lipoprotein [HDL] and low density lipoprotein [LDL]. Finally, serum creatinine was measured according to the method described by **Slot** [32]**,** and liver enzymes were quantified by ELISA.

Histological studies:

Following the rats' scarification, tissue samples were obtained, and the midline abdominal incision was made after the animals had been anesthetized with halothane.

The pancreas and liver were swiftly exposed when the abdominal cavity was opened. Liver and pancreatic samples were collected, preserved in 10% neutral buffered formal saline, dehydrated in increasing alcohol grades, and then cleaned in Benzol. Following four hours of embedding samples from each group in paraffin with a melting point between 55°C and 56°C, paraffin blocks were created. Hematoxylin and eosin were used to stain 5µm paraffin sections so they could be examined under a light microscope.

Statistical analysis:

SPSS 17.0 software was used to process the statistical data. Normal-distributed quantitative data were presented as mean ± SD. The normality of data was tested by **Kolmogorov–Smirnov test.** After determining the statistical difference using one-way analysis of variance [ANOVA], a Bonferroni post hoc Tukey multiple comparison test was used to calculate the least significant differences [LSD]. A significance level of $P<0.05$ was deemed to be statistically significant.

ESULTS

Food intake of the studied rats:

Induction of type 2 DM by Alloxan and HFD led to a significant increase in food intake in diabetic rats when compared to control group**.** ZN supplementation in the diabetic rats led to a significant decrease in the amount of the food intake compared to the diabetic group. However, Food intake in this group was still higher than the control and ZN groups in a significant manner. There were insignificant changes in the control and ZN groups throughout the experimental period.

Body weight at different durations of the studied rats:

Alloxan and HFD resulted in significant decrease in body weight in both diabetic rat groups when compared to the control group and ZN group. ZN supplementation in the diabetic rats induced a significant increase in body weight in the diabetic rats. However, body weights in these groups were still lower than the control group and ZN group in a significant manner, figure [1].

Fasting Blood glucose in the studied rats:

There were insignificant changes of the blood glucose level in all groups in day 0. Starting from day 3 of the experiment [after induction of diabetes by Alloxan at a dose of 120 mg/ kg], there were significant changes in blood glucose level when compared to the control group and ZN group. This increase in blood glucose level continued till the end of the experimental period in a significant manner compared to the control group and ZN group.

ZN supplementation improved the hyperglycemia, as there was a significant decrease of the blood glucose level in diabetic rats when compared to the diabetic group. This decrease was noticed at day 28 and continued till the end of the experimental period. However, blood glucose in these groups was still higher than the control group and ZN group on a significant manner.

Glycosylated hemoglobin [HbA1C] in the studied rats:

Alloxan and HFD administration resulted in significant increases in HbA1c level in the diabetic rats when compared to the control group and ZN group.

ZN supplementation in diabetic rats caused a significant decrease in HbA1c levels in the diabetic rats when compared to diabetic group. However, HbA1c levels still higher in these groups than the control group and ZN group in a significant manner.

Insulin and HOMA-IR levels in the studied rats:

Induction of type 2 DM by Alloxan and HFD ingestion led to a significant decrease in the insulin levels and increase in HOMA-IR in both the diabetic rat groups when compared to the control group and ZN group.

ZN supplementation in the diabetic rats led to a significant increase in insulin level and decrease in HOMA-IR in the diabetic rats. However, insulin levels still lower and HOMA-IR levels still higher in these groups than the control and ZN groups in a significant manner. There were insignificant changes in insulin and HOMA-IR levels in the control and ZN groups throughout the experimental period.

Lipid profile in the studied rats:

Alloxan and high fat diet [HFD] ingestion led to a significant increase in the total cholesterol, triglycerides [TG] and low density lipoprotein cholesterol [LDL-C] associated with a significant reduction of high density lipoprotein cholesterol [HDL-C] in the diabetic rats when compared to the control and ZN groups.

Treatment of the diabetic rats with zinc for 8 weeks led to a significant decreases of TC, TG and LDL-C levels and significant increase of HDL-C when compared to the diabetic group. However, it failed to decrease them significantly to their level in the control and ZN groups.

Oxidative stress parameters:

Induction of type 2 DM led to a significant increase in MDA levels and a significant decrease of TAC and antioxidant enzymes in the diabetic rats when compared to the control and ZN groups.

Zinc supplementation improved the state of oxidative stress induced by DM as Zn induced a significant decrease in MDA level and an increase in antioxidant enzymes. However, antioxidant enzymes still lower in these groups than control group and ZN group in a significant manner, while the level of TAC increase insignificantly with the control and ZN groups.

Creatinine level in the studied rats:

There was a significant increase in creatinine level in the diabetic rats when compared to the control and ZN groups. ZN supplementation in

diabetic rats led to a significant decrease in creatinine level when compared to the diabetic group. This improvement led to insignificant changes in creatinine level in the diabetic compared to the control group.

Changes in liver enzyme [ALT, AST] in the studied rats:

Induction of type 2 DM led to a significant increase in ALT and AST levels in the diabetic rats compared to the control group. Treatment with zinc supplementation in the diabetic rats led to a significant decrease of ALT and AST levels when compared to the diabetic group.

This improvement led to change in liver enzymes in the diabetic rats treated with zinc compared to the control group. However, the differences did not reach statistical significance.

Histopathological results of light microscopic examination of the liver and pancreatic tissue

Microscopic examination of liver section in the control rats showed normal hepatic structure with polyhedral hepatocytes.

The hepatocytes were arranged in strands alternating with blood sinusoids forming a network around a central vein. Kupffer cells with normal activity were distributed within the blood sinusoids**.** After induction of DM, liver section showed periportal fibrosis, vacuolated cytoplasm, intense inflammatory cell infiltration around the central veins and portal triads with portal vessels congestion.

Zn supplementation showed moderate perivascular inflammatory cells infiltration, normal distribution of hepatic cords radiating from the central vein [CV] with central, rounded, vesicular nuclei with some vacuolated cytoplasm in hepatocytes. Microscopic examination of pancreatic tissue of the control rats showed normal pancreatic tissue formed of pancreatic acini, which showed basal nuclei and amphophilic cytoplasm. The islet of Langerhans's showed islet cells arranged in trabecular and acinar pattern with abundant eosinophilic cytoplasm and central small nucleus. Islets have regular shape with a large number of β-cells which have a normal round shape with will-distinct round nuclei.

Induction of DM showed decreased islets size and β-cells number, irregular islets shape with degenerated connective tissue sheet. The exocrine pancreatic tissue showed perivascular cellular infiltration, focal necrosis, dilated ducts. Zn supplementation showed marked improvement with restored size of islets of Langerhans. Also regular islets cells with increased number and abundant eosinophilic cytoplasm and central small nuclei; most of these cells restored their rounded shape while few of them still with elongated shape.

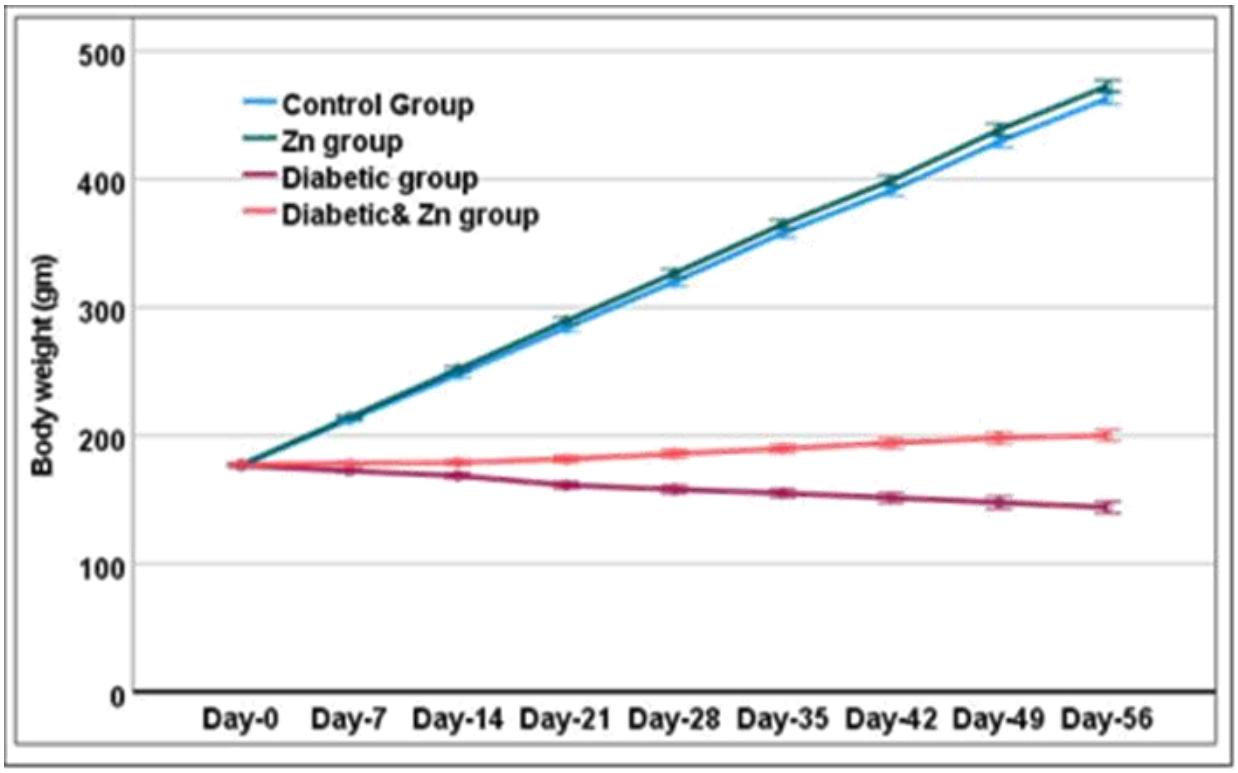
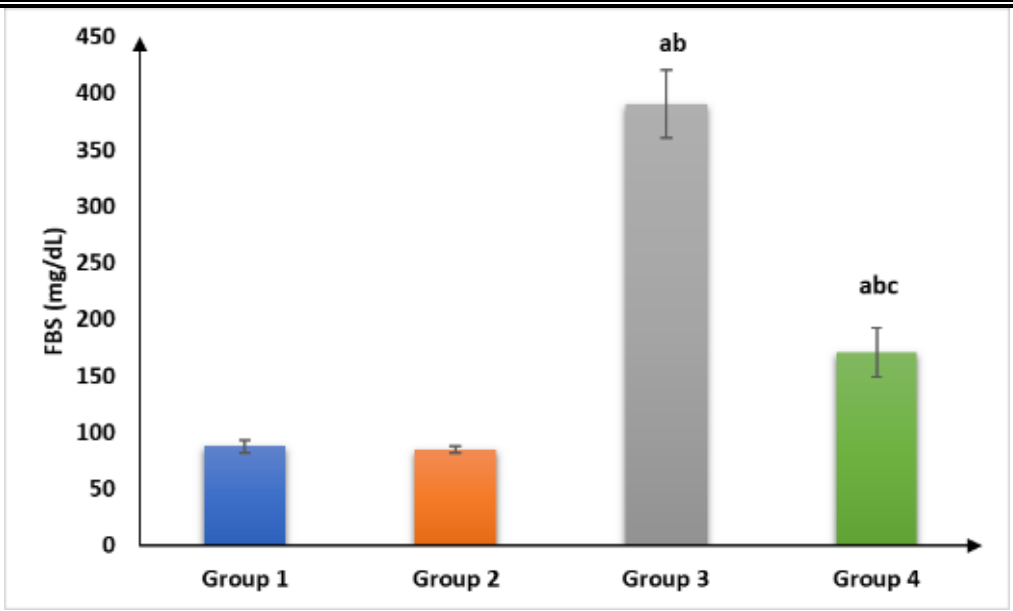


Figure [1]: Changes in body weight at different durations in the studied four groups

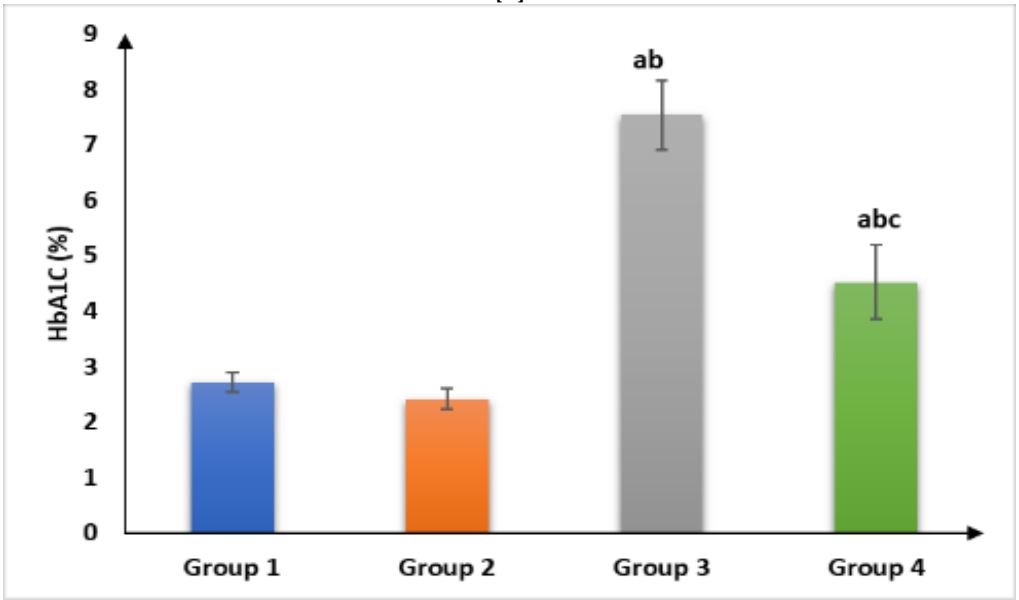
Table [1]: Food intake [grams/day] in the studied four groups

	Group 1 [n=8]	Group 2 [n=8]	Group 3 [n=8]	Group 4 [n=8]
Mean ± SD	16.5 ± 2.07	15.9 ± 4.18	36.3 ± 2.21 [ab]	30.2±3.79[abc]
Range	14 – 19	9 – 20	33 - 39	24 - 36

a: significance versus Group 1, b: significance versus Group 2, c: significance versus Group 3.



[A]



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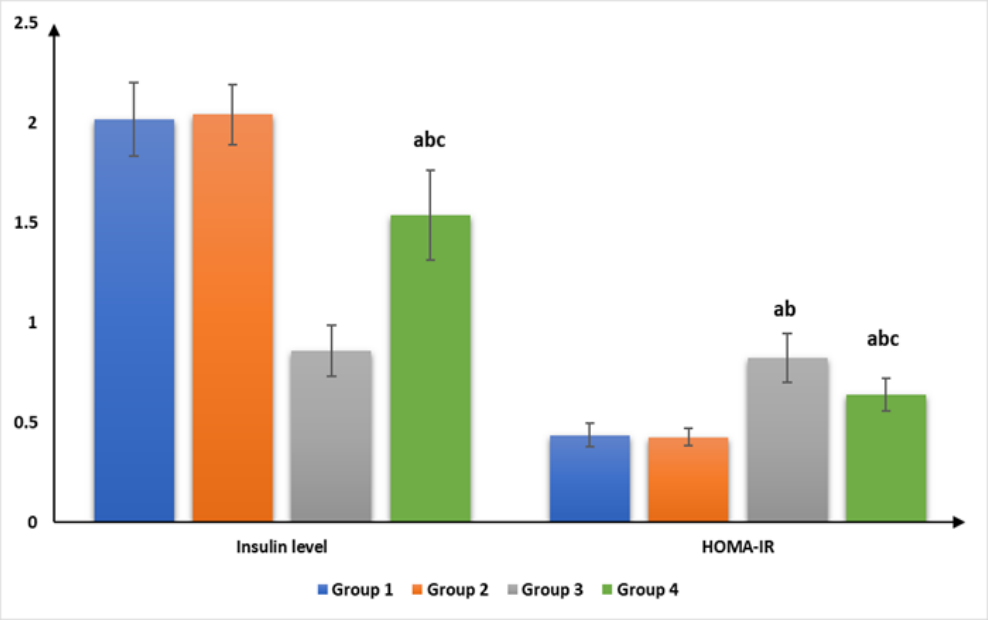
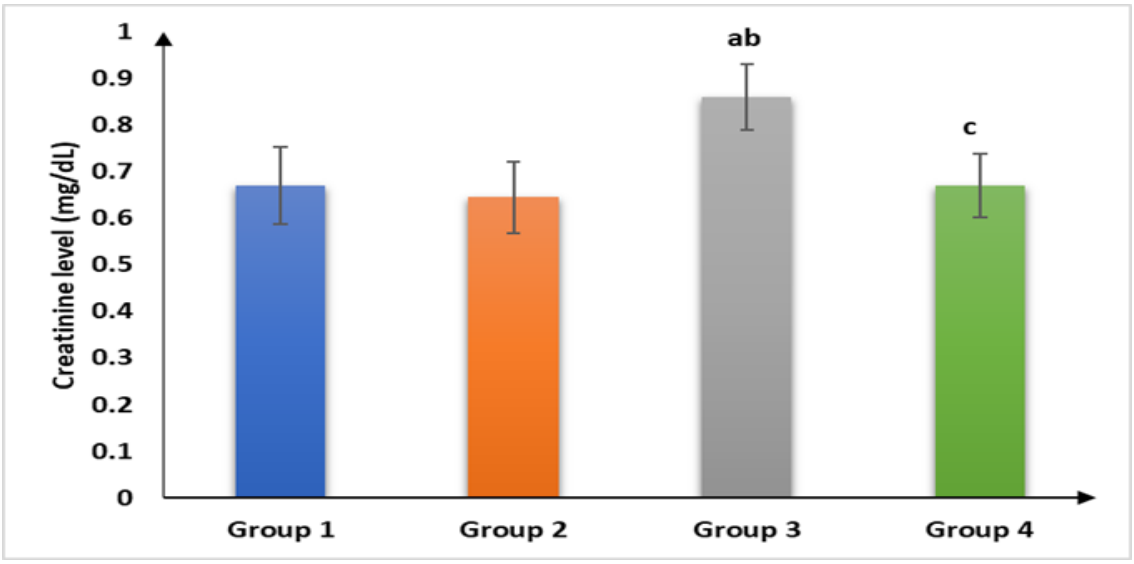
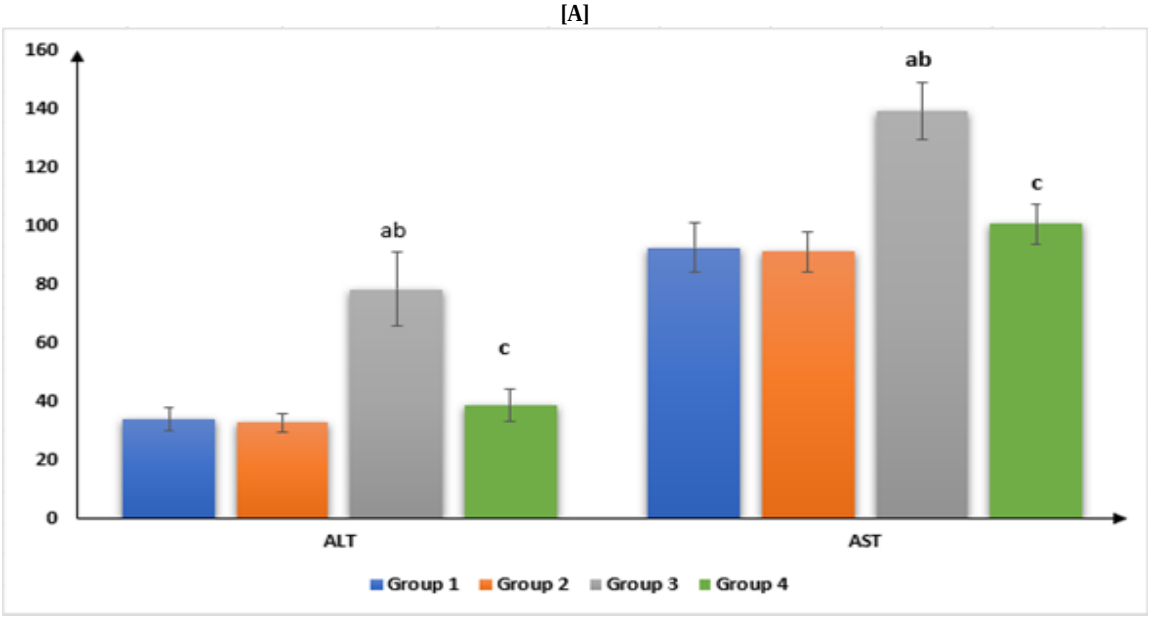


[C]

Figure [2]: [A] Changes in FBS, [B] HBA1c and [C] Insulin level and HOMA-IR of the studied groups; a: significance versus Group 1, b: significance versus Group 2, c: significance versus Group 3, FBS: Fasting blood sugar, HbA1C: Hemoglobin A1C, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance.



[A]



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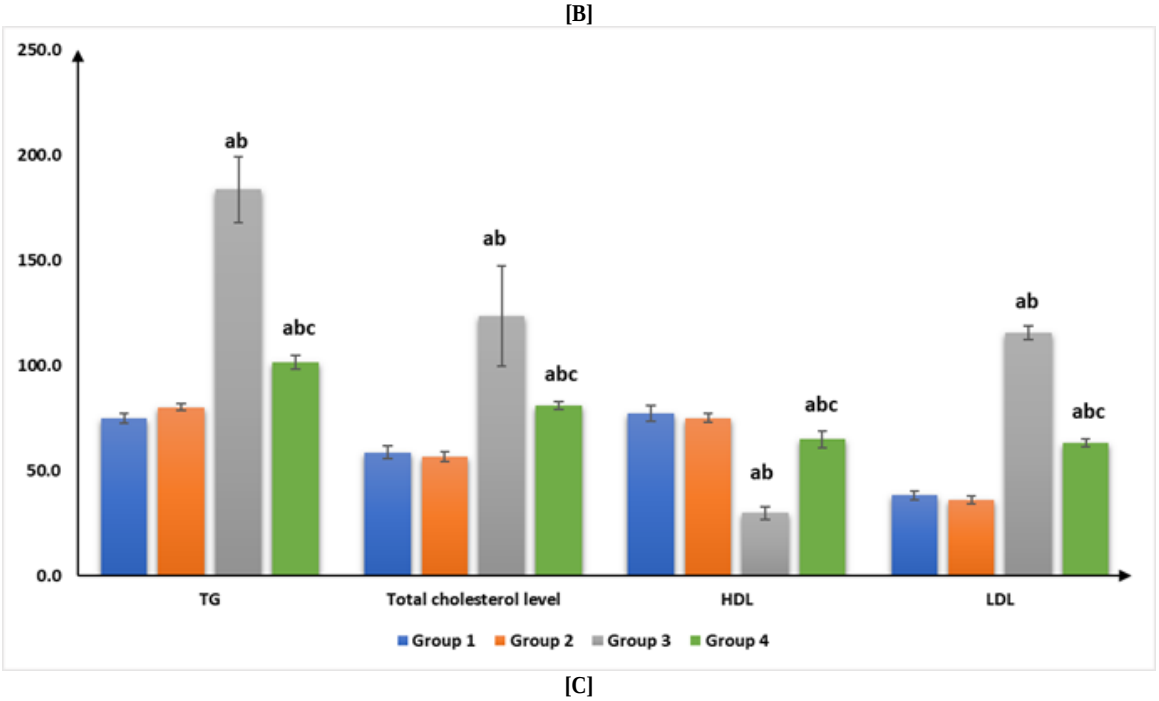
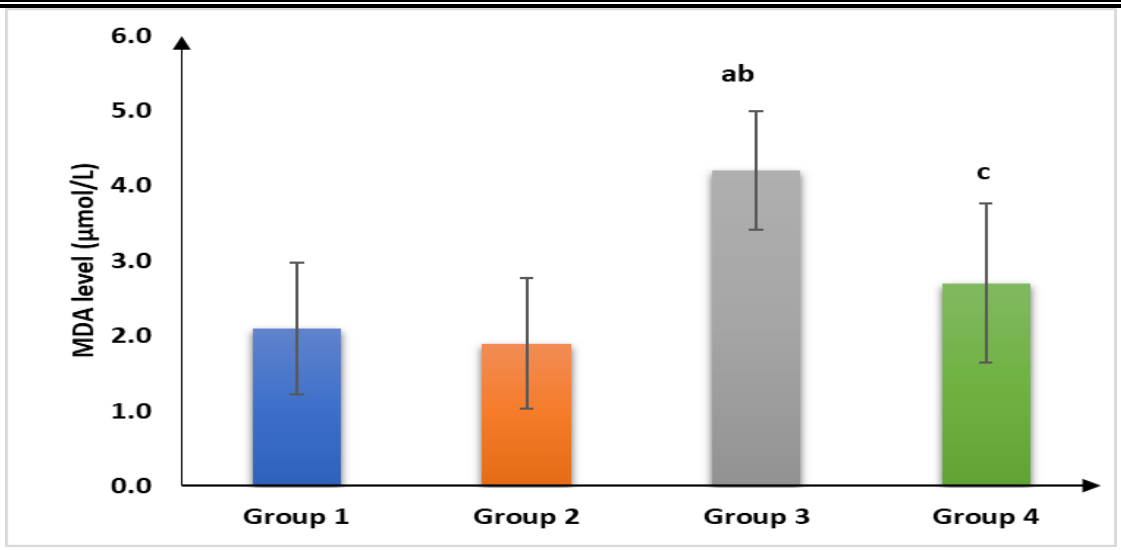
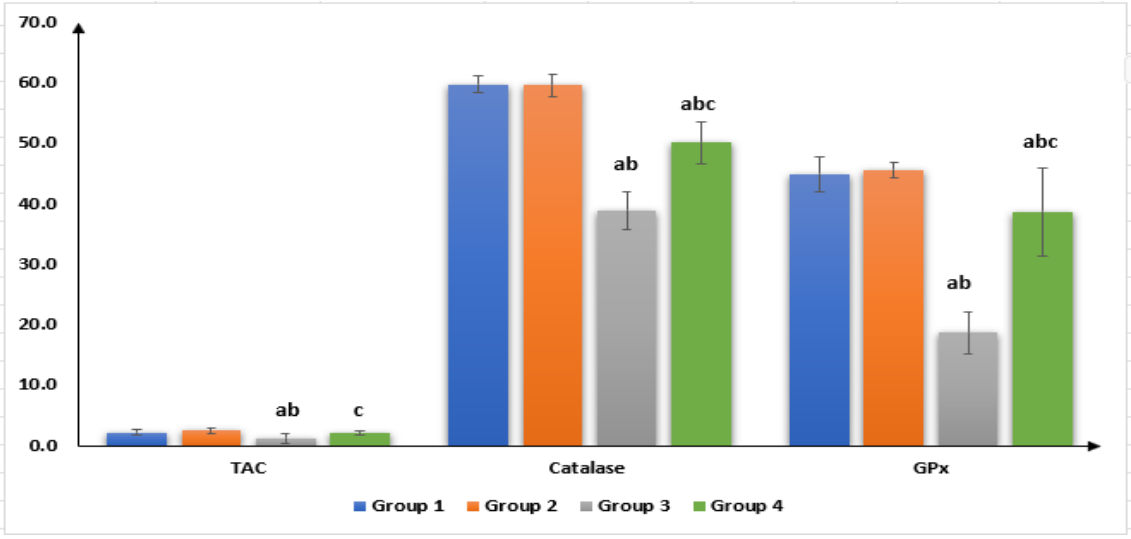


[C]

Figure [3]: [A] Changes in creatinine level, [B] ALT and AST and [C] Lipid profile of the studied groups; a: significance versus Group 1, b: significance versus Group 2, c: significance versus Group 3.



[A]



[B]

Figure 4: [A] Changes in MDA level and [B] TAC and antioxidant enzymes of the studied groups

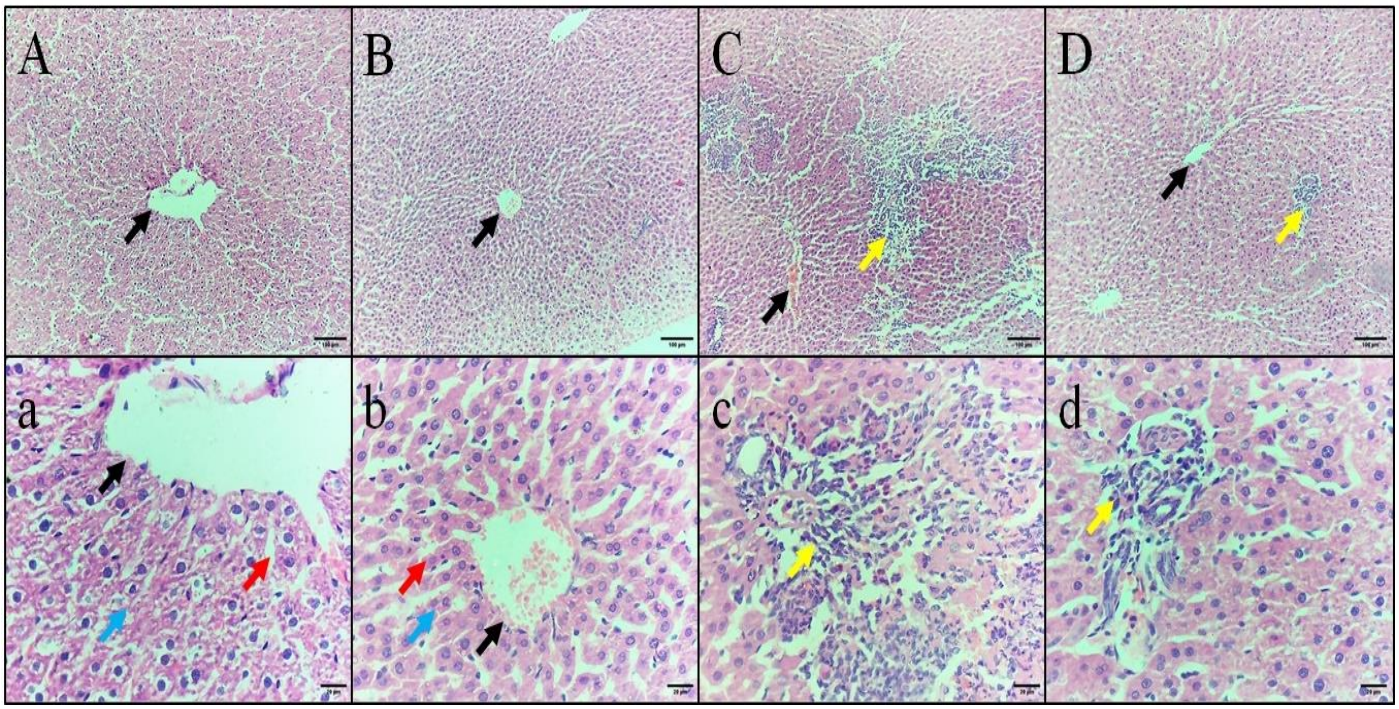


Figure [5]: Plates 2 H&E micrographs of liver sections of [A, a] Normal control group and [B, b] Zn treated group [C, c] diabetic group, [D, d] diabetic+ Zn treated group, Black arrow: central vein, Blue arrow: polyhedral hepatocytes, Red arrow: blood sinusoids with Kupffer cells, Yellow arrow: inflammatory cells infiltration. Upper row original magnification= 100X, lower row= 400X and scale bar= 100 µm and 20 µm respectively.

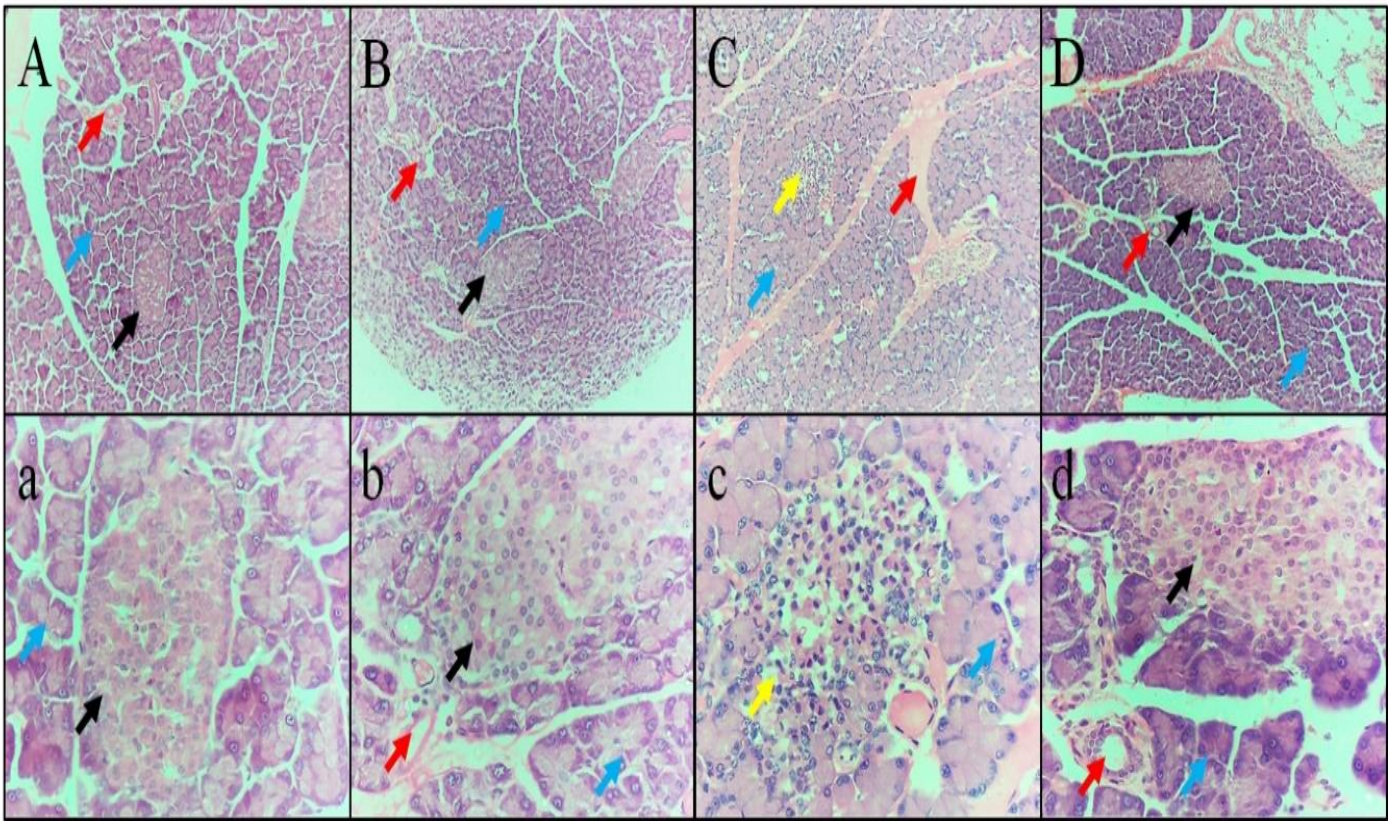


Figure [6]: H&E micrographs of pancreatic sections of [A, a] Normal control group and [B, b] Zn treated group. [C, c] diabetic group. [D, d] diabetic+ Zn treated group. Black arrow: islet of Langerhans with β cells, Blue arrow: exocrine acini cells, Red arrow: blood vessels, Yellow arrow: necrotic islet of Langerhans cells. Upper row original magnification =100X, lower row =400X and scale bar= 100 µm and 20 µm respectively.

DISCUSSION

Diabetes mellitus [DM], is a dangerous and chronic disease marked by consistently elevated blood glucose levels brought on by either insufficient insulin production or the body's inability to use the insulin that is generated [33]. It has long been believed that elevated free radical generation or compromised antioxidant defenses are linked to complications of diabetes [34].

According to **Akure *et al.*** [35], zinc is a necessary trace element that has significant anti-inflammatory, antioxidant, and apoptotic properties. It can also affect signal transmission and molecular function. The aim of the present work was to study the effect of dietary zinc supplementation on type 2 diabetes mellitus induced by Alloxan in adult male albino rats fed on HFD. The results of present work showed that the induction of type 2 DM by Alloxan and HFD led to a significant increase in food intake and significant decrease in body weight when compared to control group and ZN group.

According to **Yin *et al.*** [36], this rise can be caused by the metabolic alterations that take place in the body during diabetes mellitus. The body loses fluid and calories when blood sugar levels are high because it attempts to flush out the extra glucose. Consumption of food and water may rise as a result of this calorie and fluid loss since it may increase hunger and thirst.

ZN supplementation in diabetic rats caused a decrease in the amount of the food intake and an increase in body weight when compared to the diabetic group. However, there was still a significant increase in food intake in these groups when compared to the control group.

This was explained by **Khorshidi *et al.*** [37], zinc's function in energy metabolism, appetite control, and adipokine modulation may influence body obesity. A low-protein diet combined with or without a marginal zinc deficit is linked to increased adiposity, decreased appetite, and decreased lean body mass. Zinc is a crucial component of energy metabolism-related enzymes as well as Zn metalloenzymes that are necessary for the synthesis of proteins, nucleic acids, and new tissues. Additionally, it controls the hormones adiponectin, insulin, ghrelin, and leptin, which control fat accumulation and adiposity. Changes in adipose tissue mass may be determined by variations in tissue-specific adipokine concentrations linked to zinc status, which may alter the risk of obesity [37].

Induction of type 2 DM led to a significant increase of blood glucose and in HOMA-IR and HbA1c levels associated with a significant decrease of insulin levels when compared to control rats. A lack of insulin due to the selective death of β-cells in the islets of Langerhans by free radicals resulting from the metabolism of alloxan may be the cause of the elevated blood glucose level [38]. This damage is supported by our histological data, which indicated that the diabetic group had irregularly shaped islets with degraded entering connective tissue, as well as a reduction in islet size and β-cell population.

ZN supplementation improved hyperglycemia, HbA1c and insulin level and in HOMA-IR level in significant manner when compared to diabetic rats.

According to **Olechnowicz *et al.*** [39], zinc is a necessary trace element for the regular production, storage, and release of insulin by pancreatic β-cells. There are many phases in the mechanism by which zinc controls insulin secretion. First, zinc is kept in the pancreatic β-cells' insulin granules. When blood glucose levels are high, it reaches the β-cells and triggers the release and synthesis of insulin. This procedure involves the

co-release of zinc, which stabilizes the insulin molecule and controls its release from the granules [40]. When type 2 DM was induced in diabetic rats, TG, TC, and LDL levels significantly increased while

HDL levels significantly decreased. According to **Obi-Ezeani *et al.*** [41], metabolic abnormalities in diabetic states cause hypercholesterolemia because the enzyme hydroxyl methyl gluteryl Co-A [HMG Co-A] reductase is responsible for the synthesis of cholesterol, and insulin inhibits this enzyme. It follows that a lack of insulin will increase the production of cholesterol. Thus, one of the main causes of hypercholesterolemia in diabetes may be an increase in the intestinal cholesterol acyltransferase-dependent cholesterol esterification.

Another explanation is that hyperglycemia can affect lipid metabolism in a number of ways, including lowering the activity of the enzyme lipoprotein lipase [LPL], which is essential for the digestion of lipoproteins. LPL activity declined in diabetes, which may cause triglyceride levels to rise and HDL levels to fall [42].

The levels of TG, TC, LDL, and HDL in diabetic rats improved when they were given ZN supplements. It has been demonstrated that supplementing with zinc increases the activity of lipoprotein lipase [LPL], an enzyme essential to lipoprotein metabolism. HDL levels rise as a result of LPL's hydrolysis of triglycerides in HDL particles [43].

Oxidative stress markers

When type 2 diabetes was induced in rats, oxidative stress was shown by a significant rise in MDA and a fall in antioxidant enzymes in comparison to control rats.

According to **Casares *et al.*** [44], oxidative stress is limited by hyperglycemia, which is linked to diabetes. In diabetes, the hexokinase becomes saturated when the glucose level rises, and the extra glucose is partially broken down in the insulin-independent tissues using the polyol pathway. Aldose reductase uses NADPH and H+ from the pentose-phosphate pathway as cofactors to convert glucose to sorbitol, which is then oxidized to NADP+.

Zinc supplementation improved the oxidative stress induced by DM. It decreased MDA and increased the antioxidant enzymes in significant manner. Antioxidant enzymes need a cofactor to sustain their catalytic activity, which might be the mechanism. Accordingly, cytosolic SOD requires copper and zinc to function, but mitochondrial SOD requires manganese [17].

One well-known metal that is an antioxidant is zinc. It is a well-known sulfhydryl group protector and an essential part of antioxidant enzymes like SOD [45]. Additionally, it contributes to the production of glutathione, a potent antioxidant that may stop lipid peroxidation and scavenge free radicals [46].

Liver enzymes

Alloxan and HFD ingestion led to a significant increase of ALT and AST levels in diabetic rats when compared to control group.

Maroua *et al.* [47] described how alloxan's hepatotoxic impact causes the death of hepatic cells. The buildup of amino acids like alanine and glutamic acid in the blood as a result of the body's protein breakdown explains the rise in transaminases. Because transaminases have considerable enzymatic activity, they may convert these amino acids into carboxylic compounds like pyruvic acid and α ketoglutamic acid, which can then be converted into glucose [48].

Another factor is hyperglycemia, which can harm the body's tissues and blood vessels, including the liver. Liver inflammation and oxidative stress can be brought on by elevated blood glucose levels. Liver impairment is indicated by elevated ALT and AST values [49]. Additionally, immunological factors or the harmful effects of Alloxan may cause liver disease.

According to **Mukhlif *et al.*** [38], oxidative stress brought on by free radical aggregation results in the destruction of liver cells and lipid peroxidation of cell or mitochondrial membranes, which triggers an inflammatory immune response.

When compared to the diabetic group, zinc treatment improves the levels of the liver enzymes AST and ALT in diabetic rats. The metals of this element have chelating and anti-free radical/anti-oxidant properties, which may be responsible for the correction of plasma transaminase activity and cell membrane stability [50].

As a result, zinc protects the liver under a variety of harmful circumstances. These results are in line with those of **Kataba *et al.*** [51], who proposed that zinc benefits rat histological and enzymatic changes.

Serum creatinine

Induction of type 2 DM by Alloxan and HFD ingestion led to a significant increase in creatinine level in diabetic rats when compared to control.

According to **Zhang *et al.*** [52], alloxan has been shown to induce acute tubule-interstitial nephritis, which in turn leads to nephrotoxicity. Renal alterations mostly affect the proximal convoluted tubules' epithelium and range from swelling to necrosis.

Another explanation is provided by **Riyani *et al.*** [53], who claimed that hyperglycemia brought on by Alloxan can harm the body's tissues and blood vessels, including the kidneys. Reduced kidney function and protein leaks into the urine can result from damage to the glomeruli. Creatinine builds up in the blood when renal function is compromised, which raises the amount of creatinine.

It was found that ZN supplementation in diabetic rats caused improvement in the level of creatinine. Its preventive function explains the drop in renal parameter rate following the administration of ZN supplements. Zn is a non-toxic metal with an antioxidant ability that neutralizes free radicals to prevent or slow down oxidation, enhancing tissue function to prevent cell membrane rupture [54].

In conclusion, administration of Zn to diabetic rats by a dose of 100mg /kg led to improvement in food intake, a state of hyperglycemia, lipid profile, liver enzymes which was illustrated by histopathology of pancreatic and liver tissues. Also, it led to improvement of oxidative stress and renal dysfunction induced by DM.

The results of the current study should be treated cautiously due to small sample size in each group and short duration of the study [limiting steps of the current work]. Future clinical trials are recommended to validate these results.

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