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BIVALENT METAL IONS IN DIABETES MELLITUS

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Diabetes mellitus (DM) is characterized by hyperglycemia and various disorders of carbohydrate metabolism. In both types of DM numerous changes have been found in the intracellular and extracellular ionic concentrations. Some metal ions misbalances could be involved in pathogenesis of DM or in diabetes complications. In a large number of cases of magnesium and zinc concentrations were low in diabetic patients. Hypomagnesemia is a risk factor for vascular complications of diabetes. In our studies magnesium treatment reduced the experimental DM effects on non-pregnant female genital system. Zinc has an atheroprotective effect in DM patients. Some clinical studies have demonstrated that some antidiabetes drugs as metformin increased intracellular magnesium level. Correcting the metal ions misbalances in diabetic patients must be a target of therapy.

Key words: diabetes mellitus, magnesium, zinc, copper, manganese, calcium, metformin effects.

INTRODUCTION

Diabetes mellitus is one of the most often and dangerous disease for human pathology. The metabolism of bivalent metal ions (macro and trace elements) is altered in DM. The DM influences all tissues from our body. The diabetes complications are important causes of death. Unfortunately, the number of patients with diabetes grows. The clinical and experimental studies have revealed a large number of factors involved in the pathogenesis of DM. Bivalent metal ions concentration imbalances are among these.

PECULIARITIES IN ION IMBALANCES

Magnesium

Magnesium is the second most abundant intracellular cation and is very an important factor for about 300 enzymes activity. This metal is a bivalent cation localized in big part intracellular. Only 0.5 % from total magnesium of the human body is distributed in human plasma. This cation in involved in insulin secretion and in tissue sensibility to insulin. There are experimental and clinical data about the misbalances in magnesium concentration in DM and about the magnesium role in DM clinical evolution. Mather et al. (1978) involved hypomagnesemia in pathogenesis of DM. Low Mg levels is correlated in these patients with enhanced HbA1c levels (Srinivasan, 2012). The low level of magnesium could be considered as a risk factor for DM. Hypomagnesemia increases insulin resistance. The activation of TRPM 6 (a membrane magnesium channel) is important for insulin effects. The glucose level control by insulin involves the activation of TRPM6.In gestational diabetes pathogeny is involved an impairment of TRPM 6 activation by insulin (Nair et al., 2012). The low intake of magnesium is associated to type 2 DM in elderly (Huang et al., 2012) and a higher urine loss of magnesium and zinc was observed in DM patients compared to healthy control subjects (Walter et al., 1991). Hypomagnesemia and glomerular hyperfiltration are observed in patients with type 2 DM (Pham et al., 2012). Serum magnesium had significant negative correlations with glomerular hyperfiltration.

The low intra and extra cell magnesium concentration is correlated with endothelial dysfunction, insulin resistance and inflammation (Kanbay et al., 2012). The low intake of magnesium is associated to type 2 DM in elderly (Huang et al 2012). A higher urine magnesium and zinc loss was observed in DM patients compared to healthy control subjects (Walter et al., 1991). Our data (Dosa et al. 2012) showed a higher magnesium and zinc urinary elimination in adult NIDDM patients. Metformin treatment three months significantly reduced magnesium urinary loss but not zinc elimination (Fig. 1). The influence of antidiabetic drugs on metal cations concentrations and the relationship between glucose level decreasing effect and cations concentrations changes are important therapeutic problems. Metformin, one of the most used oral antidiabetic drug increased intracellular magnesium concentration (Dosa et al., 2011). We consider that change in cell magnesium level is involved in the antidiabetes biguanids mechanism of action.

The hypomagnesemia is involved also in the development of DM complication (renal and cardiovascular diseases). Hypertriacylglycerolemia from type 2 diabetes mellitus, i.e. non-insulin dependent diabetes mellitus (NIDDM) patients is associated with hypomagnesemia. The magnesium deficit favors the development of atherogenesis (Altura and Altura, 2006).

There are some different mechanisms by which magnesium can reduce atherogenesis in DM:

1. Reduction of free radical formation and of the oxidative stress
2. The decrease of proinflammatory cytokines synthesis
3. The increase of tissue sensibility to insulin
4. By decreasing the calcium entry in the endothelial cells
5. The reduction of dyslipidemia

Leukocytes, lipid peroxidation and free radicals, the chemokines and adhesion molecules are involved in atherogenesis in patients with DM (especially in type 2 DM). Various magnesium organic salts (orotate, pidolate, acexamate and others) decrease the peroxidic radical generation in different experimental situations (Nechifor et al., 1998, Rayssiguier et al., 1993).

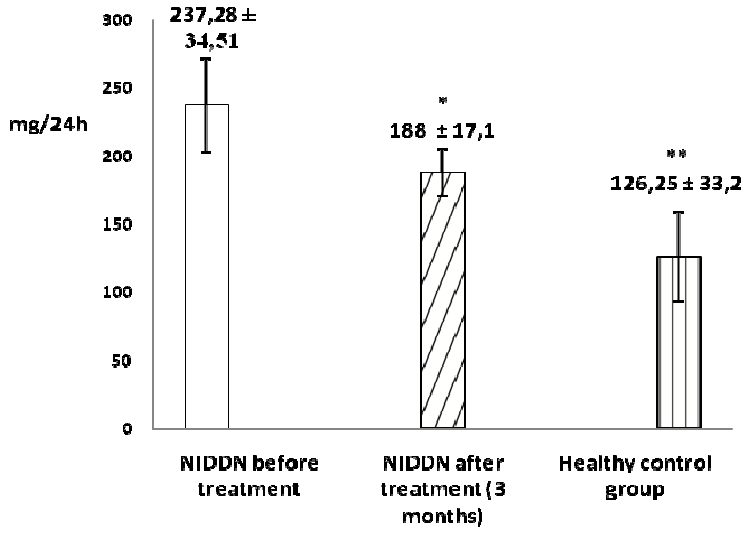

Fig. 1. Metformin influence on urinary magnesium loss in NIDDM adult patients (* $p<0.05$. * * $p<0.01$ vs. NIDDM before treatment)

In our studies (Nechifor et al., 2001), magnesium acexamate 0.5 mM/kg/day significantly reduced the hepatic level of MDA in alloxan-induced diabetes mellitus in rats and, after 14 day of treatment significantly decreased the blood glucose level.

Despite a good DM management the vascular complications remain important therapeutic challenge. The effect of magnesium diet supplementation on the apparition and development of DM complications is a major and open problem. Hypomagnesemia is a risk factor for diabetic rethinopathy (McNair et al., 1978). There are clinical studies that showed that long term additional magnesium intake

stabilized the evolution of retinopathy in diabetic patients with low magnesium level (De Leeuw et al. 2006). A similar effect of magnesium was observed concerning the peripheral diabetic neuropathy progression (De Leeuw et al 2004). Our data obtained during experimental streptozotocin induced diabetes in female non-pregnant rats showed that diabetes produced a significant endometrial atrophy and increased the number of atretic ovarian follicles. $MgCl_2$ administration (1 mmol/Kg/day daily) 8 weeks significantly reduced the endometrium atrophic diabetes effect and diminished the number of atretic ovarian follicles (Gales et al. 2012). Magnesium supplementation positively influences the evolution of neuropathy in Mg-depleted type I diabetic patients (De Leeuw et al., 2004).

Zinc

Zinc affects glucose homeostasis in animals and humans and zinc metabolism disorders are risk factors for type 2 DM (NIDDM). This metal ion is involved in insulin metabolism and in zinc deficient animals and human peoples the insulin secretion and the tissue sensibility to insulin is decreased (Quarterman et al., 1966; Arquilla et al., 1978; Kinlaw et al., 1983). An impairment of zinc metabolism is present in diabetes.The zinc plasma level is lower in DM patients than in normal adult peoples. This deficit may contributes to polymorphonuclear leukocyte activation, and by this way in involved in the development of vascular complications in type 2 DM (Karahan et al. 2001). Zinc deficiency enhances the generation of proinflammatory cytokines, including IL-1β, IL-2, IL-6, and TNF-α (Foster and Samman 2012**).** Some papers have reported increased l urinary zinc excretion in both types of DM (Cunningham et al., 1994, Dosa et al., 2011, Estakhri et al., 2011). In diabetic patients, after zinc supplementation appears a tendency for a decrease of HbA1c.

In both types of DM, the inflammatory cytokines reduces pancreatic beta islets secretion an favors the beta cells apoptosis (Foster and Samman 2012, Donath et al., 2003). Acting as anti-inflammatory factors, zinc ions block the pancreatic cells apoptosis and could play a major role in increasing the insulin secretion. The dislipidemic states are often associated to DM and are involved in vascular diabetic complication pathogenic mechanisms. A potential high-density-lipoprotein-raising effect of zinc is other way for zinc atheroprotective effect in DM patients (Foster et al., 2010).

Copper

The increased copper levels found in NIDDM diabetics (Zargar et al., 1998). In DM (type I and also type II) were found higher levels of Cu and decreased concentrations of Zn and Mg compared with controls (Viktorínová et al., 2009; Dosa et al. 2010). There are positive correlation between the plasma copper levels and the glycated hemoglobin concentrations.

Regarding the mechanisms by which copper could be involved in the pathogenesis of DM surly the enhancement of peroxidation is an important element. Recently Zang et al. (2012) showed that copper is a potent extracellular blocker for TRPM2 channel.TRPM2 is a calcium-permeable nonselective cation channel. This channel is a Na^+ and Ca^{2+} - permeable melastatin related transient receptor potential 2 (TRPM2) channel can be gated by ADP-ribose (Nazıroğlu, 2011). The changes of ratio between intracellular cations concentrations could be involved in DM. Triethylenetetramine (TETA) is the first in a new class of anti-diabetic substances, which act by targeting copper-mediated pathogenic mechanisms. TETA prevents tissue damage and suppresses copper-mediated oxidative stress (Cooper, 2012). Another copper chelating compound which clearly decreased the copper plasma level is tetrathimolibdate. This substance decreases also serum triglyceride concentration and ROS level (Tanaka et al. 2009). In alloxan-induced diabetes in rats, copper formazanate administration (3 weeks daily) do not influenced the glycemic status but slowly increased the rats mortality (Nechifor et al. 2001).

Manganese

This trace element is important for antioxidant defense. Mn-SOD plays an important role in this process. Manganese superoxide dismutase (MnSOD) is a key mitochondrial-specific enzyme involved in antioxidant activity of cell. The elevated mitochondrial level of reactive oxygen species plays a role in some forms of muscle insulin resistance (Boden et al. 2012). The enhancement of mitochondrial antioxidant activity decreased the insulin resistance in skeletal muscle induced by high fat diet. An adequate Mn intake in is indicated to prevent insulin resistance and diabetes type 2 (Rodríguez-Rodríguez et al., 2011). Manganese-SOD activity protects the prokaryotic and eukaryotic cells against various types of stress (Benov and Fridovich, 1995, Stoica et al., 2010). We think that Mn-SOD plays also a role in human cell protection against the hyperglycemic and oxidative stress from DM.

Calcium

Calcium involvement gluco-lipidic metabolism and glycemia regulation is complex. L-type calcium channels are important for the stimulation of insulin secretion by glucose in beta pancreatic cells (Wollheim and Sharp, 1981). Cytosolic Ca(2+) play an important role in controlling insulin secretion in pancreatic β-cells. The Na(+)/Ca(2+) exchanger, a carrier that can mediate the transport of Ca(2+) across the plasma membrane acts as a protector factor against intracellular calcium overload and is involved in the insulin secretion (Cui et al. 2012). Ca(2+) influx in the beta cells is crucial(together the stimulation ATP synthesis and membrane depolarization for glucose induced insulin release (Tarasovet al. 2012). On the other hand there are data that involve calcium ions in the mechanism of vascular and renal diabetes complications. L/N-type calcium channel blockers provide renal protection and reduced the progression of diabetic nephropathy in diabetic rats (Hayashi, 2011). A calcium channel blocker, azelnidipine decreases

the urinary albumin levels in diabetic patients (Ando et al., 2011). Hypercalciuria is one of the early manifestations of diabetic nephropathy (Asai et al., 2012).

The formation and accumulation of advanced glycation end products (AGEs) is one of most important way for induction of diabetes vascular complications. There are receptors activated by AGEs. Nifedipine and other calcium blockers inhibit the AGEs receptors activation and by this mechanism reduced the vascular damages in diabetes (Yamagishi, 2010).

CONCLUSIONS

The metal ion metabolism disorders play an important role the DM evolution and may contribute to the progression of diabetic complications. The oral antidiabetic drugs influence the intracellular or/and extracellular bivalent metal concentrations and also the ratio between different bivalent cation. This is a significant part of antidiabetes action of drugs. Correcting the metal ions misbalances in diabetic patients must be a target of therapy.

REFERENCES

1. Ando K., Haneda M., Ito S., Kashihara N., Node K., Nangaku M., Shimosawa T., Kishimoto J., Fujita T. – Design and rationale of Japanese evaluation between Formula of Azelnidipine and amlodipine add on olmesartan to Get antialbuminuric effect study (J-FLAG): evaluation of the antialbuminuric effects between calcium channel blocker with sympatholytic action in hypertensive patients with diabetes and albuminuria. *Cardiovasc. Drugs Ther.*, 2011, 25, 341-347.
2. Arquilla E.R., Packer S., Tarmas W., Miyamoto S. – The effect of zinc on insulin metabolism, *Endocrinology,* 1978,103,1440-1449.
3. Asai O., Nakatani K., Tanaka T., Sakan H., Imura A., Yoshimoto S., Samejima K., Yamaguchi Y., Matsui M., Akai Y., Konishi N., Iwano M., Nabeshima Y., Saito Y. – Decreased renal α-Klotho expression in early diabetic nephropathy in humans and mice and its possible role in urinary calcium excretion, *Kidney Int.*, 2012, 81, 539-547.
4. Baker S.J.L., Navis G., Gans R.O.B. – Copper chelation as a potential treatment for left ventricular hypertrophy in type 2 diabetes, *Diabetologia*, 2009, 52, 2244-2245.
5. Benov L., Fridovich I. – Superoxide dismutase protects against aerobic heat shock in Escherichia coli, *J. Bacteriol.,* 1995, 177, 3344-3346.
6. Boden M.J., Brandon A.E., Tid-Ang J.D., Preston E., Wilks D., Stuart E., Cleasby M.E., Turner N., Cooney G.J., Kraegen E.W. – Overexpression of manganese superoxide dismutase ameliorates high-fat diet-induced insulin resistance in rat skeletal muscle, *Am J. Physiol. Endocrinol. Metab*., 2012, 303, E798-805.
7. Cooper G.J. – Selective divalent copper chelation for the treatment of diabetes mellitus, *Curr. Med. Chem*., 2012,19, 2828-2860.
8. Cui K.Z., Liu D., Liu J.W., Xu Y., Li Y.B., Sun Y.M., Su Y. – Role of the Na(+)/Ca(2+) exchanger on the development of diabetes mellitus and its chronic complications, *Biochem. Biophys. Res. Commun.*, 2012, 426, 445-447.
9. Cunningham J.J., Fu A., Mearkle P.L., Brown R.G. – Hyperzincuria in individuals with insulin-dependent diabetes mellitus: concurrent zinc status and the effect of high-dose zinc supplementation, *Metabolism*, 1994, 43, 1558-1562.

10. De Leeuw C., De Block C., van Gaal L. – Can long term magnesium supplementation stabilize the progression of diabetic retinopathy. pp. 129-133, in "*Advances in magnesium research – New Data*" (Porr P.J., Nechifor M., Durlach J., Eds.), John Libbey Eurotext, Paris, 2006.
11. De Leeuw I., Engelen W., De Block C., van Gaal L. – Long-term magnesium supplementation influences favourably the natural evolution of neuropathy in Mg-depleted type I diabetic patients, *Magnesium Res*., 2004, 17, 109-114.
12. Donath M.Y., Størling J., Maedler K., Mandrup-Poulsen T. – Inflammatory mediators and islet beta-cell failure: a link between type 1 and type 2 diabetes. *J. Mol. Med. (Berl).*, 2003, 81, 455-470.
13. Doşa M.D., Catrinoiu D., Hangan L.T., Galeş C., Nechifor M. – Research on the influence of biguanides treatment on copper concentration in non-insulin-dependent diabetes mellitus patients, *Therap. Pharmacol. Clinical Toxicol.*, 2010,14, 53-56.
14. Doşa M.D., Galeş C., Nechifor M. – Influence of metformin treatment on urinary magnesium and zinc loss in NIDDM adult patients, Abstracts Book, p.48, in "*XIIIth International Magnesium Symposium*", Merida, 2012.
15. Doşa M.D., Hangan L.T., Crauciuc E., Galeş C., Nechifor M. – Influence of therapy with metformin on the concentration of certain divalent cations in patients with non-insulin-dependent diabetes mellitus, *Biol Trace Elem Res.*, 2011, 142, 36-46.
16. Estakhri M., Djazayery A., Eshraghian M.R., Majdzadeh R., Jalali M., Karamizadeh Z., Chamari M., Peyrovi Milani M. – Serum Zinc Levels in Children and Adolescents with Type-1 Diabetes Mellitus, *Iran J. Public Health*, 2011, 40, 83-88.
17. Foster M., Petocz P., Samman S. Effects of zinc on plasma lipoprotein cholesterol concentrations in humans: A meta-analysis of randomised controlled trials, *Atherosclerosis*, 2010, 210, 344-352.
18. Foster M., Samman S. – Zinc and regulation of inflammatory cytokines: implications for cardiometabolic disease, *Nutrients*, 2012, 4, 676-694.
19. Gales C., Zamfir C., Radulescu D., Stoica B., Nechifor M. – Research involving the effect of magnesium and metformin on the non-pregnant uterus and ovary in experimentally-induced diabetes mellitus, *Magnes. Res*., 2012, 125, abstr. p. 6.
20. Hayashi K.L. – T-type Ca channel blockers for kidney protection: ready for sophisticated use of Ca channel blockers, *Hypertens Res.*, 2011, 34, 910-912.
21. Huang JH, Lu YF, Cheng FC, Lee JN, Tsai LC. Correlation of magnesium intake with metabolic parameters, depression and physical activity in elderly type 2 diabetes patients: a cross-sectional study. *Nutr J*., 2012,11:41-43.
22. Kanbay M., Yilmaz M.I., Apetrii M., Saglam M., Yaman H., Unal H.U., Gok M., Caglar K., Oguz Y., Yenicesu M., Cetinkaya H., Eyileten T., Acikel C., Vural A., Covic A. – Relationship between serum magnesium levels and cardiovascular events in chronic kidney disease patients, *Am J Nephrol.,* 2012, 36, 228-237.
23. Karahan S.C., Değer O., Orem A., Uçar F., Erem C., Alver A., Onder E. – The effects of impaired trace element status on polymorphonuclear leukocyte activation in the development of vascular complications in type 2 diabetes mellitus, *Clin. Chem. Lab. Med.*, 2001, 39, 109-115.
24. Kinlaw W.B., Levine A.S., Morley J.E., Silvis S.E., McClain C.J. – Abnormal zinc metabolism in type II diabetes mellitus, *Am J Med*., 1983, 75, 273-277.
25. Mather H.M., Nisbet J.A., Burton Gh., Poston G.J., Bland J.M., Bailey P.A., Pilkington T. R.E. – Hypomagnesemia in diabetes, *Clin. Chem. Acta,* 1978, 95, 235-242.
26. McNair P., Christiansen C., Madsbad S., Lauritzen E., Faber O., Binder C., Transbøl I. – Hypomagnesemia, a risk factor in diabetic retinopathy, *Diabetes*, 1978, 27, 1075-1077.
27. Nair A.V., Hocher B., Verkaart S., van Zeeland F., Pfab T., Slowinski T., Chen Y.P., Schlingmann K.P., Schaller A., Gallati S., Bindels R.J., Konrad M., Hoenderop J.G. – Loss of insulin-induced activation of TRPM6 magnesium channels results in impaired glucose tolerance during pregnancy, *Proc. Acad. Sci. USA,* 2012, 109, 11324-11329.
28. Nazıroğlu M. – TRPM2 cation channels, oxidative stress and neurological diseases: where are we now? *Neurochem Res*., 2011, 36, 355-366.

29. Nechifor M., Danila Gh., Paduraru I., Teslariu E., Filip C., Negru A. – The influence of magnesium acexamate and zinc acexamate on peroxidic radicals generation in experimental induced intoxication in rats, Abstracts book, p.57, in "*6th European Magnesium Congress*", Budapest, 1998.
30. Nechifor M., Teslariu E., Mindreci I., Mihailovici S., Matei V., Filip C., Miftode M., Danila Gh. – The Influence of Magnesium, Chromium and Copper in Alloxan – Induced Diabetic Rats. pp.375-380, in "*Advances in Magnesium Research-Nutrition and Health*" (Yves Rayssiguier Y., Mazur A., Durlach J., Eds.), John Libbey Eurotext, Eastleigh, England 2001.
31. Pham P.C., Pham P.M., Pham P.T. – Patients with diabetes mellitus Type 2 and hypomagnesemia may have enhanced glomerular filtration via hypocalcemia, *Clin. Nephrol.*, 2012, 78, 442-448.
32. Quarterman J, Mills CF, Humphries WR. The reduced secretion of, and sensitivity to insulin in zinc-deficient rats, *Biochem. Biophys. Res. Commun.,* 1966, 25, 354-358.
33. Rayssiguier Y., Gueux E., Brussiere L., Durlach J., Mazur A. – Dietary Magnesium affects susceptibility of lipoproteins and tissue to peroxidation in rats, *J. Am. Coll. Nutr.,* 1993,12, 133-137.
34. Rodríguez-Rodríguez E., Bermejo L.M., López-Sobaler A.M., Ortega R.M. – An inadequate intake of manganese may favour insulin resistance in girls, *Nutr Hosp*., 2011, 26, 965-970.
35. Srinivasan A.R., Niranjan G., Kuzhandai Velu V., Parmar P., Anish A. – Status of serum magnesium in type 2 diabetes mellitus with particular reference to serum triacylglycerol levels, *Diabetes Metab Syndr.,* 2012, 6, 187-189.
36. Stoica B.A., Rusu M., Petreus T., Nechifor M. – Manganese SOD Mimics Are Effective Against Heat Stress in a Mutant Fission Yeast Deficient in MitochondrialSuperoxide Dismutase, *Biol. Trace Elem. Res.,* 2011, 144, 1344-1350.
37. Tanaka A., Kaneto H., Miyatsuka T., Yamamoto K., Yoshiuchi K., Yamasaki Y., Shimomura I., Matsuoka T., Matsuhisa M. – Role of the copper Ion in the Pathogenesis of Type 2 diabetes, *Endocrine J.*, 2009, 56, 699-706.
38. Tarasov A.I., Semplici F., Ravier M.A., Bellomo E.A., Pullen T.J., Gilon P., Sekler I., Rizzuto R., Rutter G.A. – The mitochondrial Ca2+ uniporter MCU is essential for glucose-induced ATP increases in pancreatic β-cells. PLoS One. 2012;7: e39722.
39. Viktorínová A., Toserová E., Krizko M., Duracková Z. – Altered metabolism of copper, zinc, and magnesium is associated with increased levels of glycated hemoglobin in patients with diabetes mellitus, *Metabolism*, 2009, 58, 1477-1482.
40. Walter R.M.Jr, Uriu-Hare J.Y., Olin K.L., Oster M.H., Anawalt B.D., Critchfield J.W., Keen C.L. – Copper, zinc, manganese, and magnesium status and complications of diabetes mellitus, *Diabetes Care.,* 1991, 14, 1050-1056.
41. Wollheim C.B., Sharp G.W. – Regulation of insulin release by calcium, *Physiol Rev*., 1981, 61, 914-973.
42. Yamagishi S. – Calcium antagonists: current and future applications based on new evidence. Calcium antagonists and diabetes. *Clin Calcium*., 2010, 20, 77-82.
43. Zargar A.H., Shah N.A., Masoodi S.R., Laway B.A., Dar F.A., Khan A.R., Sofi F.A., Wani AI. – Copper, zinc, and magnesium levels in non-insulin dependent diabetes mellitus. *Postgrad Med J.,* 1998, 74, 665-668.
44. Zeng B., Chen G.L., Xu S.Z. – Divalent copper is a potent extracellular blocker for TRPM2 channel, *Biochem Biophys Res Commun.*, 2012, 424, 279-284.