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ORIGINAL ARTICLE

The Effects of Subchronic Intake of Magnesium Hydrocarbonate-Rich Mineral Water on Body Weight and Cardiovascular Variables in Rats With Streptozotocin -Induced Diabetes

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Abstract

Background/Aim: Optimal intake of magnesium minerals is essential in maintaining the coordinated physiological functions of cells, tissues and organs. The importance of this element is reflected in the fact that it is the fourth most abundant cation in the human body, participating as a cofactor in more than three hundred enzymatic reactions. Its presence is necessary for the proper functioning of a number of vital functions, such as glycaemic control, the work of the heart and the vascular system and it can potentially play a role in the regulation of body weight. Aim of this study was to investigate the effects of subchronic intake of magnesium hydrocarbonate-rich water on changes in body weight, organ weight and cardiovascular variables in rats with streptozotocin-induced diabetes.

Methods: Wistar rats (n = 28) were divided into 4 groups: two control groups, on tap water (TW-C, n = 7) and magnesium hydrocarbonate-rich water (MW-C, n = 7); and two experimental groups with streptozotocin-induced diabetes, on tap water (TW-DM, n = 7) and magnesium hydrocarbonate-rich water (MW-DM, n = 7). The values of body weight, organ weight and cardiovascular parameters were compared after 6 weeks between control groups of rats on subchronic treatment with tap water (TW-C) and magnesium hydrocarbonate-rich water (MW-C) and between groups with streptozotocin-induced diabetes on tap water (TW-DM) and with magnesium hydrocarbonate-rich water (MW-DM).

Results: By comparing the values of cardiovascular parameters between groups, significant ($p < 0.05$) positive effects of magnesium hydrocarbonate-rich water were registered on the values of systolic and pulse blood pressure in diabetic rats fed with magnesium hydrocarbonate-rich water (MW-DM) compared to those fed with tap water (TW-DM). In contrast, no significant effect of magnesium hydrocarbonate on changes in body weight and organ weight was observed.

Conclusion: Based on the results, the beneficial effects of magnesium hydrocarbonate-rich water in the regulation of blood pressure can be clearly observed. Potential effects on other cardiovascular variables and body weight and organ weight should be further investigated.

Key words: Magnesium; Diabetes; Blood pressure; Body and organ weight; Rat.

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Introduction

Magnesium is the fourth most abundant cation in the human body, while at the intracellular level, it occupies the second place.[1] The body of a healthy person contains approximately 1,000 mmol of magnesium. About 60 % of magnesium is found in bones, of which 30 % is exchangeable and functions as a stabiliser of serum concentration. About 20 % is found in muscles, 19 % in other soft tissues and less than 1 % in extracellular fluid. Normal serum values of healthy individuals range from 0.7 to 1.1 mmol/L. Approximately 20 % of that value is bound to proteins, 65 % is ionised and the rest is complexed with various anions such as phosphate and citrate.[2] Magnesium participates as a cofactor in more than 300 enzymes and thereby regulates several basic functions such as muscle contraction, neuromuscular conduction, glycaemic control, myocardial contraction and blood pressure. In addition, magnesium plays a vital role in energy production and cellular energy metabolism, active membrane transport of other ions, cellular replication, protein synthesis and bone development.[3-5] Also, magnesium acts as an essential cofactor of several enzymes involved in carbohydrate metabolism and is very important in the regulation of heart rhythm, vascular tone, peripheral vascular resistance and endothelial function.[6, 7]

A significant connection between altered magnesium homeostasis and the occurrence of type 2 diabetes mellitus has been established. Numerous epidemiological studies indicate a high prevalence of hypomagnesaemia in subjects with type 2 diabetes and a faster progression of diabetes in hypomagnesaemia states has been observed.[8-12] Additionally, it has been observed that hypomagnesaemia is more present in people with pre-diabetes, insulin resistance or diabetes compared to the general population.[13] Low serum magnesium levels are associated with an increased risk of diabetes possibly via insulin resistance routes.[14] It has been shown that oral magnesium supplementation in patients with type 2 diabetes mellitus with hypomagnesaemia can improve glucose levels as well as insulin sensitivity after eating and during fasting.[15] Similar effects on sugar regulation were observed in rats with streptozotocin-induced diabetes, using mineral waters with iso-osmolar concentrations of magnesium.[16]

Magnesium-deficient diet and hypomagnesaemia conditions may be contributing factors in the pathophysiology of hypertension.[17] Considering the increasing prevalence and incidence of hypertension, the identification of effective and safe preventive measures that offer even modest blood pressure-lowering effects could have a significant impact on public health. Several lines of evidence from laboratory studies have suggested potential mechanisms by which magnesium exerts its effects on blood pressure. Magnesium can play a key role in the regulation of blood pressure by directly stimulating the formation of prostacyclin and nitric oxide, modulating endothelium-dependent and endothelium-independent vasodilation, reducing vascular tone and reactivity, as well as preventing vascular damage through its antioxidant and anti-inflammatory effects.[18-23] Besides, an inverse relationship between magnesium intake and blood pressure has been observed and epidemiological data show an increased incidence of hypertension in areas where water with small amount of magnesium is consumed.[24] Various observational and experimental studies emphasise the role of magnesium deficiency in the pathogenesis of hypertension.[25]

Hypomagnesaemia is also associated with an increased risk of developing cardiac arrhythmias.[26] Electrocardiogram (ECG) changes associated with magnesium deficiency vary and depend on the degree of magnesium loss. Mild hypomagnesaemia leads to sinus tachycardia, tall T wave and ST segment depression, while severe hypomagnesaemia causes shortening of the PQ interval, prolonged QRS and QTc.[27] Several studies have demonstrated an association between a low serum magnesium and an increased risk of developing premature ventricular contraction, ventricular tachycardia and polymorphic ventricular tachycardia (*torsades de pointes*).[26, 28-31] The use of magnesium, as a potent antiarrhythmic agent, is justified by a high percentage in patients with confirmed supraventricular arrhythmia and accompanying decrease in the intracellular concentration of magnesium with normal or reduced serum concentration. When administered as monotherapy, magnesium increases atrial antiarrhythmic efficacy.[32] Besides, magnesium therapy has been shown to be an effective therapeutic method in patients diagnosed with ventricular tachycardia.[25] The use of magnesium supplements can be potentially effective in the case when the patient suffers from ventricular tachycardia or ventricular fibrillation resistant to conventional therapy.[33]

Methods

The research was carried out within the project of the Ministry of Education, Science and Technological Development of the Republic of Serbia, No 200110/00402, ethically approved by the Ministry of Agriculture, Forestry and Water Management of the Republic of Serbia and based on the existing permission of the Ethics Committee for the Protection of the Welfare of Experimental Animals of the Faculty of Medicine of the University of Belgrade.

In this experimental study lasting for 6 weeks, male Wistar albino rats obtained from the vivarium of the Military Medical Academy in Belgrade were used, which at the beginning of the experiment were 25-30 days old and weighed around 160 g. The rats were kept individually in plexiglass-transparent cages, under constant ambient conditions (temperature 21 ± 2 °C; air humidity 55 ± 5 %; light-dark cycle for 12 h with the beginning of the light period at 07:30 h), with precise daily measurement of intake food and water. The bottom of the cage was lined with sand, and food and water were available *ad libitum*.

Diabetes mellitus (DM) was induced by a single administration of streptozotocin ($C_8H_{15}N_3O_7$, *Sigma-Aldrich*, *Darmstadt*, *Germany*) (100 mg/kg) in saline solution (0.9 % NaCl). Glycaemic values from blood samples from the tail vein were measured 72 h after streptozotocin injection and then weekly. Ordinary tap water or mineralised magnesium hydrocarbonate-rich water (oligomineral, magnesium hydrocarbonate, natural spring water "Mg Mivela" produced by *Nova Sloga d.o.o. Trstenik, Serbia*; with mineral composition (mg/L), cations: Mg^{2+} 343.000 Na^{+} 138.000 Ca^{2+} 21.670, K^{+} 9.510, anions: HCO_3^- 2109.400, Cl^- 13.400, SO_4^{2-} < 1.000, F^- 0.205, according to the manufacturer's declaration on the purchased products.

All experimental animals (28 in total) were divided into 4 groups (with 7 animals in each individual group):

1. The group that drank tap water plus a single intraperitoneal (ip) treatment with saline solution (0.9 % NaCl) (TW-C);
2. The group that drank mineralised water rich in magnesium hydrocarbonate plus a single ip treatment with saline solution (0.9 % NaCl) (MW-C);
3. The group that drank tap water plus a single ip treatment with streptozotocin (100 mg/kg) in saline solution (0.9 % NaCl) (MW-DM);
4. The group that drank mineralised water rich in magnesium hydrocarbonate plus a single ip treatment with streptozotocin (100 mg/kg body weight) in saline solution (0.9 % NaCl) (MW-DM).

The concentration of glucose in blood obtained from the tail vein was determined using an *ACCU-CHEK* analyser (*Roche Diabetes Care, Inc, Indianapolis, USA*). During the research, changes in body weight were registered weekly in all experimental groups. After the experimental period lasting 6 weeks, cardiovascular variables (systolic blood pressure, diastolic blood pressure, mean arterial pressure, pulse arterial pressure and heart rate) were evaluated by a non-invasive method through the tail artery [(Rat Tail Cuff Method Blood Pressure Systems (MRBP) -R), *IITC Life Science Inc, Los Angeles, CA, USA*)] and then animals were sacrificed with a rat guillotine when organ weights (heart, liver, right kidney, left kidney) were measured.

Statistical analysis

Statistical analysis of the data was done in the SPSS v 23.0 application. The normality of data distribution was tested with the Shapiro-Wilk test. ANOVA test with Tukey post hoc analysis was used to compare the statistical significance of the difference in parameter values between groups. P value of less than 0.05 in the test was considered a statistically significant difference.

Results

Comparison of body weight values between control groups of rats on magnesium hydrocarbonate-rich water (MW-C) and tap water (TW-C) and experimental groups of rats with streptozotocin-induced diabetes on magnesium hydrocarbonate-rich water (MW-DM) and tap water (TW-DM)

By comparing the values of body weights during a period of 6 weeks, a decrease in weight was observed ($p < 0.01$) in the experimental groups of rats MW-DM (175.40 ± 9.23 g) and TW-DM (168.00 ± 4.74 g) compared to control groups of rats MW-C (435.90 ± 9.08 g) and TW-C (433.40 ± 8.08 g) (Figure 1).

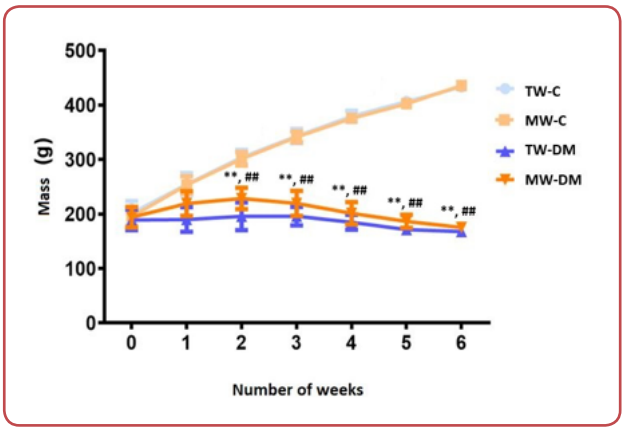

*Figure 1: Change in body weight of control (TW-C and MW-C, ** p < 0.01) and experimental (MW-DM and TW-DM, ## p < 0.01) groups of rats in a period of 6 weeks. A statistically significant decrease in body weight in the experimental groups is present compared to the control group*

Comparison of organ weight values between control groups of rats on magnesium hydrocarbonate-rich water (MW-C) and tap water (TW-C) and experimental groups of rats with streptozotocin-induced diabetes on magnesium hydrocarbonate-rich water (MW-DM) and tap water (TW-DM)

When examining the organ weight, a significantly lower heart weight ($p < 0.01$) was noted in the experimental groups MW-DM (0.95 ± 0.22 g) and TW-DM (0.91 ± 0.30 g) compared to the control groups MW-C (1.40 ± 0.11 g) and TW-C (1.40 ± 0.15 g). Additionally, a smaller liver weight ($p < 0.05$) was observed in the MW-DM experimental group (10.32 ± 2.32 g), compared to the TW-C control group (14.34 ± 1.77 g). No statistically significant differences were registered in the weight of the left and right kidneys comparing the experimental and control groups (Table 1).

Comparison of cardiovascular parameters between control groups of rats on magnesium hydrocarbonate-rich water (MW-C) and tap water (TW-C) and experimental groups of rats with streptozotocin-induced diabetes on magnesium hydrocarbonate-rich water (MW-DM) and tap water (TW-DM)

Statistical analyses revealed a significant decrease in systolic ($p < 0.05$) and pulse ($p < 0.01$) pressure in the experimental group of rats with streptozotocin-induced diabetes who drank magnesium hydrocarbonate-rich water (MW-DM; systolic blood pressure 111.50 ± 6.45 mm Hg; pulse pressure 41.50 ± 0.57 mm Hg), compared to the experimental group with diabetes that

Table 1: Comparison of body weight and organ weight (heart, liver, right kidney, left kidney) between control groups of rats on subchronic treatment with tap water (TW-C) and magnesium hydrocarbonate-rich water (MW-C) with groups of rats with streptozotocin-induced diabetes on subchronic treatment with tap water (TW-DM) and magnesium hydrocarbonate-rich water (MW-DM) for a period of 6 weeks

Parameters	Groups (mean value ± SD)			
	TW-C	MW-C	TW-DM	MW-DM
Body weight (g)	433.40 ± 8.08**, ##	435.90 ± 9.08**, ##	168.00 ± 4.74	175.40 ± 9.23
Heart weight (g)	1.40 ± 0.15**, ##	1.40 ± 0.11**, ##	0.91 ± 0.30	0.95 ± 0.22
Liver weight (g)	14.34 ± 1.77 #	13.39 ± 1.98	11.21 ± 2.37	10.32 ± 2.32
Right kidney weight (g)	1.49 ± 0.12	1.33 ± 0.17	1.35 ± 0.36	1.30 ± 0.47
Left kidney weight (g)	1.38 ± 0.53	1.26 ± 0.14	1.33 ± 0.29	1.43 ± 0.30

*Results are presented as mean ± SD. **p < 0.01 vs TW-DM; # p < 0.05 vs MW-DM; ## p < 0.01 vs MW-DM;*

Table 2: Comparison of the values of cardiovascular variables and glycaemia between control groups of rats on subchronic treatment with tap water (TW-C) and magnesium hydrocarbonate-rich water (MW-C) with groups of rats with streptozotocin-induced diabetes on subchronic treatment with tap water (TW-DM) and magnesium hydrocarbonate-rich water (MW-DM)

Cardiovascular variables and glycaemia	Groups (mean value ± SD)			
	TW-C	MW-C	TW-DM	MW-DM
TA systolic (mm Hg)	119.29 ± 5.19	121.43 ± 7.94	125.75 ± 8.42	111.50 ± 6.45*
TA diastolic (mm Hg)	77.86 ± 6.31	78.00 ± 7.83	73.75 ± 7.37	70.00 ± 6.48
TA mean (mm Hg)	91.67 ± 5.41	92.48 ± 7.58	91.083 ± 7.705	83.83 ± 6.47
TA pulse (mm Hg)	41.43 ± 5.29**	43.43 ± 4.47*	52.00 ± 1.41	41.50 ± 0.57**
Heart rate (min-1)	407 ± 16**, ##	413 ± 16**, ##	359 ± 14	361 ± 12
Glycaemia (mmol/L)	6.60 ± 0.26**	6.46 ± 0.60**	30.81 ± 17.58	13.97 ± 5.34*

*Results are presented as mean ± SD; TA – arterial blood pressure (lat. tensio arterialis); *p < 0.05 vs TW-DM; **p < 0.01 vs TW-DM; ## *p < 0.01 vs MW-DM;*

drank tap water (TW-DM; systolic blood pressure 125.75 ± 8.42 mm Hg; pulse pressure 52.00 ± 1.41 mm Hg). Significant lower pulse pressure values were observed in the control groups exposed to magnesium hydrocarbonate-rich water (MW-C; pulse pressure 43.43 ± 4.47 mm Hg; $p < 0.05$) and tap water (TW-C; pulse pressure 41.43 ± 5.29 mm Hg; $p < 0.05$), compared to the experimental group TW-DM (pulse pressure 52.00 ± 1.41 mm Hg). Besides, significantly higher heart rate values ($p < 0.01$) were registered in experimental groups MW-C (heart rate 413 ± 16 beats per minute) and TW-C (heart rate 407 ± 16 beats per minute), compared to experimental groups MW-DM (heart rate 361 ± 12 beats per minute) and TW-DM (heart rate 359 ± 14 beats per minute). Glycaemia was significantly higher in TW-DM group (30.81 ± 17.58 mmol/L) compared to all other groups: TW-C (6.60 ± 0.26 mmol/L, $p < 0.01$), MW-C (6.46 ± 0.60 mmol/L, $p < 0.01$), and MW-DM (13.97 ± 5.34 mmol/L, $p < 0.05$). By comparing the groups, no statistically significant differences were observed in the values of diastolic and mean arterial blood pressure (Table 2).

Discussion

The results of this study indicated a statistically significant decrease in body weight, heart and liver weight in the experimental groups with streptozotocin-induced diabetes (MW-DM and TW-DM) compared to the control groups (MW-C and TW-C). Similarly, earlier published study also compared body weight values between rats with streptozotocin-induced diabetes and a control group over a period of 10 weeks. During the first 7 days, a gradual decrease in body weight was observed in rats with diabetes, followed by a slight increase, which never returned to the initial values until the end of the follow-up period. At the same time, a constant increase in body weight was observed in the group of control rats. At the end of the ten-week follow-up, a statistically significant decrease in weight was recorded in the experimental group of rats with diabetes (334 ± 6 g) compared to the control group (484 ± 28 g).[34] Such data are in agreement with the results obtained in this research and indicate a connection between diabetes and the consequent decrease in body weight.

Numerous studies point out the potential role of magnesium as an important aetiological factor in the development of essential arterial hypertension. Although the pathogenesis and exact role of magnesium in regulation of blood pressure is still an unclear phenomenon, it has been established that magnesium affects the contractility of the smooth muscles of arterial blood vessels.[25] An extensive number of experimental studies in various animal models indicate a pathophysiological link between hypertension and lower blood or tissue magnesium content.[35-37] Besides, researchers successfully induced hypertension in rats whose diet was low in magnesium.[38] A similar correlation between primary magnesium deficiency and the development of essential hypertension has been observed in humans. A study conducted in Japan (participants were 380 students), showed a clear correlation between elevated values of systolic blood pressure or essential hypertension present in the family history and lower serum and erythrocyte values of magnesium ions. These findings indicate that magnesium nutritional deficiency is at least one of the potential factors in the development of essential hypertension in students with a positive family history, as well as that genetic predisposition to the development of hypertension is associated with primary magnesium deficiency.[39] Numerous studies have analysed the effect of consuming magnesium in the form of a food supplement on blood pressure. In an earlier published research, 70 subjects with high-normal blood pressure values were divided into two groups: the first consumed only water with a low mineral content for 4 weeks; while the second group in the same period drank water enriched with minerals, combined with natural mineral water. Among the subjects who initially showed a low level of magnesium excretion (which indicates a magnesium deficiency), those who consumed two mineral-rich waters during 4 weeks showed a statistically significant decrease in blood pressure values.[40] During a meta-analysis that included randomised double-blind placebo-controlled studies, it was proven that consuming magnesium in the form of supplements with a mean dose of 368 mg/day during an average time period of 3 months significantly reduced systolic blood pressure values by as much as 2.00 mm Hg (95 % CI 0.43 to 3.58) and diastolic blood pressure by 1.78 mm Hg (95 % CI 0.73 to 2.82). Additionally, decreased blood pressure values in the group receiving magnesium supplements were accompanied by an increase in serum magnesium values by 0.05 mmol/L (95 % CI 0.03 to 0.07), compared with placebo.[41] A similar study

showed that the consumption of magnesium as a dietary supplement leads to a small but certainly clinically significant reduction in both systolic (a decrease of 3-4 mm Hg) and diastolic blood pressure (a drop of 2-3 mm Hg).[42] These studies suggest that dietary magnesium has a potential to lower blood pressure in certain patient groups. The occurrence of ventricular tachycardia is mostly correlated with existing heart diseases, metabolic disorders, electrolyte imbalances, hypoxaemia or acidosis. However, it is known that conditions of hypomagnesaemia can have arrhythmogenic effects.[43] The results of performed tests did not show a statistically significant decrease in heart rate between the control group of rats fed with magnesium hydrocarbonate-rich water (MW-C) and those fed with tap water (TW-C). A significant decrease in heart rate was not observed between the experimental group with streptozotocin-induced diabetes drinking magnesium hydrocarbonate-rich water (MW-DM) and the group with streptozotocin-induced diabetes drinking tap water (TW-DM). However, in one study it was observed that the quartile of subjects with the lowest serum magnesium concentration had as much as a 50 % greater chance of developing atrial fibrillation, compared to subjects with normal and higher daily intake. When patients on diuretic therapy were excluded from the study, the results remained identical, suggesting that low serum magnesium concentration is associated with the development of atrial fibrillation even in patients without cardiovascular comorbidities.[44] Hypomagnesaemia is generally a common phenomenon among patients with clinically manifest atrial fibrillation,[45] which is why it is considered that the application of magnesium and thus the normalisation of hypomagnesaemia, can be used as a potential therapeutic modality in alleviating the symptoms of atrial fibrillation in patients on chronic digoxin therapy. Besides, the results of one study suggested that the application of magnesium can potentially reduce the prevalence of ectopic foci in the heart chambers in digoxin-treated patients with a diagnosis of chronic atrial fibrillation and accompanying hypomagnesaemia of low or moderate degree.[46] Such data from a large number of studies point to the potentially beneficial effects of magnesium in lowering and stabilising heart rhythm. The results of previous study conducted on rats with experimentally induced diabetes mellitus using streptozotocin, demonstrated the increase of the of serum glycaemia level and the changes of the lipid profile in these rats compared to the healthy controls. On the other hand, subchronic intake of magnesium hydrocarbonate-rich mineral water alone did not result in any significant changes of these parameters. Additionally, this study showed that subchronic intake of magnesium hydrocarbonate-rich mineral water in the control group of rats can result in decreased concentrations of fibrinogen. This finding could suggest possible new approach in the treatment of various pro-thrombogenic disorders.[47]

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Conflict of interest

None.

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