

MAGNESIUM URINARY EXCRETION IN DIABETIC ADOLESCENTS

Žaneta Drižiene¹, Donatas Stakisaitis², Janina Balsiene³Vilnius University, Medical Faculty, Lithuania: Centre of Pediatrics¹, Institute of Oncology²; M. Romeris University, Lithuania: Study Center for Central and Eastern Europe³

Summary: Objective: to define peculiarities of urinary magnesium (Mg) excretion in diabetic adolescents; to elucidate gender-related differences in Mg urinary excretion; to determine urinary Mg excretion differences between diabetic and age-matched healthy children. The diurnal, nocturnal and 24-h urinary Mg level in adolescent boys and girls (aged 13–17 years) with type I diabetes mellitus (DM) and in age-matched control groups of healthy boys and girls was examined. Additionally the adolescent girls were examined during different phases of their menstrual cycle. Results: Diurnal, overnight and 24-h Mg urinary excretion in diabetic adolescent boys and girls was significantly higher than in healthy ones. In diabetic boys 24 h Mg excretion was higher than in diabetic girls (4.59 ± 1.4 vs. 3.34 ± 1.5 mmol; $p < 0.05$). The investigation showed gender-related differences in Mg urinary excretion in healthy adolescents: 24-h Mg urinary excretion was significantly higher in boys than in girls (2.66 ± 0.9 vs. 2.1 ± 0.9 mmol; $p < 0.05$). The level of Mg in the nocturnal urine of boys and girls was significantly higher than in diurnal. Urine Mg was negatively related to height in adolescent girls. Conclusion: Diabetic adolescents excrete significantly more Mg with urine as compared to healthy ones.

Key words: Adolescent; Magnesium; Gender; Menstrual cycle; Diabetes mellitus

Introduction

Current epidemiological, clinical and experimental data suggest that the pathogenesis of primary arterial hypertension may be gender-related. Men tend to have a higher predisposition to hypertension (19). The same antihypertensive treatment has different efficacy in men and women (43, 27). Decreased blood and tissue magnesium (Mg) may predispose to arterial hypertension (4). Experimental data show that the increased gender-dependent vascular reactivity may be related to changes in extracellular or intracellular Mg ion level (1, 48, 16). Clinical data concerning Mg effects on blood pressure are highly contradictory (14). Higher Mg urinary excretion may predispose to Mg depletion in hypertensive subjects (26). Our previous investigations had revealed changes in Mg urinary excretion in hypertensive adolescent boys: 24-h Mg urinary excretion was found significantly higher in hypertensive than in normotensive adolescent boys (42).

Hypermagnesuria is not related to blood Mg concentration (5). Studies in children failed to reveal a statistically significant dependence of urinary Mg excretion on Mg intake with food (46). No clear dependence was found between Mg excretion and Mg intake with medicinal preparations in adult subjects either (6).

In diabetic patients, Mg levels in bones and muscles, as well as in erythrocytes are decreased (10,41). Hypomagne-

semia in diabetes mellitus (DM) patients can be related not only to inclination to hypertension, but also to the development of diabetic angiopathy (31, 32). Low concentrations of ionised Mg in blood serum is characteristic of DM children (20).

In this article, we have presented data on diurnal, nocturnal, and 24-h Mg excretion in DM adolescents of both sexes. We have investigated whether Mg excretion is dependent on day and night variability. The control group of girls was examined during the different phases of their menstrual cycle.

Materials and methods

Mg urinary level was investigated in 23 adolescent boys and 32 adolescent girls aged 13 through 17 years with type I diabetes mellitus. The children were treated with insulin. DM had been diagnosed no less than 6 months before study. The patients attend the hospital diabetic clinic for full clinical and biochemical assessment. In all patients before recruiting DM had been compensated for no less than two months; their received standard care with adjusted insulin dosage. Within the study period, no concomitant diseases were diagnosed in the children. No diabetic children with retinopathy, chronic renal lesion, microalbuminuria, proteinuria were enrolled, and all patients had a normal serum creatinine level.

Results

In diabetic girls and boys the diurnal diuresis was: 0.96 ± 0.5 l (duration 14.8 ± 0.9 h) in girls and 1.1 ± 0.6 l in boys (14.6 ± 0.8 h), nocturnal 0.58 ± 0.3 l (duration 9.2 ± 0.9 h) and 0.65 ± 0.3 l (9.4 ± 0.8 h), respectively. DM duration in girls was 5.9 ± 3.7 and in boys 6.3 ± 3.8 years. The diabetic adolescents' body weight and BMI are presented in Tab. 1.

Mg was monitored in the diurnal and nocturnal urine of healthy postpubertal boys ($n=27$) and girls ($n=42$) aged 13–17 years (Tab. 1). The control groups comprised age-matched children with no consideration to their sexual maturity level. The children received no special food or liquid diets, their physical activity was usual. The study groups contained no adolescents actively going in for sports. Urine was collected according to the accepted procedure. The children were advised to keep regular sleeping hours: to go to bed at about 9–10 p.m. and to get up at about 7–8 a.m. Diurnal urine was collected throughout the day, excluding the first urination after awakening in the morning and including the last urination before going to bed. Nocturnal urine was collected during the first urination just upon awakening in the morning and during awakenings at night if necessary. The diurnal diuresis was 0.5 ± 0.3 l (duration 13.6 ± 1.3 h) in girls and 0.49 ± 0.25 l in boys (13.7 ± 1.7 h), nocturnal diuresis being 0.29 ± 0.15 l (duration 10.4 ± 1.3 h) and 0.3 ± 0.2 l (10.3 ± 1.7 h), respectively.

Additionally urinary Mg excretion in healthy adolescent girls ($n=15$, mean age 14.8 ± 0.9) was monitored in different phases of their menstrual cycle. All the girls, who had regular menstrual cycles, were monitored on the days including the 5th day (during the follicular phase, when estrogen and progesterone levels were close to minimal), on the 13th day (during the ovulation phase, when estrogen level was maximal), and on the 20th day (during the luteal phase, when progesterone level was close to maximal).

Urinary Mg concentration was tested by spectrophotometry, using special kits for Mg investigation (*Aqua-Medica*, Poland).

The impact of various factors on Mg excretion was investigated by means of correlation analysis. Student's t test was used to show the significance of the data.

Permission to carry out the study was obtained from the Lithuanian Bioethics Committee (Protocol No. 01-35; 11.07.2001).

Magnesium urinary concentration and excretion in control groups. We have found that 24-h urinary excretion of Mg in boys was significantly higher as compared to girls (Tab.1). This difference was not related to diuresis. No significant differences in the day, night and 24-h urine volume of girls and boys were determined ($p > 0.05$). The level of Mg in the nocturnal urine of boys and girls was significantly higher as compared to the Mg level in diurnal urine (3.2 ± 0.7 vs. 2.5 ± 0.6 mmol/l; $p < 0.05$ in boys; and 2.9 ± 0.7 vs. 2.3 ± 0.9 mmol/l; $p < 0.05$ in girls, respectively).

There was a significant correlation between 24-h Mg urinary excretion and height ($r = -0.34$; $p < 0.05$) in healthy adolescent girls. This relationship was absent in age-matched boys ($r = 0.10$; NS).

Magnesium urinary level and excretion in DM patients. Diurnal, overnight and 24-h Mg excretion in diabetic boys was higher than in diabetic girls (Tab. 1). This difference was not related to diuresis (no significant differences in the day, night and 24-h urine volume of girls and boys were determined, $p > 0.05$).

The Mg level in the nocturnal urine was significantly higher compared to the diurnal urine of diabetic boys and girls (3.5 ± 1.2 vs. 2.6 ± 0.7 mmol/l; $p < 0.05$ in boys; and 3.0 ± 0.9 vs. 2.3 ± 0.9 mmol/l; $p < 0.05$ in girls, respectively).

Daily urinary Mg was positively related to weight both in DM boys and girls ($r = 0.40$ and $r = 0.37$ respectively; $p < 0.05$) as well as to body mass index (BMI) ($r = 0.37$ and $r = 0.42$ respectively; $p < 0.05$).

Diurnal, overnight and 24-h Mg urinary excretion in diabetic boys and girls was significantly higher than in healthy ones (Tab. 1). First of all it was related to diuresis – the diurnal, nocturnal and 24-h volume of urine in diabetic girls and boys was significantly greater than in healthy ones ($p < 0.05$). The Mg/creatinine ratio in diurnal and nocturnal urine in diabetic girls and boys was significantly higher than in healthy ones ($p < 0.05$). The distribution according to Mg excretion level in the groups of healthy and DM children is shown in Fig. 1.

24-h urinary Mg excretion per kilogram of body weight in diabetic girls was definitely higher than in healthy girls (0.065 ± 0.01 vs. 0.04 ± 0.02 ; $p < 0.01$). The difference was de-

Tab. 1: Height, body weight and Mg excretion in urine data of examined adolescents.

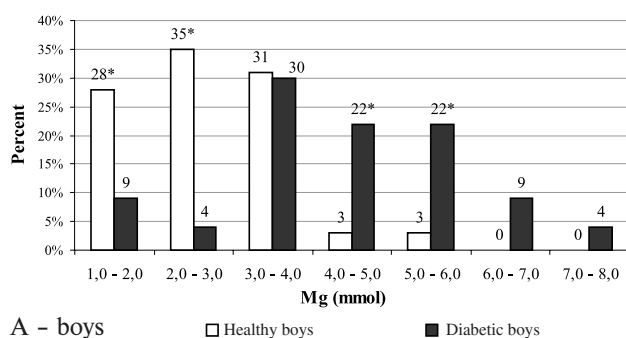
Investigated adolescents groups	n	Height (cm)	BMI	Urinary excretion of Mg (mmol)		
				Diurnal	Nocturnal	24-h
Healthy boys	27	174.2 ± 8.2	19.9 ± 2.2	1.45 ± 0.7	1.19 ± 0.5	$2.66 \pm 0.9^*$
Healthy girls	42	165.2 ± 6.4	20 ± 20.1	1.23 ± 0.6	0.88 ± 0.4	$2.1 \pm 0.9^*$
Diabetic boys	23	169.2 ± 7.1	20.4 ± 3.6	$2.59 \pm 1.2 \blacktriangledown$	$2.0 \pm 0.8 \blacktriangledown$	$4.59 \pm 1.4 \blacktriangledown$
Diabetic girls	32	163.2 ± 3.2	20 ± 3	$1.9 \pm 1.1 \blacktriangledown$	$1.5 \pm 0.8 \blacktriangledown$	$3.34 \pm 1.5 \blacktriangledown$

* – $p < 0.05$, healthy boys versus healthy girls

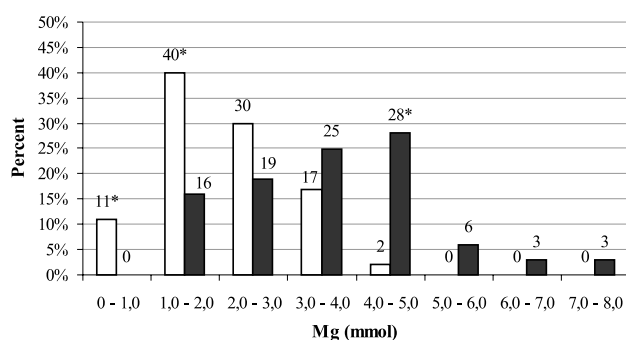
▼ – $p < 0.05$, DM boys versus DM girls

terminated by comparing this index in diabetic and healthy boys (0.085 ± 0.03 vs. 0.04 ± 0.01 ; $p < 0.01$). In diabetic boys, urinary Mg excretion per kilogram of body weight within 24-h was significantly higher than in diabetic girls (0.085 ± 0.03 vs. 0.065 ± 0.01 ; $p < 0.01$).

Girls of DM group exhibited a significant inverse correlation between 24-h Mg excretion and duration of the disease ($r = -0.48$; $p < 0.05$). Such relationship was not characteristic of boys ($r = -0.14$; NS). No significant correlation between 24-h Mg excretion and 24-h insulin dose was determined in the study groups of boys and girls ($r = -0.14$; NS in boys and $r = 0.14$; NS in girls).



A - boys □ Healthy boys ■ Diabetic boys



B - girls □ Healthy girls ■ Diabetic girls

Fig. 1: Distribution of urinary Mg excretion in the groups of healthy and diabetic adolescent. * - $p < 0.05$, compared data for healthy and diabetic subjects.

Discussion

Current knowledge suggests that Mg depletion may be involved in the pathogenesis of essential hypertension (34, 14). Clinical evidence indicates Mg supplementation sometimes to be a useful adjunct to the treatment of hypertension (26).

In DM patients, enhanced Mg excretion may be caused by 1) hyperglycemia and hyperglucosuria, which act as osmotic diuresis; 2) metabolic acidosis, which induces Mg excretion in the distal tubules (36); 3) hypophosphatemia and hypokalemia, which reduce Mg absorption in the loop of Henle and the distal tubule (9). Insulin enhances urine

accumulation in the thick ascending limb of the loop of Henle (9,30). Therefore increased Mg excretion is also related to insulin deficiency. DM children usually show a lowered ionised Mg concentration in blood serum, which is a sign of Mg depletion in the body (20).

Investigation of gender-related differences in Mg turnover may explain the higher prevalence of hypertension in men, as well as some mechanisms involved in the progression of this disease, and in diabetics, as an important risk group of essential hypertension. Some changes capable of contributing to hypertension in adulthood may be found in childhood.

Gender-related Mg turnover peculiarities in healthy subjects. We have found that 24-h urinary Mg excretion in adolescent boys is significantly higher than in adolescent girls. Differences in both 24-h urinary excretion and urinary level of Mg may result from gender-related physiological differences in its turnover. Magnesium balance depends on renal excretion, which is regulated mainly in the thick ascending limb of Henle's loop (23). Experimental data show age- and gender-related differences in reabsorption of Mg and calcium ions in renal tubules, but molecular mechanisms of such differences are still unclear (45).

Examination of serum Mg in children and adults did not show gender-related differences (21, 40, 2). Increased urinary Mg was not found to be associated with hypermagnesemia (5). Extensive trials did not show any significant correlation between urinary excretion and dietary intake of Mg in children (46). No correlation between the dose of oral Mg supplementation and urinary excretion of Mg in adults was found (6). Therefore some other gender-related factors and mechanisms were supposed to be involved in renal excretion of Mg and its depletion.

Depletion of Mg may be associated with relative insulin resistance, impaired glucose tolerance and hyperinsulinemia in normal subjects (37). Physiological doses of insulin markedly increase renal Mg excretion (12). It is known that there are gender-related differences in insulin resistance of cells and tissues. Insulin resistance is higher in men than and women (17).

There are gender-related differences in tissue Mg. Magnesium content in the girls' hair is significantly higher as compared to the boys' hair (25). Muscle Mg levels are significantly higher in women than in men (38). The reasons for such differences have not been disclosed yet, but they may be associated with the above-mentioned gender-related differences in Mg urinary excretion.

It has been clearly established that the observed circadian rhythm of blood pressure coincides with a rhythmic release of catecholamines (47). There are data showing the dependence of Mg urinary excretion on the activity of the sympatic nervous system (7), which is higher in men than in women (3). Therefore gender-related differences in diurnal and nocturnal blood pressure may be associated with Mg excretion differences in adolescent boys and girls (22).

Clinical evidence showed serum-ionised and total Mg to be significantly lower during the luteal phase than in the follicular and the ovulation phases of the menstrual cycle (33). Placebo-controlled clinical trials showed hormone replacement therapy with estrogens and progesterone producing a significant decrease in urinary excretion of magnesium (39). We failed to find any literature data on physiological mechanisms of the effect of female sex hormones on renal Mg excretion. Ovariectomy and estrogen supplementation had no effect on intestinal Mg absorption in female rats (8). Girls exhibited a significant negative correlation between 24-h urinary excretion of Mg and height. Height may be a risk factor of hypertension in boys (28,13).

There is a clear-cut evidence of a relationship between calcium and Mg homeostasis, and there are known gender-related differences in calcium transport across the cell membrane, metabolism, and excretion (18,45,24). Diurnal and nocturnal calcium urinary excretion differs in men and women. This phenomenon may be associated with gender-related circadian changes in serum growth hormone and parathyroid hormone (15). Growth hormone increases the urinary excretion of magnesium (29). A possible association between gender-related differences in calcium homeostasis and Mg excretion cannot be ruled out.

Investigation of mechanisms of the above-mentioned gender-related differences in children may explain predisposition to Mg deficiency-related conditions in adult males. These mechanisms can also suggest prophylactic means of Mg deficiency-related essential hypertension.

Mg turnover peculiarities in Type I DM patients. The study has shown that urinary Mg excretion levels in DM girls' and boys' diurnal, nocturnal and circadian urine are reliably higher than in healthy adolescents. First of all this is related to a significantly higher diuresis of DM post-pubertal children compared to the control group. Mg excretion level in diurnal urine of DM girls and boys showed a direct correlation with body weight and BMI, which was not defined in healthy ones. Mg excretion per kilogram of body weight in DM girls and boys was significantly higher than in healthy adolescents. Besides, the Mg/creatinine ratio in the diurnal, nocturnal and circadian urine of DM girls and boys was reliably higher than in healthy girls and boys. The higher Mg excretion in DM patients can be related to a number of factors. In DM patients, glucosuria disturbs the renal tubular reabsorption of cation from glomerular filtrate. However, in the presence of aglucosuria Mg excretion with urine in DM children remains abnormally high (35). It is a well-known fact that in DM children are increased glomerular filtration rate, however with no effect on Mg excretion (35,44).

Mg excretion in diurnal, nocturnal and 24-h urine was reliably higher in DM boys than in DM girls. We failed to find analogous data on Mg urinary excretion in DM children and its relation to gender. However, there were reports on a clearly reliably direct correlation between HbA₁ and Mg excretion in adult female patients with compensated

DM, though this correlation was not characteristic of analogous male patients (4).

DM girls exhibit an inverse correlation between Mg excretion and duration of the disease. Other authors report that Mg excretion also depends on the administered dose of insulin (12).

In spite of maintaining a normal blood glucose concentration, hypomagnesemia has been diagnosed in 25 per cent of patients (20). Mg turnover derangements and Mg deficiency in DM patients can be one of the reasons for arterial hypertension in diabetic patients (11).

Conclusion

Adolescent boys and girls ill with diabetes mellitus showed a significantly higher level of diurnal, overnight and 24-h urinary excretion than healthy ones. Diabetic girls and boys showed a direct relation of diurnal Mg excretion to body weight and body mass index. The higher Mg excretion might be indicative of a higher risk of Mg depletion.

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Dr. Donatas Stakisaitis,
Vilnius University, Medical Faculty,
Polocko 2, LT-2001, Vilnius,
Lithuania.
e-mail: donatasstakisaitis@VVKT.LT