

Chapter 6

SUMMARY AND CONCLUSIONS

Diabetes is associated not only with hyperglycemia due to insulin resistance or hypo-insulinemia but also hyperzincuria, altered metabolic states of carbohydrate, proteins, lipids and increased oxidative stress. Presence of hyperzincuria signifies the loss of zinc in diabetes. Zinc is an important trace element and a cofactor in many metabolic and anti-oxidative defense mechanisms and its depletion raises further concerns. The present study was conducted to evaluate the potential of zinc as an important micronutrient in regulating hyperglycemia, hypo-insulinemia, lipidemia, oxidative stress and carbohydrate metabolism in liver. The study also investigated the effects of diabetes and zinc on metabolic functions like glucose uptake and its turnover in liver using ^{14}C labeled glucose for uptake and radiorespirometry techniques, zinc homeostasis by undertaking biokinetics study using ^{65}Zn , calcium homeostasis, mRNA expression of Glut 2 and histoarchitecture of liver using light and electron microscopic studies. The results of the various investigations obtained in the present study are summarized as follows:

- Diabetic animals showed decreased body weights besides the fact that they consumed more diet in comparison to the normal control animals. However with zinc supplementation there was appreciable gain in the body weights of the diabetic animals though the values were still low in comparison to the normal control rats. It shows the potential of zinc to maintain healthy metabolism in improving the body weights which were much reduced under diabetic conditions.
- Diabetic rats supplemented with zinc showed near normal serum glucose levels which however were increased during diabetes but insulin levels were not significantly improved. Even the levels of Hb A1C were normalized on simultaneous zinc treatment to the diabetic rats. This

clearly demonstrates the insulin-like role of zinc in reducing hyperglycemia.

- Biokinetics studies using ^{65}Zn , showed that there is imbalance in zinc homeostasis due to decreased half-life of the radioisotope in the diabetic rats. Upon zinc supplementation, the biological half-life showed significant improvement in liver as well as whole body of the diabetic rats. Analyses of disturbed zinc levels in serum, urine and liver of diabetic animals showed that there is imbalance in the distribution of the zinc as well as loss from the body. However, zinc treatment to diabetic rats showed some clear signs of improvement in the zinc metabolism and distribution.
- Zinc treatment to diabetic rats resulted in decreasing the values of cholesterol, triglycerides and LDL which were elevated during diabetes. The HDL levels too showed improvement on zinc supplementation though not statistically significant in comparison to diabetic rats. However, it clearly showed that overall lipid profile of diabetic rats is much improved on zinc treatment which indicates that zinc is a promising candidate in reducing lipid anomalies in diabetes.
- As observed in the present study, diabetes causes severe oxidative stress and disturbances in oxidative defense mechanism. It was observed that there was a significant decrease in the levels of GSH and increase in the GSSG levels in diabetic rats. It was further observed that activity of GR, Catalase and SOD was significantly reduced in the diabetic rats. There was a statistically significant increase in the levels of LPO which was evidenced by increased MDA levels in liver of diabetic rats. Diabetic rats subjected to zinc treatment showed reduction in levels of MDA and GSSG and activities of GR, SOD and Catalase were significantly increased which indicates that zinc is efficient in reducing the oxidative damage because of its antioxidative property to prevent protein oxidation and also as a cofactor in various enzymes.

- Increase in MT content in liver of diabetic rats was observed in this study and increase in MT content suggests the protective mechanism of the liver operates against the oxidative damage. At the same time, zinc supplementation to the diabetic rats maintained the increased MT content in diabetic rats thus assisting in antioxidative action.
- In the present study, no variation was observed in the activities of the hexokinase, SDH and Glucose-6-phosphate isomerase among all the treatment groups. However, there was an increase in the activities of LDH, glucose-6-phosphatase and glycogen phosphorylase in diabetic rats when compared to the normal control rats. There was also a significant decrease in the levels of the liver glycogen in diabetic rats. Zinc supplementation to the diabetic rats normalized carbohydrate metabolism enzymes which included glucose-6-phosphatase, lactate dehydrogenase and glycogen phosphorylase. Further, glycogen levels were also restored to within the normal limits. There was an increase in the ^{14}C -glucose uptake in zinc supplemented diabetic rats which however was decreased in diabetic rats. The turnover of glucose was also increased when zinc was supplemented to the diabetic rats though it remained still lower in comparison to normal rats. The observed decrease in the mRNA expression of the Glut 2 during diabetes was also enhanced on the zinc supplementation to the diabetic rats
- In present study, no variation was observed in the calcium levels and Ca^{2+} ATPase activity in the liver and ^{45}Ca uptake in liver was also was more or less the same in all the treatment groups. There was again no difference in the levels of cAMP in the liver of all the treatment groups, however a significant decrease in the cAMP levels was observed in the serum of the diabetic animals. Zinc supplementation to the diabetic rats was capable of increasing the depressed cAMP levels in the diabetic rats but not to the range of normal animals.

- There was decrease in the activity of Na⁺/K⁺ ATPase in liver of the diabetic rats and zinc treatment to the diabetic animals though enhanced the activity but it was not statistically significance.
- A significant increase in the activities of liver marker enzymes viz; ALP, ALT and AST in liver of diabetic rats was observed and zinc treatment was successful in reducing the elevated activity.
- Histological observations showed that zinc supplementation to the diabetic rats were quite effective in reducing the changes which resulted in structural damage to the liver of the diabetic rats. Zinc treatment to diabetic rats also lowered lipid accumulation and improved the glycogen content in the hepatocytes of diabetic rats.

Conclusions

The present study indicates that the diabetic complications are further enhanced by the paucity and homeostatic imbalance of zinc in the diabetic animals and zinc supplementation caused a significant improvement in the retention of zinc which brought about normalization of various parameters and effectively combated the oxidative stress by strengthening the antioxidative defense mechanism in the diabetic rats. Therefore, it is concluded that zinc mimics insulin-like action in alleviating hyperglycemia as well as regulating glucose metabolism and it therefore can be regarded as a potential candidate for the therapeutic intervention in diabetes.