BioMetals (2005) 18:293–294
DOI 10.1007/s10534-005-3684-z

Preface

Zinc and Diabetes

Wolfgang Maret
Division of Human Nutrition, Departments of Preventive Medicine & Community Health and Anesthesiology, University of Texas Medical Branch, 700 Harborside Drive, Galveston, TX 77555 USA (Tel: +409-772-4661; Fax: +409-772-6287; E-mail: womaret@utmb.edu)

Diabetes mellitus, a chronic metabolic disorder is due to absolute (Type 1, IDDM, insulin-dependent diabetes mellitus) or relative (Type 2, NIDDM, non-insulin-dependent diabetes mellitus) insulin deficiency. Sequelae of diabetes make this disease a major health risk in terms of microvascular disease that leads to kidney failure, blindness, and nerve damage, and macrovascular disease that leads to amputations, cardiovascular disease, and stroke. Diabetes is also discussed as a risk factor for Alzheimer's disease and cancer. While formerly called "adult-onset diabetes," Type 2 diabetes is now being diagnosed increasingly in young adults and children. According to recent estimates, 220 million people worldwide will be affected by Type 2 diabetes by 2010. In the US, Type 2 accounts for approximately 95% of the cases of diabetes, resulting in an annual economic toll of approximately 100 billion dollars. The epidemic proportions of the disease demand extraordinary efforts to define pathobiochemical pathways and strategies for prevention and to find new therapeutic approaches.

Why zinc? Among the many essential inorganic micronutrients, zinc is second in abundance to iron in the human body. The significance of zinc in biology can be appreciated from the sheer number of zinc proteins. Zinc has catalytic functions in hundreds of enzymes, structural functions in thousands of proteins, and regulatory functions in a yet uncounted number of proteins. Basic science discoveries in zinc biology have not reached the practice of medicine in the manner they did for iron despite the fact that clinical or even subclinical zinc deficiency and perturbations of zinc metabolism are now recognized as factors in the pathogenesis of several chronic diseases.

With so many functions of zinc it is not surprising that zinc and diabetes intersect at several junctures in metabolism (Chausmer 1998; Tallman & Taylor 1999). Zinc enzymes such as insulin-degrading enzyme or sorbitol dehydrogenase and transcription factors such as peroxisome proliferator-activated receptors, PPARs, might serve as examples. What seems to be particularly relevant for the relation between zinc and diabetes is the imbalance of redox metabolism in the disease. Such "oxidative stress" can release zinc from some of its coordination environments in proteins and interfere with zinc homeostatic mechanisms (Maret 2004). The released zinc affects signal transduction, generation of metabolic energy, mitochondrial production of reactive species, and perhaps even genetic programs. In addition, zinc ions, while redox-inert, have pronounced effects on redox metabolism. Depending on how much zinc is readily available, zinc can either increase the cell's antioxidant capacity or elicit oxidative stress. Hence tight biological control must balance the pro-antioxidant and pro-oxidant potential of zinc ions. Discoveries of zinc-dependent events in the pathobiochemistry of diabetes stem from various disciplines and are scattered in the scientific literature. Thus, it appeared that a symposium with protagonists from these disciplines would enhance knowledge and might serve as a platform to bring the resulting understanding of the role of zinc in diabetes to the attention of a larger part of the scientific community.

In the following proceedings of the symposium, **Michael Dunn** summarizes the structural and biophysical studies that identified insulin as an allosteric protein, in which zinc / ligand interactions control the assembly and disassembly of the hexameric storage form; **Carla Taylor** critically evaluates the protective effects of zinc supplementation in rodent models of Type 1 and Type 2 diabetes; **Michel Seve and coworkers** (Chimienti

et al. 2005) report the cloning of a pancreatic beta-cell specific zinc transporter belonging to the ZnT family. This protein, ZnT-8, makes zinc available in the insulin-storing secretory granules of the islets of Langerhans; **Hiromu Sakurai and Yusuke Adachi** focus on the pharmacology of zinc complexes with antidiabetic activity. They designed ligands that endow zinc complexes with significantly enhanced glucose-lowering activity when compared to zinc salts; **Lu Cai and coworkers** (Song *et al*. 2005) provide a biochemical perspective on the protective function of zinc in the diabetic heart; **Hajo Haase and Wolfgang Maret** discuss that zinc might be a physiological modulator of insulin signal transduction and that inhibition of protein tyrosine phosphatases is one mechanism for the insulinomimetic effects of zinc.

The exploration of the role of zinc in diabetes has created new opportunities for prevention and perhaps even for therapy of the disease as additional support for the antidiabetogenic properties of zinc continues to emerge from experiments in both laboratory animals (Schott-Ohly *et al*. 2004) and humans (Roussel *et al*. 2003).

Acknowledgments

Contributions from Novo Nordisk through Dr. Niels Kaarsholm, from Sankyo and Ursapharm, the help from Reinhart Hoffmann from the Deutsche Diabetes Stiftung, and the support from the Biometals Organizing Committee made this symposium possible and are greatly acknowledged.

References

Chausmer AB. 1998 Zinc, insulin and diabetes. *J Am Coll Nutr* **17**, 109–115.

Chimienti F, Favier A, Seve M. 2005 ZnT-8, a pancreatic beta-cell-specific zinc transporter. *Biometals*, this issue.

Dunn M. 2005 Zinc-ligand interactions modulate assembly and stability of the insulin hexamer. *Biometals*, this issue.

Haase H, Maret W. 2005 Protein tyrosine phosphatases as targets of the combined insulinomimetic effects of zinc and oxidants. *Biometals*, this issue.

Maret W. 2004 Zinc and sulfur: A critical biological partnership. *Biochemistry* **43**, 3301–3309.

Roussel A-M, Kerkeni A, Zouari N, Mahjoub S, Matheau J-M, Anderson RA. 2003 Antioxidant effects of zinc supplementation in Tunisians with type 2 diabetes mellitus. *J Am Coll Nutr* **22**, 316–321.

Schott-Ohly P, Lgssiar A, Partke H-J, Hassan M, Friesen N, Gleichmann H. 2004 Prevention of spontaneous and experimentally induced diabetes in mice with zinc sulfate-enriched drinking water is associated with activation and reduction of NF-kB and AP-1 in islets, respectively. *Exp Biol Med* **229**, 1177–1185.

Song Y, Wang J, Li X, Cai L. 2005 Zinc and the diabetic heart. *Biometals*, this issue.

Sakurai H, Adachi Y. 2005 The pharmacology of the insulinomimetic effect of zinc complexes. *Biometals*, this issue.

Tallman DL, Taylor CG. 1999 Potential interactions of zinc in the neuroendocrine-endocrine disturbances of diabetes mellitus type 2. *Can J Physiol Pharmacol* **77**, 919–933.

Taylor CG. 2005 Zinc, the pancreas, and diabetes: Insights from rodent studies and future directions. *Biometals*, this issue.