The possible role of magnesium deficiency in diabetic nephropathy

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Zusammenfassung

Bis heute gibt es über den Einsatz von Magnesium beim Diabetiker keine klinisch überzeugenden Daten. Aber es gibt eine Reihe attraktiver Hypothesen aufgrund biochemischer und molekularbiologischer Forschung, die vernünftige Anhaltspunkte für die Annahme geben, daß Magnesiummangel den Prozeß auf dem Wege zu diabetischen Spätschäden beschleunigt und verstärkt. Die Autoren versuchen mit dieser Arbeit, einen verständlichen Überblick der relevanten Literatur zu geben. Aufgrund neuerer Daten der Amerikanischen Diabetes Gesellschaft besteht kein Zweifel daran, daß bei der Betreuung von Diabetikern mehr auf die Entwicklung eines Magnesiummangels geachtet und spezifisch therapiert werden sollte, da Magnesiummangel bei Diabetikern mit höherer Prävalenz auftritt. Ob die prophylaktische Gabe von Magnesium bei Diabetikern ohne Magnesiummangel nützlich ist, um die Entwicklung der diabetischen Spätschäden günstig zu beeinflussen, ist noch unklar. Angesichts einer immer größeren Anzahl von Diabetikern unter den Patienten an der Dialyse mit entsprechend hohen Behandlungskosten und individuellem Leid, scheint es gerechtfertigt, aufgrund des generellen zytoprotektiven Effekts von Magnesium solches zur supportiven Therapie als Sekundär- und Tertiärprävention beim Diabetiker einzusetzen.

Summary

The rationale for magnesium application in diabetes is speculative. But there are some attractive hypothesises based on molecular and biochemical research demonstrating how magnesium deficiency may enhance and accelerate the process resulting in diabetic late complications. The authors surveyed the relevant literature to stimulate further research in the field. The effort to find out if there is magnesium deficiency or not in diabetics has to be improved. Beside serum magnesium measurement we propose to apply the magnesium loading test. And there is no doubt that diabetics with magnesium deficiency have to be supplemented. In patients without magnesium deficiency it is not clear if magnesium application is also useful to avoid or to slow down the progression of diabetes late complications. But in general, it is true that magnesium deficiency enhances cytotoxic effects of whatever origin and that plentiful magnesium supply protects against toxic and pathological influences.

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Introduction

The number of patients suffering from diabetes long-term complications has increased. Prevalence of patients with diabetic nephropathy in patients on renal replacement therapy is 25% in Europe, but its incidence increased over 50% during the last years. Hyperglycemia is the leading cause of diabetes long-term complications [6]. Vascular dysfunction is induced thereby by multiple pathways. First, there is atherosclerosis which occurs more extensively and earlier than in the general population. Second, there is a specific microangiopathy with a thickening of the capillary basement membran and an increase of both carbohydrate and protein components, especially type IV collagen as main feature. The cells of the mesangium increase in size and number and intend to produce to much of extracellular matrix which expands and reduces filtration surface of single nephrons. Thus, there is an increase of filtration pressure in the remaining intact nephrons, which is followed pathophysiologically by microalbuminuria and finally increasing proteinuria and a decrease of glomerular filtration rate depending on the progression of interstitial fibrosis and glomerulosclerosis. Beside hyperglycemia there are numerous progression factors of diabetes late complications such as hyperlipidemia or dyslipidemia, oxidative stress, endothelial dysfunction, increased platelet adhesiveness and so on. In addition, the prevalence of hypomagnesemia or magnesium deficiency were shown to be increased in diabetes [3, 8, 9, 19] and may be involved in the progression of diabetes complications [8, 11]. In the following the key role of hyperglycemia in the pathophysiology of diabetes complications is highlightened, especially regarding the possible role of magnesium.

Pathophysiological mechanisms

I. Activation of proteinkinase C [PkC]

High intracellular glucose levels cause glycolysis which secondary stimulates via diacylglycerol proteinkinase C in an organspecific manner. Activation of this important signal transduction pathway can have multiple consequences:

- increase of the expression of growth factor such as vascular endothelial growth factor (VEGF), endothelial growth factor (EGF) and platelet derived growth factor (PDGF) [18]
- activation of cytosolic phospholipase A_2 (c PLA_2) and increased production of arachidonic acid (AA) and prostaglandines (PGs). PGE_2 dilates microvessels and could be responsible for the early rise of GFR.

In progressing diabetic nephropathy the concentrations of the dilatatory prostaglandines PGE_2 and PGI_2 decrease, but the vasoconstrictoric prostaglandines PGH_2, PGG_2 and thromboxane A_2 (TXA_2) increase, clinically resulting in a fall of glomerular filtration rate and increased filtration pressure in the remaining intact nephrons, damaging the integrity of the basal membrane and leading to proteinuria [4, 5]. In addition the increased activity of $cPLA_2$ - caused by activated PkC - was shown to inhibit Na^+/K^+-ATPase. Inhibition of Na^+/K^+-ATPase - which plays a direct role in regulating cell volume - was shown to result in cell swelling and even burst by ouabain [3]. Thus, preterm cell death especially along the renal tubular system and consecutively interstitial fibrosis may occur.

- PkC regulates gene expression involved in the protein turnover of

basement membran and extracellular matrix as well as production of glycosylation enzymes is affected. And very recently it was reported that hyperglycemia can also induce genes coding for inhibitory enzymes of cyclin-dependent kinases, which in turn are regulating enzymes of PkC [11, 17, 23].

II. Non-enzymatic glycation

High intracellular glucose reacts with circulating and tissue-structur proteins in a non-enzymatic and irreversible reaction and forms advanced glycation endproducts (AGEs). Restricted AGE-formation happens physiologically, but occurs extensively in chronic hyperglycemic states. The accumulation of AGEs causes pathological changes in the cell [8, 12, 1]:

- increased formation of reactive oxygen metabolites (ROM) and oxidative stress.
- oxidized proteins and lipids lead to dysfunction of cell membranes.
- interference with ligands of extracellular matrix and change of signal transduction pathways
- interaction with specific receptors (RAGEs) on monocytes, macrophages, endothelid and mesangium cells thereby influencing gene expression.
- induction of a pre-inflammatory state with depletion of cytokines in macrophages by AGE-RAGE interaction leading to enhanced PkC-activity.
- alteration of the expression of genes responsible for protein turnover of membranes and extracellular matrix in endothel and mesangium cells following AGE-RAGE interaction.
- the physiological endothelial response to nitric oxide (NO) is supressed by AGEs, which could be responsible for hypertension and rapid progression of micro- and macrovessel disease.

III. The polyol-pathway and redox alterations

In hyperglycemia more glucose is reduced to sorbitol with a consumption of NADPH. Catalyzed by polyoldehydrogenase, sorbitol is oxidized to fructose in a second step thereby increasing NADH concentration. An activated polyol-pathway is associated with stimulation of $cPLA_2$ and a decreased Na^+/K^+-ATPase activity [4, 3, 11]. A high $NADH/NAD^+$ ratio - called pseudohypoxia - causes an increase of reactive oxygen metabolites reducing antioxidative capacities and increasing oxidative stress. And in addition low NADPH levels stimulate diacylglycerol (DAG) via the pentose phosphate shunt enhancing the PkC pathway mentioned above. Pathophysiologically the following biochemical alterations may occur:

- polyoles increase intracellular osmolarity because of their polarity and cell membranes get more leaky for sodium and chloride ions: an increasing amount of water enters the cell.
- changes of intracellular electrolyte metabolism such as inhibition of the sodium/calcium exchanger increase the Na^+/Ca^{2+}-ratio, whereas potassium decreases and $cPLA_2$ is activated.
- imbalance of the ROM/antioxidants-relation leads to oxidative stress, lipidperoxidation, membrane dysfunction and causes damage of vasculature, glomeruli and enhanced production of extracellular matrix.

Possible impact of Magnesium

Mg-deficiency seems to contribute to diabetic nephropathy [8, 9, 19, 21]. The prevalence of magnesium deficiency among diabetics is not known at the very moment. But from the pathophysiological point of view one has to consider that hyperglycemia causes osmotic diuresis whereby renal magnesium reabsorption mechanisms will be hampered. That is why we expect renal magnesium wasting in diabetics with a bad metabolic control and the development of magnesium deficiency in this patients. A respective clinical trial was begun. And in addition there are some findings underlining a relationship between magnesium and glucose homeostasis [15] which may even involve an interaction at the binding of insulin to its receptor [16, 14].

The authors tried to give a comprehensive scheme of the molecular mechanisms and biochemical processes involved in the pathogenesis of diabetes late-complications in figure 1. Possible sites of the impact of magnesium are indicated therein and summarized as follows:

1. Magnesium regulates oxidative stress. It was shown that a lack of magnesium results in an increased production of reactive oxygen meta-

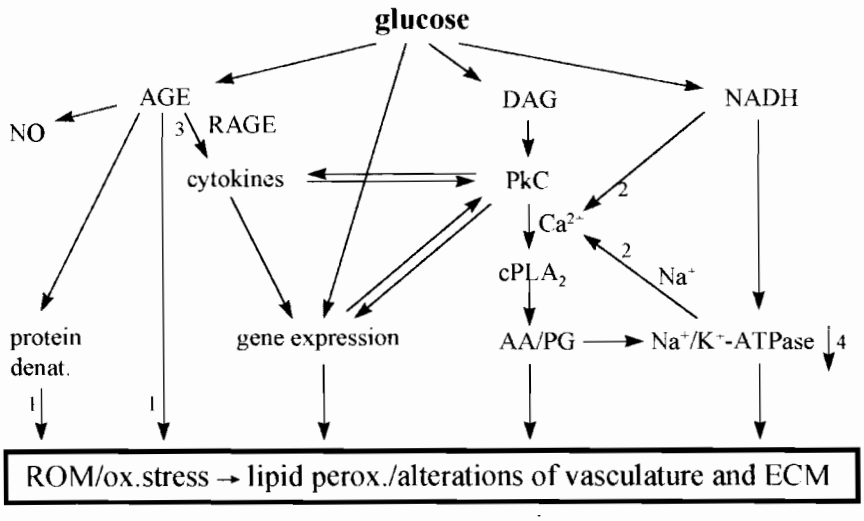

Fig. 1: **Pathophysiological pathways of hyperglycemia leading to diabetic nephropathy.** (Abreviations: AGE: advanced glycation endproducts. RAGE: receptors for advanced glycation endproducts. NO: nitric oxide. DAG: diacylglycerol. PkC: proteinkinase C. $cPLA_2$: cytosolic phospholipase A_2. AA: arachidonic acid. PG: prostaglandines. ROM: reactive oxygen metabolites. ECM: extracellular matrix. perox: peroxidation. ox: oxidative. denat: denaturation. Numbers 1-4: pathway which may be influenced by Mg^{2+}; explanation in the text.)

bolites (ROM), oxidative stress and its complications. Neuromuscular activity is increased, and catecholamine depletion induces a sympathikotonia antagonizing the effect of insulin.

2. During hypomagnesemia the cell looses potassium and sodium, whereas calcium accumulates and - similar to the results of the polyol-pathway - leads to an enhanced synthesis of prostaglandines and thromboxane.
3. Magnesium affects the metabolism of cytokines and transscription-factors, altering thereby the metabolic pathway AGEs - cytokines - PkC and affecting the activity of cPA_2 and prostaglandin-synthesis.
4. Additionally in magnesium deficiency Na^+/K^+-ATPase is inhibited.

Should we supply magnesium as well as antioxidants in the treatment of diabetes? The role of magnesium in the pathophysiology of diabetes late complications is speculative just to now. Very recently it was shown in obese zucker rats that after 8 weeks of high dietary magnesium intake glycosuria and glycated hemoglobin were reduced [22]. If hyperglycemia is the main pathophysiological movens in the development of diabetes complications, one has to expect a positive impact of magnesium therein. The results of a long term study in diabetic rats will be published in a few months.

The American Diabetes Association already recommends to substitute magnesium in case of magnesium deficiency [2]. But they propose to do MR-phosphorous spectroscopy for the detection of magnesium deficiency which is to expensive and time consuming for routine application. Our group is investigating at the very moment the prevalence of magnesium deficiency in diabetics using the magnesium loading test modified for outpatients [7].

Concluding remarks

The rationale for magnesium application in diabetes is speculative. But there are some attractive hypothesises demonstrating how magnesium deficiency may enhance and accelerate the processus resulting in diabetic late complications at a molecular and biochemical level. Experimental work will give further evidence to verify the hypothesises. It is unlikely that the short-term application of magnesium may yield convincing results. Therefore, long-term interventional clinical trials over decades are necessary to study the impact of magnesium upon late complications, but they are difficult to achieve.

The effort to find out if there is magnesium deficiency or not in diabetics has to be improved. Beside serum magnesium measurement we propose to apply the magnesium loading test [7]. And there is no doubt that diabetics with magnesium deficiency have to be supplemented. In patients without magnesium deficiency it is not clear if magnesium application is also useful to avoid or to slow down the progression of diabetes late complications, and further investigations have to be done. In general, there is no doubt that magnesium deficiency enhances cytotoxic effects of whatever origin and that plentiful magnesium supply protects against toxic and pathological influences [10].

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