Gender-related Magnesium Urinary Excretion in Type I Diabetes Mellitus in Adolescents

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Background: Decreased blood and tissue magnesium (Mg) may predispose to essential arterial hypertension, which is more frequent in males. Investigation of the physiological mechanisms of arterial blood pressure (BP) regulation in both sexes might explain this gender-related difference. Essential hypertension commonly manifests in adulthood, but may have a latent onset in childhood, so investigations of Mg turnover in children might help explain why male and type I diabetes mellitus (DM) patients of both sexes are more prone to essential hypertension.

Material and methods: Mg was examined in diurnal and nocturnal urine of healthy adolescent boys (n = 27) and girls (n = 42) aged 13–17 years. Urinary Mg (both during day and night) was monitored 24-h concomitantly with blood pressure (hourly) in healthy adolescents (n = 22). Mg urinary level was investigated in 23 adolescent boys and 32 adolescent girls aged 13–17 years with type I diabetes mellitus.

Results: The investigation showed gender-related differences in Mg urinary excretion in healthy adolescents: 24-h magnesium urinary excretion was significantly higher in boys than in girls (2.66 ± 0.9 mmol *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 ($r = –0.34$; $p < 0.05$) in adolescent girls.

Diurnal, overnight and 24-h Mg urinary excretion in diabetic adolescent boys and girls was significantly higher than in healthy ones. Urine Mg was positively related to weight ($r = 0.40$; $p < 0.05$) and body mass index ($r = 0.37$; $p < 0.05$) in diabetic adolescent girls. In boys with DM, Mg excretion with diurnal urine showed a direct dependence on the body mass index ($r = 0.42$; $p < 0.05$) and body weight ($r = 0.37$; $p < 0.05$). In diabetic boys diurnal, overnight and 24-h Mg excretion was higher ($p < 0.05$) than in diabetic girls (24-h Mg excretion 4.59 ± ± 1.4 *vs*. 3.34 ± 1.5 mmol; $p < 0.05$).

Conclusion: Mg urinary excretion is related to gender and height. Diabetic adolescents excrete significantly more Mg with urine as compared to healthy.

Key words*:* adolescent, magnesium in urine, gender differences, 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 [1]. The same antihypertensive treatment has a different efficacy in men and women (2, 3).

Decreased blood and tissue magnesium (Mg) may predispose to arterial hypertension [4]. Experimental data show that enhanced vascular reactivity, which is gender-dependent, may be related to changes in extracellular or intracellular Mg ion levels (5–7). Clinical data concerning the effects of Mg on blood pressure are highly contradictory (8). Higher Mg urinary excretion may predispose to Mg depletion in hypertensive subjects (9). Our previous investigations suggest 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 (10).

Hypermagnesuria is not related to blood Mg concentration (11). Studies in children failed to reveal a statistically significant dependence of urinary Mg

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excretion on Mg intake with food (12). Also, no clear dependence was found between Mg excretion and Mg intake with medicinal preparations in adult subjects (13).

In diabetic patients, Mg levels in bones and muscles, in erythrocytes are decreased (14, 15). Hypomagnesaemia in DM patients can be related not only to inclination to hypertension, but also to the development of diabetic angiopathy (16, 17). Low concentrations of ionised Mg in blood serum is characteristic of DM children (18).

We present data on diurnal, nocturnal, and 24-h magnesium excretion in healthy and DM adolescents of both sexes. As BP exhibits a circadian rhythm, we investigated whether Mg excretion is dependent on day and night variability.

MATERIALS AND METHODS

Mg was monitored in diurnal and nocturnal urine of healthy adolescent boys (n = 27) and girls (n = 42) aged 13–17 years (Table). Investigations were performed in 2000–2002. Urine was collected according to the directions. The children were advised to stick to a definite sleeping regime: 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, including the last urination before going to bed. Nocturnal urine was collected during first urination just upon awakening in the morning and during awakenings at night. In girls and boys the diurnal and nocturnal volumes diuresis were as follows: diurnal – 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.

Mg urinary level was investigated also in 23 adolescent boys and 32 adolescent girls aged 13–17 years with type I diabetes mellitus. The children were treated with insulin. DM had been diagnosed no less than 6 months before. In the study period, no concomitant diseases were diagnosed in the children. Neither there were patients in whom within 6 weeks ketoacidosis was confirmed clinically or by laboratory tests.

In diabetic girls and boys, the diurnal and nocturnal volumes diuresis were the following: diurnal – 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 ± 0.3l (9.4 ± 0.8 h), respectively.

The diabetes duration in girls was 5.9± 3.7 and in boys 6.3 ± 3.8 years. Data on the body weight and height of diabetic adolescents are presented in Table.

The study subjects were recruited with regard to urinary sedimentation: subjects with struvite sedimentation (triple phosphate crystals) were not involved. Struvite salts (but not others sediments) have been shown by us to be related to a significant decrease of Mg content in urine (19). Of 75 healthy adolescent urine samples, in 2 (2.6%) and of 57 DM patients in 2 (3.5%) struvite salts were found. Urinary sedimentation was determined after urine centrifugation by light microscopy (×100).

Urinary Mg concentration was tested by spectrophotometry, using special kits for Mg investigation (Seneca, Poland).

The impact of various factors on Mg excretion and the relation of Mg excretion to BP were investigated by means of correlation analysis. To show the statistical significance of the difference between two means, we used a Student's t test.

A permission from the Lithuanian Bioethics Committee (Prot. No. 01–35; 11.07. 2001) was obtained for carrying out the study.

RESULTS

Mg urinary concentration and excretion. We found a 24-h urinary excretion of Mg in boys to be significantly higher than in girls (Table). 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 than in diurnal 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).

In healthy adolescent girls there was a significant correlation between 24-h Mg urinary excretion

Table. **Data on height, body weight and Mg urinary excretion of adolescents**

Adolescent groups	n	Height cm	Body weight kg	Urinary excretion of Mg (mmol)		
				Diurnal	Nocturnal	24-h
Healthy boys	27	174.2 ± 8.2	60.6 ± 8.6	1.45 ± 0.7	1.19 ± 0.5	2.66 ± 0.9
Healthy girls	42	165.2 ± 6.4	55.7 ± 8.9	1.23 ± 0.6	0.88 ± 0.4	2.1 ± 0.9
Diabetic boys	23	169.2 ± 7.1	57 ± 11.8	2.59 ± 1.2	2.0 ± 0.8	4.59 ± 1.4
Diabetic girls	32	163.2 ± 3.2	53.9 ± 9	1.9 ± 1.1	1.5 ± 0.8	3.34 ± 1.5

and height (r = –0.34; p < 0.05). Such a relationship was absent in adolescent boys (r = 0.10; NS).

Mg urinary level and excretion in DM patients. In diabetic boys diurnal, overnight and 24-h Mg excretion was higher than in diabetic girls (Table). 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).

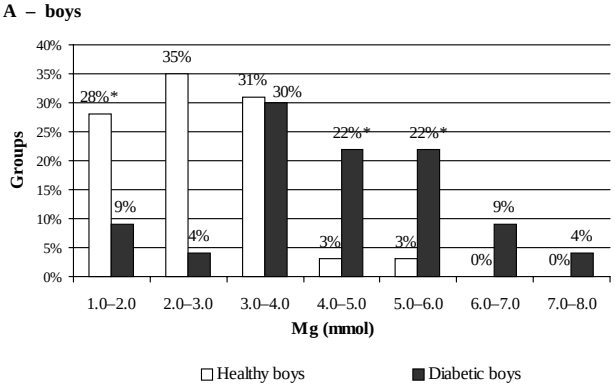
The level of Mg for diabetic boys and girls in nocturnal urine was significantly higher than in diurnal (3.5 ± 1.2 *vs*. 2.6 ± 0.7 mmol/l, p < 0.05, in boys and 3.0 ± 0.9 *vs*. 2.3 ± 0.9 mmol/l; p < 0.05 in girls).

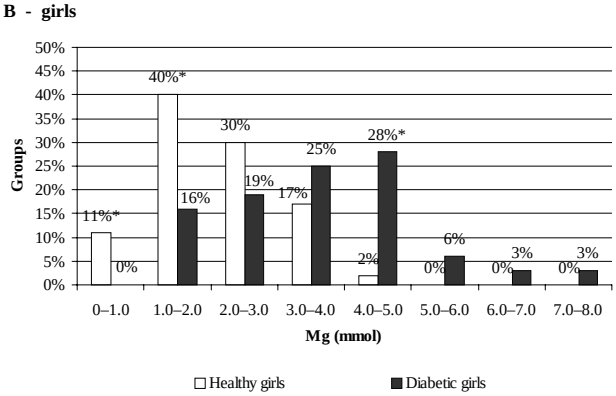
Urinary Mg was positively related to weight (r = = 0.40; p < 0.05) and body mass index (BMI) (r = = 0.37; p < 0.05) in diabetic adolescent girls. In diabetic boys, Mg excretion with diurnal urine directly depended on BMI (r = 0.42; p < 0.05) and on body weight (r = 0.37; p < 0.05).

Diurnal, overnight and 24-h Mg urinary excretion in diabetic boys and girls was significantly higher than in healthy ones (Table). This of first is all 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 girls and boys (girls (healthy *vs*. diabetic): diurnal 1.4 ± ± 2.5 *vs*. 0.31 ± 0.1, p < 0.01; nocturnal 1.3 ± 2.1 *vs*. 0.32 ± 0.1, p < 0.01; boys: diurnal 0.98 ± 1.9 *vs*. 0.30 ± 0.1, p < 0.01; nocturnal 1.26 ± 2.4 *vs*. 0.37 ± ± 0.4, p < 0.05).

The Mg excretion level was evaluated in the groups of healthy and DM children (Fig. 1).

In diabetic girls, Mg excretion per kilogram body weight in 24-h urine was definitely higher than in healthy girls (0.065 ± 0.01 *vs*. 0.04 ± 0.02; p < < 0.01). The difference was determined by comparing this index in diabetic and healthy boys (0.085 ± 0.03 *vs*. 0.04 ± 0.01; p < 0.01). In diabetic boys, Mg excretion per kilogram body weight in 24-h urine was significantly higher than in diabetic girls (0.085 ± 0.03 *vs*. 0.065 ± 0.01; p < 0.01).





* p < 0.05, compared data for healthy and diabetic subjects.

Fig. 1. Distribution of urinary Mg excretion in the groups of healthy and diabetic adolescents

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

DISCUSSION

Current knowledge suggests that Mg depletion could be involved in the pathogenesis of essential hypertension (4, 8). Clinical evidence shows magnesium supplementation to be sometimes a treatment useful adjunct in hypertension (9).

In DM patients, enhanced Mg excretion can be caused by (1) hyperglycemia and hyperglucosuria, which act as osmotic diuresis; (2) metabolic acidosis, which induces Mg excretion in the distal tubules (20); (3) hypophosphataemia and hypokalaemia, which reduce Mg absorption in the loop of Henle and the distal tubule (21). Insulin enhances urine accumulation in the loop of Henle (21, 22). Therefore increased Mg excretion is related also to insulin deficiency. DM children usually show a lowered ionised Mg concentration in the blood serum, which is a sign of Mg depletion in the body (18).

Investigation of gender-related differences in Mg turnover might explain the higher prevalence of hypertension in men as well as some mechanisms involved in the progression of this disease and hypertension 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 found 24-h urinary Mg excretion in ado-

lescent boys to be significantly higher than in adolescent girls. Differences in both the 24-h urinary excretion and urinary level of Mg may result from gender-related physiological differences in its turnover. Glomerular filtration is the main mechanism involved in the urinary excretion of magnesium (23). Experimental data show age- and gender-related differences in reabsorption of magnesium and calcium ions in renal tubules, but the molecular mechanisms of such differences remain to be unclear (24).

Examination of serum Mg in children and adults didn't show gender-related differences (25, 26). Increased urinary Mg was not found to be associated with hypermagnesaemia (11). Extensive trials didn't show any significant correlation between urinary excretion and dietary Mg intake in children (12). No correlation between the dose of oral Mg supplementation and urinary Mg excretion in adults was found (13). Therefore some other gender-related factors and mechanisms are 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 (27). Physiological doses of insulin markedly increase renal magnesium excretion (28). Gender-related differences in insulin resistance of cells and tissues are known to exist. Insulin resistance is higher in male rats and men than in female rats and women (29).

There are gender-related differences in tissue Mg. Magnesium content in hair was significantly higher in girls than in boys (30). Muscle Mg levels were significantly higher in women than in men (31). The reasons for such differences haven't been disclosed yet, but they may be associated with the above-mentioned gender-related differences in Mg urinary excretion.

There are data showing Mg urinary excretion to depend on the activity of the sympatic nervous system (32), which is higher in men than in women (33). Therefore gender-related differences in diurnal and nocturnal BP may be associated with Mg excretion differences in adolescent boys and girls. Our investigations revealed different patterns of magnesium excretion relationship with BP in adolescent boys and girls. We found a significant positive correlation between nocturnal urinary Mg excretion and arterial blood pressure (systolic, diastolic and mean) in boys. Adolescent girls exhibited a significant negative correlation between their nocturnal Mg excretion and blood pressure (diastolic and mean) during the luteal phase of their menstrual cycle (34).

We failed to find any literature data on the physiological mechanisms of the effect of female sex hormones on renal Mg excretion. Ovarectomy and estrogen supplementation has no effect on intestinal Mg absorption in female rats (35).

Our investigations revealed a significant positive correlation of height with nocturnal and diurnal blood pressure in boys, but not in girls. 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 (36, 37).

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

Mg turnover peculiarities in Type I DM patients. Our studies showed that urinary Mg excretion levels in DM girls and boys in diurnal, nocturnal and circadian urine were reliably higher than in healthy adolescents. This difference can be explained first of all a by significantly higher diuresis of DM adolescents compared to control. Mg excretion level in diurnal urine of DM girls and boys showed a direct correlation with body weight and BMI, which was not the fact in healthy adolescents. Mg excretion per body weight kilogram in DM girls and boys was significantly higher than in healthy adolescents. Also, 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 cation reabsorption from glomerular filtrate. However, also in the presence of aglucosuria Mg excretion with urine in DM children remains abnormally high (38). It is a well-know fact that in DM children glomerular hyperfiltration is a frequent occurrence, however with no effect on Mg excretion (39).

In DM boys Mg excretion in diurnal, nocturnal and 24-h urine was reliably higher than in DM girls. We failed to find in the literature analogous data on Mg urinary excretion in DM children and its relation to gender. However, there are reports on a clearly reliable direct correlation between HbA_1 and Mg excretion in adult female patients with compensated DM, however, this correlation was not characteristic of analogous male patients (40).

DM girls exhibit an inverse correlation between Mg excretion and disease duration. Other authors report also on Mg excretion depending on the dose of insulin (16). Our data for children did not confirm this relationship.

Increased urinary Mg excretion in DM adolescent boys and girls can indicate a more frequent occurrence of Mg "hypersecretors" (*i.e.* of subjects with enhanced Mg excretion in their urine). In spite of maintaining a normal blood glucose concentration, in 25% of patients hypomagnesaemia was diagnosed (18, 41).

Mg turnover derangements and Mg deficiency in DM patients can be one of the reasons for arterial hypertension in diabetic patients (42).

CONCLUSIONS

Magnesium urinary excretion is related to gender and height. 24-h Mg urinary excretion was significantly higher in adolescent boys than in girls.

Boys and girls ill with diabetes mellitus showed a significantly higher level of diurnal, overnight and 24-h Mg excretion than healthy ones. Diabetic girls and boys showed a direct relation of Mg excretion to body weight and body mass index.

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CUKRINIU DIABETU SERGANČIŲ PAAUGLIŲ SU LYTIMI SUSIJUSI MAGNIO EKSKRECIJA ŠLAPIME

S a n t r a u k a

Sumažėjusi magnio jonų (Mg) koncentracija kraujyje ir audiniuose gali būti vienas iš arterinės hipertenzijos rizikos rodiklių. Vyrai yra labiau linkę sirgti hipertenzija. Mg apykaitos tyrimai aktualūs, nes negalima atmesti, kad pirminė arterinė hipertenzija, kuriai būdinga Mg stoka, prasideda vaikystėje, o jos klinikinis pasireiškimas dažniausiai atsiranda suaugus. Yra žinoma, kad sergantieji cukriniu diabetu (CD) sudaro arterinės hipertenzijos rizikos grupę. Mg kiekis CD sergančiųjų kauluose, raumenyse ir eritrocituose yra sumažėjęs, o sumažėjusi Mg koncentracija audiniuose gali lemti arterinio kraujospūdžio padidėjimą. Sumažėjusi jonizuoto Mg koncentracija kraujo serume (rodanti Mg išsekimą organizme) būdinga CD sergantiems vaikams. Straipsnyje pateikiami magnio ekskrecijos su šlapimu duomenys.

Tirta I tipo cukriniu diabetu sergančių paauglių (13–17 metų) mergaičių (n = 32) ir berniukų (n = 23) Mg ekskrecija dienos, nakties ir paros šlapime. Taip pat tirtas sveikų paauglių berniukų (n = 27) ir mergaičių (n = 42) Mg kiekis šlapime.

Tiriant CD sergančių berniukų ir mergaičių grupes, nustatyta, kad nakties šlapime Mg koncentracija patikimai didesnė nei dienos. Tyrimai parodė su lytimi susijusius magnio jonų išskyrimo su šlapimu skirtumus: CD sergančių berniukų Mg ekskrecija dienos, nakties ir paros šlapime yra patikimai didesnė nei mergaičių. Taip pat nustatėme, kad sveiki berniukai su šlapimu per parą išskiria statistiškai patikimai daugiau Mg nei mergaitės. CD sergančių berniukų išskirtas Mg kiekis vienam kilogramui kūno svorio (skaičiuojant paros šlapime išskirtą Mg) buvo aiškiai didesnis nei sergančių mergaičių. CD sergančių mergaičių ir berniukų dienos šlapimo tyrimai parodė tiesioginę Mg ekskrecijos koreliaciją su kūno svoriu ir kūno svorio indeksu ($p < 0,05$). CD sergančioms mergaitėms nustatyta atvirkštinė priklausomybė tarp Mg ekskrecijos paros šlapime ir ligos trukmės ($p < 0,05$), o sergantiems berniukams tokia koreliacija nebūdinga. Buvo rasta, kad per dieną, naktį ir parą išskirto Mg kiekis CD sergančių mergaičių šlapime buvo aiškiai didesnis nei sveikųjų ($p < < 0,01$). Taip pat Mg ekskrecija didesnė CD sergančių berniukų nei sveikų dienos, nakties ir paros šlapime ($p < < 0,01$).

Raktažodžiai: paaugliai, magnis šlapime, cukrinis diabetas, lytis