Clinical Journal of Diabetes Care and Control
ISSN: 2642-0872

Research Article *Volume 3 Issue 2*

Regulation of Zinc Status, Carbohydrate Metabolism and Antioxidants Levels by Vitamin C of Alloxan-Induced Diabetic Rats Fed Zinc Deficiency Diet

Kechrid Z* and Fatmi W

[1]Laboratory of Applied Biochemistry and Microbiology, University of Badji Mokhtar-Annaba, Algeria

***Corresponding author:** Zine Kechrid, Laboratory of Applied Biochemistry and Microbiology, University of Badji Mokhtar-Annaba, Annaba 23000, Algeria, Tel: 00213 773345102; Email: kechridzine@yahoo.fr

Received Date: September 04, 2020; **Published Date:** October 06, 2020

Abstract

The purpose of this study was to evaluate the beneficial effect of vitamin C supplementation on biochemical parameters, antioxidant status, and zinc status in diabetic rats fed zinc-deficient diet. Forty male albino Wistar rats were divided into 5 groups. The first group was non-diabetic rats. The second and third groups were diabetic given a zinc-adequate diet (ZA); and zinc-deficient diet (ZD) respectively. The forth and the fifth groups received also a zinc adequate diet and zinc-deficient diet with supplementation of vitamin (ZA+VitC and ZD+VitC). Diabetes was induced with alloxan. Body weight and food intake were measured regularly. After four weeks of dietary manipulation, the fasting animals were killed. The results revealed that dietary zinc intake significantly increased glucose, lipids, triglycerides, urea, AST, ALT, liver GST and TBARS levels in ZD rats. In contrast, the levels of zinc, total proteins, ALP, LDH, liver glycogen, GSH, GSH-Px and CAT were decreased. Interestingly, vitamin C seems to be effective in restoring the previous parameters to their normal levels. It can be assumed that vitamin C supplementation acted as an antioxidant, which significantly reduced the severity of zinc-deficiency metabolic perturbations in diabetic rats.

Keywords: Alloxan Antioxidant; Diabetes; Zinc Deficiency; Vitamin C

Abbreviations: ZA: Zinc-Adequate; ZD: Zinc-Deficient; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; ALP: Alkaline Phosphatase; LDH: Lactate Dehydrogenase.

Introduction

Diabetes mellitus is one of the major health problem and a common metabolic illness, which is characterized by high blood glucose concentration as a result of insulin lack or the presence of insulin resistance in peripheral tissues, or both. Many scientific reports mentioned that oxidative stress is associated with the pathogenesis of diabetes. Zinc is an essential trace element within cells and is necessary for a broad range of physiological processes. The mineral is an integral part of cell membranes, and functions to maintain the structural integrity of cells as well as playing a role in the functions of insulin and carbohydrate metabolism. It may have important antioxidant properties, as it acts as a cofactor of the superoxide dismutase, which regulates the detoxification of reactive oxygen species, regulating the expression of genes and protecting against the oxidative stress induced by chronic hyperglycemia. Zinc deficiency occurs commonly in diabetic patients. Aside from inadequate dietary zinc intake, zinc deficiency typically results from impaired absorption, desorption or increased excretion of zinc. Diabetes leads also to an increase of oxidative stress, which in turn, is thought to be closely associated with the

Kechrid Z and Fatmi W. Regulation of Zinc Status, Carbohydrate Metabolism and Antioxidants Levels by Vitamin C of Alloxan-Induced Diabetic Rats Fed Zinc Deficiency Diet. Clin J Dia Care Control 2020, 3(2): 180034.

pathogenesis of diabetes. As it was mentioned previously, that zinc is a structural part of key anti-oxidant enzymes such as superoxide dismutase, zinc deficiency results in increased oxidative stress by impairing their synthesis. Vitamin C is a water-soluble antioxidant, which efficiently scavenges free radicals and protecting cell membranes from oxidative damage. Studies have shown that supplementation of vitamin C can decrease the level of lipid peroxidation, because it is an electron donor, suggesting a direct role for the protection against oxidative damage. Moreover, the antioxidant potential of ascorbic acid is not only attributed to its capacity to quench reactive oxygen species, but also to its ability to regenerate other small antioxidant molecules, such as α-tocopherol, reduced glutathione and β-carotene [1-12]. Thus, the aim of this study was to examine the modulator effects of vitamin C administration for the prevention of the development of diabetic pathology observed in zinc deficient rats by evaluating zinc status, carbohydrate metabolism, enzymes activities and liver antioxidant parameters.

Materials and Methods

Chemicals

Alloxan, 5, 5′dithiobis-2-nitrobenzoic acid (DTNB), amyloglucosidase and vitamin C (L-ascorbic acid) were purchased from Sigma Chemical Co (St Louis, France). All other reagents were of analytical grade.

Animals

All experiments were performed with Wistar male rats weighing 200-250 g and aged 10–12 weeks. Animals were housed in individual plastic cages and were provided standard food and water ad libitum. The temperature was maintained at 22±2 °C with a standard daily photoperiod. The study protocol was approved by the Ethical Committee of our institution.

Induction of Diabetes and Diet

Fresh alloxan monohydrate solution was prepared to induce diabetes as described previously. Alloxan was dissolved in citrate buffer (0.01 M, pH 4.5, and then it intraperitoneally (i.p.) administered at a dose of 150 mg/kg body weight). Blood glucose was measured 7 days after induction of diabetes on samples taken from tail vein. The diabetic state was confirmed by a glucose-meter (ACCU-CHEK, Roche Diagnostics, Paris, France) when the glucose concentration exceeded 14 mmol/l. The diet for rats consisted of adequately (54 mg/kg) or deficient (1.2 mg/kg) quantities of Zn, as determined by atomic absorption spectroscopy. The mineral mixture supplied (in grams per kilogram diet) was calcium hydrogen orthophosphate 13; disodium hydrogen orthophosphate 7.4; calcium carbonate 8.2; potassium chloride 7.03; magnesium sulphate4; ferrous sulphate 0.144; copper sulphate 0.023; potassium iodide 0.001, manganese sulphate 0.180 and zinc carbonate 0.1. The low Zn diet contained no additional zinc carbonate.

Groups

The diabetic animals were equally divided into four groups. The first group received a diet containing 54 mg Zn/kg diet (zinc-adequate, ZA). The second group received a diet containing 1.2 mg Zn/kg diet (zinc-deficient, ZD). Vitamin C (1 g/l) [13-15] was given in drinking water to the third (ZA + VitC) and the fourth (ZD + VitC) groups.

Sample Collections

After 27 days, rats were sacrificed by cervical cut under ether anesthesia. The obtained serum was used for the determination of zinc, triglycerides, total lipids, total proteins, urea, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and lactate dehydrogenase (LDH). The pancreas, testes and a fragment of liver were excised, washed with isotonic saline and blotted to dry. The right femur, the connective tissues and muscles were removed. Pancreas, kidney, femur, and one fragment of liver were weighed and dried at 80°C for 16 h and zinc concentration in each tissue was determined. The second fragment of liver was processed immediately for assaying the oxidative stress parameters.

Measurement of Biochemical Parameters

The activities of ALT, AST, ALP and LDH were estimated using commercial kits from Spinreact, Spain (refs: AST-1001161, ALT-1001171, ALP-1001131 and LDH-1001260). Total proteins, urea, total lipids and triglycerides were also measured utilizing commercial kits (Spinreact, refs: glucose-41011, total proteins-1001291 urea-1001329, total lipids-1001270 and triglycerides-1001311).

Zinc Estimation

Dried pancreas, liver and femur were heated in silica crucibles at 480°C for 48 h and the ash was dissolved in hot 12 M hydrochloric acid for zinc analysis in a flame atomic absorption spectrophotometer (Shimadzu AA-6200; Somerset, New Jersey, USA). Standard reference materials of bovine liver and wheat flour were used to check the accuracy of zinc recovery, which exceeded 96% in the reference materials. Serum zinc was measured by flame atomic absorption spectrophotometer after 20 folds dilution. Zinc standards were prepared from a 1mg/ml zinc nitrate standard solution using 5% glycerol to approximate the viscosity characteristics.

Estimation of Oxidative Stress Parameters

Tissue preparation: Approximately 1 gram of liver was

homogenized in 2 ml of buffer solution of phosphate buffer saline 1:2 (w/v; 1g tissue 2ml TBS, pH = 7.4). Homogenate was then centrifuged at 10000x g for 15 minutes at 4°C, and then the resultant supernatant was used for the determination of TBARS, GSH, proteins, GST, GSH-Px and CAT.

TBA Reactive Substances: The lipid peroxidation level in liver homogenate was measured as malondialdehyde (MDA), which reacts with thiobarbituric acid (TBA) as a TBA reactive substance (TBARS) to produce a red colored complex with a peak absorbance at 530 nm 1984).

Reduced Glutathione (GSH): Liver GSH content was estimated using a colorimetric technique, as mentioned by Ellman modified by Jollow, et al. based on the development of yellow color when DTNB [5, 5' dithiobis-(2-nitrobenzoic acid)] is added to compounds containing sulfhydryl groups. In brief, 0.8 ml of liver supernatant was added to 0.3 ml of 0.25 % sulfosalycylic acid and then tubes were centrifuged at 2500xg for 15 minutes. 0.5 ml supernatant was mixed with 0.025 ml of 0.01 M DTNB and 1 ml phosphate buffer (0.1 M, pH=7.4). The absorbance at 412 nm was recorded. Finally, total GSH content was expressed as nmol GSH/mg proteins.

Glutathione Peroxidase (GSH-Px): Glutathione peroxidase (GSH-Px) (E.C.1.11.1.9) activity was measured by the procedure of Flohe and Gunzler.

Glutathione-s-transferase (GST): Glutathione-S-transferees (GST) (EC.2.5.1.18) catalysis the conjugation reaction with glutathione in the first step of mercapturic acid synthesis. The activity of GST was measured according to the method of Habig et al. The P-nitro benzyl chloride was used as substrate and the absorbance was measured at 340 nm at 30-second intervals for 3 min.

Catalase: Catalase (EC.1.11.1.6) activity was measured according to the method of Claiborne. The reaction mixture (3 ml) that contained 2.9 ml of 19 mmol/L H_2O_2 prepared in potassium phosphate buffer (0.1 M, pH = 7.4), and 0.1 ml of liver supernatant. The reaction was started by adding H_2O_2 and the decomposition of the later was monitored following the decrease in the absorbance at 240 nm for 2 min.

Proteins: The protein content of tissue samples were estimated by the method of Bradford using bovine serum albumin as a standard.

Liver glycogen: Determination of total liver glycogen was as that of glucose following an enzymatic hydrolysis with amyloglucosidase (EC.3.2.1.3) obtained from asperguillus Niger [16-23].

Statistical analysis: Data are given as means ± SEM. Statistical significance of the results obtained for various comparisons was estimated by applying one way Analysis of one way variance (ANOVA) followed by Student's t-test and the level of significance was set at $p<0.05$.

Results

Body Weight and Food Intake

Daily body weight gain and food intake are shown in table 1. Both parameters were significantly lower in the ZD group than in the ZA group. However, there is a significant increase in both body weight and food intake in the ZA+VitC compared to the ZA group. On the other hand, body weight gain and food intake values were significantly high in ZD+VitC group as compared to ZD.

Tissues and Serum Zinc

Zinc level in tissues and serum is presented in table 1.

Paramètres	Expérimental groups				
	ND(8)	ZA(8)	ZD(8)	ZA+VitC(8)	ZD+VitC(8)
Initial body weight (g)	215.75±14.43	225.00±28.04[a]	224.83±37.39	223.00±16.19	223.00±29.20
Final body weight (g)	350.12±16.56	286.87±12.14[a]	215.12±3.8b	304.62 ± 13.33[b]	239.5±6.61[c]
Food intake (g/day/rat)	12.25±0.11	15.50±1.10[a]	12.61±1.20[b]	17.67 ± 1.55[b]	15.21±0.40[c]
Sérum Zn (µg/dl)	154.91±2.88	77. 5±0.018[a]	68.4±0.002[b]	101.1± 0.029[b]	75.25±0.019[c]
Femur Zn (µg/g dry wt)	159.31±3.11	82. 25±3.23[a]	68.4±0.002[b]	219.2 ± 21.40[b]	193.1±17.40[c]
Liver Zn (µg/g dry wt)	83.18±2.28	67.30±2.82[a]	44. 00±3.26[b]	75.38± 0.82[b]	64.92±3.17[c]
Pancreas Zn (µg/g dry wt)	111.21±1.87	55.76±2.03[a]	40. 85±0.81[b]	63.05± 3.20[b]	50.19±1.49[c]

Table 1: Initial body weight, final body weight, food intake, serum and tissues zinc of non-diabetic rats (ND), diabetic rats fed zinc adequate diet (ZA), diabetic rats fed zinc deficient diet (ZD), diabetic rats fed zinc adequate diet and given vitamin C (ZA+VitC) and diabetic rats fed zinc deficient diet and given vitamin C (ZD+VitC) at the end of experimental period.
(8): Number of Animals.
Mean ± SEM.
a: Significantly different from ND group; b: Significantly different from ZA group; c: Significantly different from ZD group.

Zinc concentration in organs was generally lower in ZD group than in the ZA group except in femur, which was significantly high in ZD. Meanwhile, zinc concentration was significantly high in the ZA+VitC as compared to ZA group and in the

ZD+VitC group as compared to the ZD group.

Blood Biochemical Parameters

Glucose, total lipids, triglycerides, total proteins, urea, ALT, AST, ALP, LDH and liver glycogen values are indicated in Table 2.

Parameter	Experimental groups				
	ND(8)	ZA(8)	ZD(8)	ZA+VitC (8)	ZD+VitC (8)
Glucose (mg/dl)	89.75±3.19	220.79±0.07[a]	312.50±0.19[b]	200.46± 0.03b	265.8± 0.13c
Liver glycogen(mg/g fresh weight)	56.71±1.28	37.57±1.91[a]	27.861±0.54[b]	52.04± 2.11b	43.51±2.47c
Total lipids (mg/dl)	264.5±11.2	411.8±25.8[a]	892.0±12.0[b]	344.0 ± 10.5[b]	433.40±8.4[c]
Triglycerides(mg/dl)	73.75±2.86	110.88±2.18[a]	347.10±20.50[b]	91.19± 6.14b	102.5± 21.70c
Total proteins (g/dl)	8.71±0.21	6.13±0.31[a]	4.85±0.11[b]	8.10 ± 0.52[b]	5.69 ± 0.11[c]
Urea (mg/dl)	31.62±1.16	54.68±1.20[a]	59.04±1.51[b]	43.5± 2.21b	49.41±1.78c
AST (IU/L)	51.37±1.13	71.12±0.55[a]	101.56±4.30[b]	61.46±2.35b	83.69±6.99c
ALT (IU/L)	35.25±1.82	72.69±1.55[a]	100.40±5.67[b]	48.31± 1.74b	81.13±0.69c
ALP (IU/L)	228.87±9.15	171.39±5.75[a]	66.51±4.59[b]	191.46 ± 5.65[b]	100.4±16[c]

Table 2: Glucose, total lipids, triglycerides, total proteins and urea, AST, ALT, ALP and liver glycogen of non-diabetic rats (ND), diabetic rats fed zinc adequate diet (ZA), diabetic rats fed zinc deficient diet (ZD), diabetic rats fed zinc adequate diet and given vitamin C (ZA+VitC) and diabetic rats fed zinc deficient diet and given vitamin C (ZD+VitC) at the end of experimental period.
(8): Number of Animals.
Mean ± SEM.
a: Significantly different from ND group; b: Significantly different from ZA group; c: Significantly different from ZD group.

Blood glucose, total lipids, triglycerides, urea, GOT, GPT levels were higher in ZD group than in ZA group. In contrast, serum total proteins, ALP, LDH and liver glycogen levels of ZD were lower than those of ZA rats. The serum glucose, total lipids, triglycerides, urea, ALT, AST levels were significantly low in the ZA+VitC group when compared to ZA group. Meanwhile, serum glucose, total lipids, triglycerides and urea, AST, ALT levels were significantly low in the ZD+VitC group in comparison with ZD group. Whereas, the concentrations of serum total proteins, liver glycogen, LDH and ALP were high in the two groups supplemented with vitamin C compared to the two non-supplemented groups.

Oxidative Stress Parameters

The GSH, TBARS, GSH-Px, GST and catalase values are shown in Table 3.

Parameter	Experimental groups				
	ND(8)	AZ(8)	ZD(8)	AZ+VitC(8)	ZD+VitC(8)
GSH (nmol/mg prot)	22.75±1.85	15.861 ± 0.190a	13.776± .290b	18.307± 0.291b	16.821 ± 0.372c
TBARS (nmol/mg prot)	0.321±0.02	0.504 ± 0.05a	0.732± 0.03b	0.400 ± 0.02b	0.592 ± 0.03c
(µmol GSH/min/mg prot)	0.203±0.01	0.176 ± 0.03a	0.156 ± 0.03b	0.198b± 0.06b	0.171± 0.07c
GST (µmol GSH-CDNB/min/mg prot)	1.27± 0.03	1.642 ± 0.09a	2.542 ± 0.11b	1.131± 0.14b	1.749± 0.09c
CAT(µmolH_2O_2/min/mg prot)	44.91±1.98	29.19 ± 2.40a	18.42 ± 0.32b	35.37 ± 1.09b	24.07± 1.19c

Table 3: GSH, TBARS, GSH-Px, GST and CAT in liver of non-diabetic rats (ND), diabetic rats fed zinc adequate diet (ZA) , diabetic rats fed zinc deficient diet (ZD), diabetic rats fed zinc adequate diet and given vitamin C (ZA+VitC) and diabetic rats fed zinc deficient diet and given vitamin C (ZD+VitC) at the end of experimental period.

(8): Number of Animals.
Mean ± SEM.
a: Significantly different from ND group; b: Significantly different fromZA group; c: Significantly different from ZD group.

Diabetic rats fed on zinc deficient diet had higher TBARS concentration and GST activity. However, the activity of GSH-Px and catalase, as well as that of GSH concentration were lower than ZA group. The administration of vitamin C produced improvement of the above mentioned hepatic oxidative stress parameters. TBARS, GST values were lower in vitamin C supplemented animals than those of the non-supplemented groups. The GSH, GSH-Px and CAT values were high in the vitamin C supplemented groups.

Discussion

The findings from this study revealed that rats fed with zinc-deficient diet showed lower body weight gain and reduced dietary food intake compared to rats fed a zinc adequate diet. These results are in agreement with the previously published report. It was mentioned that zinc is an essential nutrient and has an interesting vital role in normal growth, protein metabolism, gene expression, immune system and in the prevention of apoptosis. However, body weight gain of diabetic rats fed on low zinc diet supplemented with Vitamin C (ZD + VitC) was higher than that of zinc deficient diet (ZD) group; this finding corroborate with those obtained by Badr, et al. who noticed a significant increase in the body weight of vitamin C treated diabetic group compared to diabetic group. Dahdouh, et al. indicated also that supplementation of vitamin C could improve the growth performance and food utilization in mice exposed to nickel. It is worth noting that rats given adequate zinc diet showed higher concentrations of serum zinc, pancreas, femur and liver when compared to zinc deficient animals. This result was in agreement with other findings [24-28]. The presence of hyperzincuria and low intestinal absorption of zinc in diabetes has prompted speculation that diabetics are more susceptible to zinc deficiency. The treatment of rats with Vitamin C increased zinc concentration of serum and tissues of both ZA and ZD rats, which might be due to high zinc bioavailability due to vitamin C supplementation. This coincides with the results of Ayinde, et al. who found that vitamin C significantly restored the level of zinc in the rat testes intoxicated by lead. The investigation results indicated that rats consumed low zinc diet presented higher concentration of blood glucose than those receiving adequate dietary zinc. It has been pointed out that zinc alteration may have an impact on glucose transporters inside the cells, which consequently affect peripheral glucose metabolism. Meanwhile, animals fed with low zinc diet showed significantly lower hepatic glycogen content than animals receiving adequate dietary zinc, this result agrees with that of Baltaci, et al. It has been reported that zinc enhance hepatic glycogenesis through its actions on the insulin signaling pathway and thus improves glucose utilization, increases hepatic glucose uptake and inhibits intestinal glucose absorption. Moreover, it has been reported that zinc inhibit glucagon secretion as well as it enhances the structural integrity of insulin by reducing glycogenolysis. In this study blood glucose was reduced in the zinc deficient animals that were treated with vitamin C in comparison to the non-treated zinc deficient rats. This finding corroborates with that of Narra, et al. [29-35].

Vitamin C might alter insulin receptors in muscles or adipose tissue by increasing membrane motility and secondary enhances glucose uptake by the diaphragm. Simultaneously, the results indicated that the treatment with vitamin C has increased hepatic glycogen concentration. This result is similar to the investigation of Bulduk, et al. who reported an increase of muscle glycogen level of diabetic rats given ascorbic acid. Therefore, it has been suggested that acerbate might inhibit glycolysis, and thus enhances storing glycogen [36-38]. The total lipids, triglycerides and urea levels of zinc deficient animals were higher than those fed sufficient zinc. Such results perhaps are due to the catabolism of lipids and proteins because of increased energy demand [24]. In this experiment; there are an increase in serum ALT and AST activities of zinc deficient rats relative to those given adequate zinc diet. This finding is similar to the reported earlier studies [24,28]. Similarly, Reiterer, et al. [39] also stated that mice fed with zinc deficient diet showed elevated concentrations of cholesterol and triglycerides in the VLDL and HDL fractions, while zinc supplementation caused an important decrease of lipids.

The reduction in serum ALP of rats given low zinc diet could be attributed to the decrease of serum zinc. Similarly, Cho et al. confirmed that zinc is present in several metalloenzymes such as ALP, because it is needed for their activities. Moreover, serum total proteins level was significantly lower of rats that received zinc deficient diet compared with the zinc adequate group. These results are in total agreement with the previous findings of Derouiche and Kechrid. Undoubtedly, zinc was reported as an essential element for the synthesis of coenzymes that mediate biogenic amine synthesis and metabolism. In addition, Oteiza, et al. [40-43] demonstrated that zinc deficiency could be associated with high rates of oxidative damage of DNA and proteins. The decreased antioxidant capacity of diabetes is the result of increased production of oxygen metabolites, which curbs the activity of the antioxidant defense system. In other words, the reduced GSH concentration in low zinc diabetic rats might be attributed to oxidative stress [44]. In agreement with previous investigations, the significant increase of TBARS level was also found in the diabetic animals fed zinc deficient diet [28]. In addition, it has been shown that hyperglycemia promotes the production of free radicals, which may possibly inhibits the antioxidant enzyme activities [45]. Moreover, the hyperglycemia induces glucose autoxidation and protein glycation, which could explain the observed decrease of GSH-Px activity. The observed increase of GST activity in

diabetic rats fed on zinc deficient diet is in agreement with the findings of Youcef, et al. [46] It can be assumed that the variations associated with zinc deficiency in diabetic rats can be prevented by vitamin C supplementation; the latter seems to be effective in restoring some biochemical parameters to their normal levels. There are noticeable augmentations in serum total proteins, as well as a remarkable reduction in serum urea, total lipids and triglycerides concentrations of animals fed low zinc diet and given vitamin C compared with the zinc deficient group. This finding is in line with the results of Badr, et al. [26] Vitamin C supplementation improves lipid profile in alloxan diabetic rats by acting through cholesterol 7α-hydroxylase to direct cholesterol into bile synthesis. Furthermore, vitamin C scavenges free radicals and decreases oxidative damage of LDL-cholesterol.

On the other hand; aminotransferases activities were decreased in animals fed inadequate zinc diet and supplemented with vitamin C when compared to the zinc-deficient group. This is in line with those of Ahna et al. who found that vitamin C prevent the increasing activities of hepatic enzymes. However, the increased activity of serum alkaline phosphatase is possibly a consequence of elevated zinc concentration. The administration of vitamin C had increased the level of GSH, but it reduced MDA concentration. Such result is likely explained on the basis that adequate ascorbic acid has radical-scavenging activity, which can regenerate other antioxidants such as GSH and α-tocopherol. The augmentation of GSH-Px activity is in good agreement with previous reports. The ascorbic acid-induced GSH-Px activity was probably due to the scavenging of oxidants such as HOCl, hydroxyl radical and reactive nitrogen species. The results of this experiment are in agreement with the literature, where the addition of vitamin C has increased catalase activity. The free-radical scavenging ability of the vitamin, results in the reduction of $O^{\cdot-}_{2,}$ which prevents the damage of catalase haem group, thereby restoring the enzyme activity [47-51].

Conclusion

To conclude, both zinc deficiency and diabetes have disturbed growth rate, zinc status, carbohydrate metabolism, antioxidant enzymes activities and the levels of GSH and MDA [52]. However, the supplementation of vitamin C has alleviated some of these perturbations, suggesting that vitamin C had a therapeutic benefit for the reduction of diabetic complications under zinc deficiency and that by its antioxidant activity.

References

1. Khan A, Lindenmayer JP, Ljuri I, Ozog V, Thanju A, et al. (2018) F143 Predictors of Relapse: Patient, Disease, Cognitive, and Functional Characteristics with Comt Gene Val158MetPolymorphism in a 2-year Follow-up. Schizophrenia Bulletin 44(1): S275.

2. Xia Tian, Yanlin Liu, Guangwei Ren , Ling Yin , Xiaoyan Liang, et al. (2016) Resveratrol limits diabetes-associated cognitive decline in rats by preventing oxidative stress and inflammation and modulating hippocampal structural synaptic plasticity. Brain Res 1650: 1-9.

3. Ching-Chiang Lin, Guey-Ju Tsweng, Cheng-Fa Lee, Bai-Hsiun Chen, Yeou-Lih Huang, et al. (2016) Magnesium, zinc, and chromium levels in children, adolescents, and young adults with type 1 diabetes. Clin Nutr 35(4): 880-884.

4. Neda Roshanravan, Mohammad Alizadeh, Mehdi Hedayati, Mohammad Asghari-Jafarabadi, Naimeh Mesri Alamdari, et al. (2015) Effect of zinc supplementation on insulin resistance, energy and macronutrients intakes in pregnant women with impaired glucose tolerance. Iran J Public Health 44(2): 211-217.

5. Judith Jansen, Eva Rosenkranz, Silke Overbeck, Sabine Warmuth, Eugenio Mocchegiani, et al. (2012) Disturbed zinc homeostasis in diabetic patients by in vitro and in vivo analysis of insulinomimetic activity of zinc. J Nutr Biochem 23(11): 1458-1466.

6. Kyria Jayanne Clímaco Cruz, Ana Raquel Soares de Oliveira, Dilina do Nascimento Marreiro (2015) Antioxidant role of zinc in diabetes mellitus. World J Diabetes 6(2): 333-337.

7. Xiao Miao, Weixia Sun, Yaowen Fu, Lining Miao, Lu Cai, et al. (2013) Zinc homeostasis in the metabolic syndrome and diabetes. Front Med 7(1): 31-52.

8. Bhupinder Kaur, Jeyakumar Henry (2014) Micronutrient status in type 2 diabetes: a review. Adv Food Nutr Res 71: 55-100.

9. Fan Yang, Bing Li, Xiaoming Dong, Wenpeng Cui, Ping Luo, et al. (2017) The beneficial effects of zinc on diabetes-induced kidney damage in murine rodent model of type 1 diabetes mellitus. J Trace Elem Med Biol 42: 1-10.

10. Barry Halliwell, Gutteridge JMC (2015) Free Radicals in Biology and Medicine. 5th ed. Oxford University Press, U S A.

11. Mustafa Sönmez, Gaffari Türk, Abdurrauf Yüce (2005) The effect of ascorbic acid supplementation on sperm quality, lipid peroxidation and testosterone levels of male Wistar rats. Theriogenology 63(7): 2063-2072.

12. Maria Jedlinska-Krakowska, Grazyna Bomba, Karol

Jakubowski, Tadeusz Rotkiewicz, Barbara Jana, et al. (2006) Impact of oxidative stress and supplementation with vitamins E and C on testes morphology in rats. J Repro Develop 52(2): 203-209.

13. Evans P, Halliwell B (2001) Micronutrients oxidant, antioxidant status. Br J Nutr 85(2): S67-S74.

14. Ashima Pathak, Vishawjyoti Sharma, Sanjeev Kumar, Dhawan DK (2011) Supplementation of zinc mitigates the altered uptake and turnover of 65Zn in liver and whole body of diabetic rats. Biometals 24(6): 1027-1034.

15. Southon S, Kechrid Z, Wright AJ, Fairweather-Tait SJ (1988) Effect of reduced dietary zinc intake on carbohydrate and zinc metabolism in the genetically diabetic mouse (C57BL/KsJdb+/db+). Br J Nutr 60(3): 499-507.

16. Amporn Jariyapongskul, Tippawan Rungjaroen, Ngamjit Kasetsuwan, Suthiluk Patumraj, Junji Seki, et al. (2007) Long-term effects of oral vitamin C supplementation on the endothelial dysfunction in the iris microvessels of diabetic rats. Microvasc Res 74(1): 32-38.

17. Buege JA, Aust SD (1978) Microsomal lipid peroxidation. Methods Enzymol 52: 302-310.

18. Ellman GL (1959) Tissue sulfhydryl groups. Arch Biochem Biophys 82(1): 70-77.

19. Jollow DJ, Mitchell JR, Zampaglione Z, Gillette JR (1974) Bromobenzene induced liver necrosis. Protective role of glutathione and evidence for 3, 4-bromobenzene oxide as the hepatotoxic metabolites. Pharmacology 11(3): 151 -159.

20. Flohe L, Gunzler WA (1984) Analysis of glutathione peroxidase. Methods Enzymol 105: 114-121.

21. Habig WH, Pabst MJ, Jakoby WB (1974) Glutathione-S-transferase the first step in mercap-turic acid formation. J Biol Chem 249(22): 7130-7139.

22. Claiborne A (1985) Catalase activity. In: Greenwald RA, ed. CRC Handbook of Methods of Oxygen Radicals Research. Boca Raton, CRC Press 283-284.

23. Bradford MM (1976) A rapid and sensitive method for the quantities of microgram quantities of protein utilizing the principle of protein - dye binding. Anal Biochem 72(2): 248-254.

24. Hans-UIrich Bergmeyer (1974) Methods of enzymatic analysis V_4. New York. San Francisco, London: Academic Press.

25. Imene Tebboub, Zine Kechrid (2019) Effect of curcuma on zinc, lipid profile and antioxidants levels in blood and tissue of streptozotocin-induced diabetic rats fed zinc deficiency diet. Arch Physiol Biochem 19: 1-8.

26. Ching-Chiang Lin, Hsiu-Hua Huang, Chiung-Wen Hu, Bai-Hsiun Chen, Inn-Wen Chong, et al. (2014) Trace elements, oxidative stress and glycemic control in young people with type 1 diabetes mellitus. J Trace Elem Med Biol 28(1): 18-22.

27. Gamal Badr, Samir Bashandy, Hossam Ebaid, Mohamed Mohany, Douaa Sayed, et al. (2012) Vitamin C supplementation reconstitutes polyfunctional T cells in streptozotocin-induced diabetic rats. Eur J Nutr 51(5): 623-633.

28. Faouzi Dahdouh, Zine Kechrid, Mohammed-Réda Djebar (2013) Beneficial effects of vitamins (C+E) supplementation against nickel-induced hepatotoxicity in mice. Advances in Bioresearch 4(2): 67-76.

29. Malika Hamdiken, Samira Bouhalit, Zine Kechrid (2018) Effect of Rutachalepensis on Zinc, Lipid Profile and Antioxidant Levels in the Blood and Tissue of Streptozotocin-Induced Diabetes in Rats Fed Zinc-Deficient Diets. Can J Diabetes 42(4): 356-364.

30. Elseweidy MM, Ali AMA, Nabila Zein Elabidine , Nada M Mursey (2017) Effect of zinc gluconate, sage oil on inflammatory patterns and hyperglycemia in zinc deficient diabetic rats. Biomed Pharmacother 95: 317-323.

31. Ayinde OC, Sunday Ogunnowo, Ogedegbe RA (2012) Influence of vitamin C and vitamin E on testicular zinc content and testicular toxicity in lead exposed albino rats. BMC Pharmacol Toxicol 13: 17.

32. Urszula Doboszewska, Bernadeta Szewczyk, Magdalena Sowa-Kućma, Karolina Noworyta-Sokołowska, Paulina Misztak, et al. (2016) Alterations of bio-elements: oxidative and inflammatory status in the zinc deficiency model in rats. Neurotox Res 29(1): 143-154.

33. Abdülkerim Kasim Baltaci, Kursat Ozyurek, Rasim Mogulkoc, Erdal Kurtoglu, Yasemin Ozkanv, et al. (2003) Effects of zinc deficiency and supplementation on the glycogen contents of liver and plasma lactate and leptin levels of rats performing acute exercise. Biol Trace Elem Res 96(1-3): 227-236.

34. Chabosseau P, Rutter GA (2016) Zinc and diabetes. Arch Biochem Biophys 611: 79-85.

35. Laerke Egefjord, Petersen AB, Jørgen Rungby (2010)

Zinc, alpha cells and glucagon secretion. Curr Diabetes Rev 6(1): 52-57.

36. Madhusudan Reddy Narra, Kodimyala Rajender, Reddy RR, Venkateswara Rao J, Ghousia Begum, et al. (2015) The role of vitamin C as antioxidant in protection of biochemical and haematological stress induced by chlorpyrifos in freshwater fish Clariasbatrachus. Chemosphere 132: 172-178.

37. Ambali SF, Shuaib K, Edeh R, Orieji BC, Shittu M, et al. (2011) Hyperglycemia induced by sub chronic co-administration of chlorpyrifos and lead in Wistar rats: Role of pancreatic lipoperoxidation and alleviating effect of vitamin C. Biology and Medicine 3(1): 6-14.

38. Bulduk E, Gönül B, Ozer C (2006) Effects of vitamin C on muscle glycogen and oxidative events in experimental diabetes. Mol Cell Biochem 292(1-2): 131-137.

39. Russell PJ, Williams A, Austin TA (2000) Inhibition of rabbit muscle isozymes by vitamin C. J Enzyme Inhib 15(3): 283-296.

40. Gudrun Reiterer, Ruth MacDonald, Browning JD, Jason Morrow, Matveev SV, et al. (2005) Zinc deficiency increases plasma lipids and atherosclerotic markers in LDL receptor-deficient mice. J Nutr 135(9): 2114-2118.

41. Young-Eun Cho, Lomeda RAR, Sang-Hoon Ryu, Ho-Yong Sohn, Hong-In Shin, et al. (2007) Zinc deficiency negatively affects alkaline phosphatase and the concentration of Ca, Mg and P in rats. Nutr Res Pract 1(2): 113-119.

42. SamirDerouiche, ZineKechrid (2016) Zinc supplementation overcomes effects of copper on zinc status, carbohydrate metabolism and some enzyme activities in diabetic and non-diabetic rats. Canadian Journal of Diabetes 40(4): 342-347.

43. Sandstead HH, Frederickson CJ, Penland JG (2000) History of zinc as related to brain function. Nutr 130(2S): 496S-502S.

44. Oteiza PL, Olin KL, Fraga CG, Keen CL (1996) Oxidant defense systems in testes from zinc-deficient rats. Proc Soc Exp Biol Med 213(1): 85-91.

45. Tingting Liang, Quan Zhang, Weixia Sun, Ying Xin, Zhiguo Zhang, et al. (2015) Zinc treatment prevents type 1 diabetes-induced hepatic oxidative damage, endoplasmic reticulum stress, and cell death, and even prevents possible steatohepatitis in the OVE26 mouse model: Important role of metallothionein. Toxicol Lett 233(2): 114-124.

46. Hong-zhi Pan, Lin Zhang, Mei-yi Guo, Hong Sui, Hui Li, et al. (2010) The oxidative stress status in diabetes mellitus and diabetic nephropathy. Acta Diabetol 47(1): 71-76.

47. Yousef MI, El-Hendy HA, El-Demerdash FM, Elagamy EI (2002) Dietary zinc deficiency induced-changes in the activity of enzymes and the levels of free radicals, lipids and protein electrophoretic behavior in growing rats. Toxicology 175(1-3): 223-234.

48. Owu DU, Antai AB, Udofia KH, Obembe AO, Obasi KO, et al. (2006) Vitamin C improves basal metabolic rate and lipid profile in alloxan-induced diabetes mellitus in rats. J Biosci 31: 575-579.

49. Taeho Ahn, Chul-HoYun, Doo-Byoung Oh (2006) Tissue-specific effect of ascorbic acid supplementation on the expression of cytochrome P450 2E1 and oxidative stress streptozotocin-induced diabetic rats. Toxicology Letters 166(1): 27-36.

50. Domenico Lapenna, Giuliano Ciofani, Chiara Cuccurullo, Sante Donato Pierdomenico, Franco Cuccurullo, et al. (2012) Ascorbic acid supplementation reduces oxidative stress and platelet biochemical function in type 2 diabetic patients. Relevance of ascorbic acid dosage and formulation. e-SPEN Journal 7(6): e245-e248.

51. Gökhan Sadi, Okkes Yilmaz, Tülin Güray (2008) Effect of vitamin C and lipoic acid on streptozotocin-induced diabetes gene expression: mRNA and protein expressions of Cu–Zn SOD and catalase. Mol Cell Biochem 309(2): 109-116.

52. Jinjuan Wan, Xianping Gea, BoL iua, Jun Xiea, Suli Cui, et al. (2014) Effect of dietary vitamin C on non-specific immunity and mRNA expression of three heat shock proteins (HSPs) in juvenile Megalobrama amblycephala under pH stress. Aquaculture 434: 325-333.