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Does Consumption of Magnesium-rich Bottled Water Improve the Outcome in Patients with Recurrent Urinary Tract Infections? An Observational Study

Panos Papandreou[1], Ioannis Karanikas[2], Katerina Maria Tassiou[3], Dimitrios Ntountaniotis[4], Maria Skouroliakou[5,*]

[1]First Department of Pediatrics, Medical School of Athens University, Athens, Greece
[2]Department of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece
[3]Faculty of Health Medicine and Life Sciences, University of Maastricht, Maastricht, Netherlands
[4]Department of Chemistry, National and Kapodistrian University of Athens, Athens, Greece
[5]Department of Nutrition and Dietetics, Harokopio University of Athens, Athens, Greece
*Corresponding author: mskour@hua.gr

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Abstract Lack of magnesium can be associated with an abnormal immune function, as proven in acute and chronic infections. Moreover, the literature suggests that patients with bacterial infections, on average, have a statistically significant decrease in serum magnesium concentration. The aim of this prospective quasi-experimental study was to examine and determine whether the consumption of magnesium-rich bottled water improves the outcome in patients suffering from recurring urinary tract infections (UTIs). More specifically, the idea was to compare the outcomes of such patients (who consumed the aforementioned water) with the outcomes of equivalent patients who consumed regular tap drinking water. Forty-four adult patients aged between eighteen and eighty-four years that had a history of recurrent UTIs, participated. Participants were divided into two groups based on the type of water they consumed. The patients that consumed the local tap drinking water constituted the group A (N=22) and the patients that consumed the magnesium-rich bottled water constituted the group B (N=22). The required daily water intake was 2.0-2.5 litres. The tests that patients underwent when they initially entered the study (T0) were the following, a) urine analysis, b) urine culture, and c) measurement of serum magnesium levels. Furthermore, these tests were repeated during a scheduled follow-up, which occurred nine months after the participants entered the study (T1). After nine months of the different type of water consumption, there was no statistically significant difference concerning the number of UTIs between the groups (group A - group B). Moreover, patient who belonged to group B, had statistically significant higher serum magnesium levels than those in group A, regardless of their age. More studies are necessary to determine the effect of consuming magnesium-rich water on recurrent UTIs.

Keywords: *urinary tract infections, drinking water, serum magnesium, water intake, bottled water*

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1. Introduction

Urinary tract infections are quite a common phenomenon. It is estimated that 70 % of women will endure a urinary tract infection at least once in their lifetime, of which the 30 % will experience recurrent urinary tract infections (UTIs) [1,2,3]. In women, bacteria will periodically enter the urinary bladder through the urethra in small quantities. Subsequently, small populations of bacteria may occasionally invade, multiply, and colonize the urinary tract. However, the appearance of the infection depends on the plethora of the bacterial population and the hosts' defence mechanisms [4].

If the bacteria form colonies in the bladder, this may result in an infection of the kidneys and may cause acute inflammation in the renal parenchyma. As a result, urinary tract infection causes acute morbidity and long-term effects, including hypertension and decreased renal function [5]. Recurrent UTIs are defined as at least 2 incidents within 6 months, or up to 3 incidents per year [6]. The symptoms of urinary tract infection are as follows: i) intense urination, ii) burning sensation in urine, iii) frequent urination with small amounts of urine, iv) hematuria, v) malodorous urine and vi) pelvic pain [7,8].

For the treatment and prevention of UTIs, it is recommended that inflicted individuals consume considerable amounts of water. Increased diuresis contributes to the elimination of pathogenic germs and frequent urination

reduces the proliferation of bacteria in the bladder. There is also a positive correlation between osmoticity and antibacterial activity within urine. In contrast, the reduced frequency of urination which occurs during the night and in mild urination conditions, contributes to the growth of the bacterial populations [9].

Urinary frequency induces high antibacterial activity through the intrinsic mechanisms of the organism [10]. Therefore, the frequent intake of liquids which result in an increased urinary frequency, elicits a significant reduction of microorganisms in patients with bacteriuria [11].

The role of magnesium in the immune response is well documented. Many studies have emphasized the role of magnesium in the defense mechanisms of the human body and have specifically highlighted how magnesium ions are involved in various stages of the immune response [12]. It is recognized that magnesium is essential for lymphocyte production and that it can stimulate the synthesis of immunoglobulins (except IgE immunoglobulins). Consequently, lack of magnesium can be associated with an abnormal immune function, as proven in acute and chronic infections [13]. T-lymphocytes are very sensitive to the action of various divalent cations, including magnesium (T-lymphocyte proliferation is inhibited) [14]. Severe magnesium deficiency inhibits B-cell production [15,16]. According to a study, patients with bacterial infections, on average, have a statistically significant decrease in serum magnesium concentration [13].

Magnesium shortage has a strong immunosuppressive role in patients with acute bacterial infections. Studies have demonstrated a significant decrease in the number of immunoglobulins IgGs in cases of magnesium deficiency [17,18]. Magnesium is involved in the phospholipid membrane stabilization and may provide protection to endothelial cells against hemodynamic stress [14,19]. In particular, magnesium deficiency could be due to inadequate intake, excessive loss, or a combination of both [20,21,22].

The aforementioned knowledge implies that increased consumption of magnesium-rich water may in fact yield beneficial effects with respect to the prevention and treatment of recurrent UTIs for individuals. The purpose of this prospective quasi-experimental study was to investigate the effects of daily consumption of magnesium-rich bottled water and compare them to the relevant effects induced by consuming regular tap water (i) on the number of UTIs and (ii) on the serum magnesium levels of patients with history of recurrent UTIs.

2. Materials and Methods

2.1. Design of the Study

The study was conducted between August 2018 and August 2019, in the Chalkida-Eretria region. The individuals included in the study sample were selected from a pool of patients who had been admitted to the Urology Department of the local hospital which covers the area of Chalkida and Eretria, and had an established history of recurrent UTIs. The patients/participants upon entering the study (T0) underwent a series of examinations: a) a urine analysis and b) a urine culture, and c) the measurement of serum magnesium levels. The participants repeated these examinations nine months after the initial examination date, during a scheduled follow-up appointment (T1). The clinical assessment tests were conducted in an appropriate, independent, certified, private laboratory in the Evia region.

The researchers communicated with patients via telephone calls to collect information about patients' total daily fluids consumption (litres/day) and personal state of health. The communication took place twice (3 and 6 months after participant recruitment).

The study was designed as a prospective quasi-experimental study. The group that consumed the tap water which is available in its corresponding location was considered as control group and named as "group A" and the group that consumed the magnesium-rich bottled water was considered as case group and named as "group B".

The daily water intake was required to be 2.0-2.5 litres. The aforementioned quantity of water intake it is rather rare to create hypercalciuria, unless participants suffer from a hormonal problem. The participants were asked before participating in the study, if they were suffering from hormonal problems. (All participants answered that they did not have). For the preparation of meals and drinks, specific water had to be used for each group, namely the bottled water for the group B and the tap water for the group A, respectively. This amount was not measured in the above consumption of 2.0-2.5 litres/day. The chemical analysis of the magnesium-rich bottled water which was publicly accessible [23] and the tap water are presented in Table 1.

Table 1. Chemical analysis of the magnesium-rich Dirfys' bottled water and the tap water

Chemical component	Magnesium-rich bottled water (Dirfys' bottled water)	Tap water
Calcium [Ca^{+2}] (mg/L)	66.9	47.7
Magnesium [Mg^{+2}] (mg/L)	21.2	0.1
Sodium [Na^{+}] (mg/L)	8.8	1.2
Potassium [K^{+}] (mg/L)	0.5	0.3
Ammonium [NH_4^{+}] (mg/L)	< 0.1 (non-detected)	< 0.1 (non-detected)
Bicarbonates [HCO_3^{-}] (mg/L)	30.7	145
Chloride [Cl^{-}] (mg/L)	15.1	<5
Sulphates [SO_4^{-2}] (mg/L)	<5	<5
Nitrates [NO_3^{-}] (mg/L)	3.2	1.5
Nitrites [NO_2^{-}] (mg/L)	< 0.05 (non-detected)	< 0.05 (non-detected)
Conductivity (μS/cm)	517	238
pH	7.8	8.0
Total Hardness [$CaCO_3$] (mg/L)	254	119
Total avoidance of heavy metals and organic carbon		

2.2. Study Population

At the beginning of the study, fifty-six patients (N=56) aged between eighteen and seventy-four years of age were assessed for eligibility based on whether they fulfilled the study's relevant inclusion criteria. Patients' inclusion criteria were:

1) No consumption of probiotic supplements, in particular, strains combined with Lactobacillus reuteri RC-14 + Lactobacillus rhamnosus GR-1 [RC14-GR1] and/or Lactobacillus rhamnosus GG + Bifidobacterium GG + 12-Bifidobacterium BB12, either given intra-vaginally (to women) or peros (orally). Consumption of the above probiotics helps in facilitating the prevention of recurrent UTIs, [24].
2) Restriction from cranberry supplements due to the protective actions they offer against recurrent UTIs [25].
3) Being ≥ 18 years of age (adulthood).
4) Having a history of recurrent UTIs and/or suffering from a urinary tract infection, either with the corresponding symptomatology or with no symptoms (bacteriuria) detected by a urine culture examination.

The cut off value for urinary infection diagnosis is suggested to be a urine level of 10^5 cfu/mL by most of the laboratories [26]. However, an alternative urinary limit of 10^3 cfu/mL is also being used, depending on the bacterium being detected [27]. In our study, a urinary limit of 10^5 cfu/mL was used for UTI diagnosis. Patients with a urinary limit of $< 10^5$ cfu/mL without clinical symptoms were not assessed.

The patients' exclusion criteria were the following: a) uterine prolapse, b) behaviours that exacerbate UTIs' clinical outcome, c) a history of pelvic surgery or incontinence, d) neurological diseases, e) anatomical malformations of the urinary system, f) the undertaking of a long-term treatment involving antibiotics, g) the supplementation of magnesium or multivitamin dietary supplements.

All patients gave their informed consent for inclusion before they participated in the study (The consent form is available from the corresponding author). Moreover, the research was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2000.

A flow diagram of the sample size of the study, from the study initiation, up until the study completion (data analysis), is presented in Figure 1.

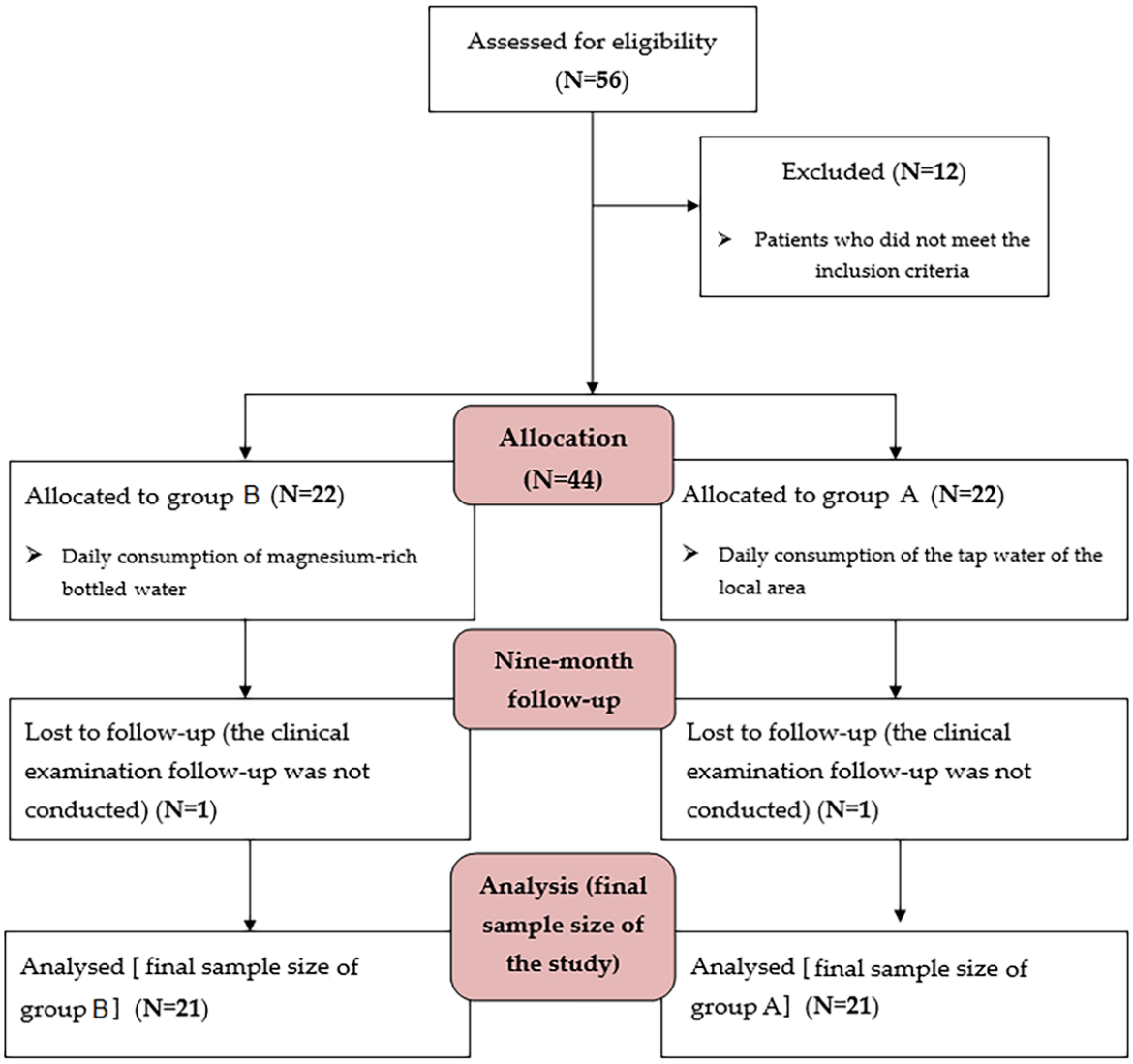

Figure 1. Study's flowchart

2.3. Statistical Analysis

The Jamovi 1.1.9 software for windows 10 was utilized in order to perform the necessary statistical analysis. The primary hypothesis was tested with a significance level of a =0.05. Statistical significance was set at P value <0.05. The Shapiro-Wilk test, Skewness, Kurtosis and histograms were applied for all continuous variables for testing normality. Descriptive statistics were performed; values are presented as mean ± SD, minimum and maximum.

The equality of variances of the continuous variables between the groups (group A - group B) was tested by applying Levene's test.

Within groups differences of the quantitative variables between the two time points (T0 and T1) were tested by applying the non-parametric paired samples Wilcoxon rank test.

Between groups differences of the qualitative variables were assessed using the independent samples χ^2 test of association. Chi-squared test was used when the expected frequencies were > 5 and Fisher's - exact was used when the expected frequencies were ≤ 5.

The difference of the mean of the quantitative variables between groups (group A - group B) was tested by applying the independent samples Student's t-test when the essential equality of variances between groups was adhered and by the Mann-Whitney U-test when equality of variances between groups were not.

A general linear model, adjusted for age, was conducted in order to evaluate the effect of the daily consumption of magnesium-rich water on the serum magnesium levels of patients.

Information related to which type of water was consumed per group was blinded to the statistician in order to decrease the detection bias.

3. Results

3.1. Sample Size of the Study

A total number of forty-four (44) patients aged between 18 to 84 years old were included in the study. One participant per group was lost during follow-up (9 months later). For the statistical analysis, each group was consisted by twenty-one (21) patients, mainly female [group A (90.5 %), group B (95.2 %)].

3.2. Clinical Characteristics of the Study's Patients Divided by Groups

The descriptive characteristics (categorical and numerical variables) of both groups (group A - group B), as well as, their statistical differences, are presented in Table 2 and Table 3, respectively.

No statistically significant differences were observed in the clinical characteristics between groups (group A - group B) (P value >0.05). Moreover, there was no statistically significant difference concerning recurrent UTI incidents between groups (group A - group B) after nine months of different type water consumption (P value =0.113).

Table 2. Clinical characteristics/Statistical differences between groups [group A - group B] (Categorical Variables).

		Group A	Group B	
		N (%)	N (%)	P value[†]
Gender	Male	2 (9.5)	1 (4.8)	0.549
	Female	19 (90.5)	20 (95.2)	
Comorbidity	None	17 (80.9)	17 (81.0)	0.498
	Hypertension	1 (4.8)	2 (9.5)	
	Hypertension and Hyperlipidemia	3 (14.3)	1 (4.8)	
	Hypertension, Hyperlipidemia and Diabetes	0	1 (4.8)	
Antibiogram results	Sterile	13 (61.9)	17 (81.0)	0.305
	E. Coli	8 (38.1)	4 (19.0)	
Pharmaceutical treatment	No infection	13 (61.9)	17 (81.0)	0.305
	Cephalosporin 2nd generation / for seven days	8 (38.1)	4 (19.0)	
Urine analysis derived during the study entry date (T0)	Sterile	16 (76.2)	17 (81.0)	0.533
	2-3 pus cells	0	1 (4.8)	
	3-5 pus cells	0	1 (4.8)	
	5-6 pus cells	1 (4.8)	0	
	8-10 pus cells	1 (4.8)	1 (4.8)	
	12-14 pus cells	1 (4.8)	0	
	70-80 pus cells	0	1 (4.8)	
	Moderate development of microorganisms	1 (4.8)	0	
	Severe development of microorganisms	1 (4.8)	0	
Urine analysis derived during the follow-up day, nine months later (T1)	Sterile	17 (81.0)	17 (81.0)	0.735
	1-2 pus cells, rare strains of microorganisms	1 (4.8)	0	
	2-3 pus cells	0	1 (4.8)	
	8-10 pus cells	1 (4.8)	1 (4.8)	
	No follow up	2 (9.5)	2 (9.5)	
Urine culture derived during the study entry date (T0)	Sterile	16 (76.2)	18 (85.7)	0.490
	E. Coli	4 (19.0)	3 (14.3)	
	Microbiological contamination	1 (4.8)	0	
Urine culture derived during the follow-up day, nine months later (T1)	Sterile	17 (81.0)	19 (90.5)	0.348
	E. Coli	2 (9.5)	0	
	No follow-up	2 (9.5)	2 (9.5)	

[†] Independent samples Chi-squared test and Fisher's - exact test was used, as appropriate. Statistical significance was set at P value < 0.05.

Table 3. Clinical characteristics/Statistical differences between groups [group A - group B] (Numeric Variables)

	Group A (N=21)			Group B (N=21)			
	Mean ±SD[‡]	Min[¶]	Max[§]	Mean ± SD[‡]	Min[¶]	Max[§]	P value[†] (95% CI[††])
Age (years)	49.9±17.6	18.0	72.0	49.4±18.2	23.0	84.0	0.931 (-10.71, +11.67)
Recurrent UTI incidents during the study (nine-month period)	0.714 ± 1.007	0.0	3.0	0.238 ±0.539	0.0	2.0	0.113 (-1.000, +0.019)

[‡] SD, Standard deviation; [¶] Min, Minimum; [§] Max, Maximum; [††] CI, Confidence interval.
[†] Independent samples Student's t-test and the non-parametric Mann-Whitney U-test was used, as appropriate. Statistical significance was set at P value < 0.05.

Table 4. Serum magnesium levels at the two time points (T0 and T1) in the two patients' groups (group A - group B).

	Group A (N=18)		Group B (N=19)		P value[†] (95% CI[††])			
	Mean ± SD[‡]		Mean ± SD[‡]		Within groups[a]		Between groups[b]	
	T0[‡‡]	T1[¶¶]	T0[‡‡]	T1[¶¶]	Group A	Group B	T0[‡‡]	T1[¶¶]
Serum Magnesium levels (mg/dL)	2.09 ± 0.23	1.92 ± 0.28	1.91 ± 0.30	2.12 ± 0.16	< 0.001 (-0.40,-0.15)	0.001 (+0.11, +0.33)	0.043 (-0.36, -0.01)	0.041 (+0.02, +0.33)

[‡] SD, Standard deviation; [‡‡] T0, The study entry date; [¶¶] T1, The follow up day, nine months later; [††] CI, Confidence interval.
[a] Within groups comparisons. Paired samples Wilcoxon rank test was used.
[b] Betweem groups comparisons. Independent samples Student's t-test and the non-parametric Mann-Whitney U-test was used, as appropriate.
[†] Statistical significance was set at P value < 0.05.

3.3. Serum Magnesium Levels

The descriptive characteristics of serum magnesium levels of both groups (group A - group B) during the study entry (T0) and during the follow up day nine months later (T1), as well as, the within and between groups statistical differences, are presented in Table 4.

During nine months of consumption of different type of water, the following observations were made. Patients belonged to group A decreased their serum magnesium levels by 0.250 mg/dL (95% CI; -0.40, -0.15) with a statistically significant degree (P value < 0.001). On the contrary, patients who belonged to group B increased their serum magnesium levels by 0.250 mg/dL (95% CI; +0.11, +0.33) after nine months of magnesium-rich bottled water consumption, with a statistically significant degree (P value =0.001).

At the study entry, the serum magnesium levels of the patients who belonged to the group B, were lower than those of the group A patients by 0.183 mg/dL (95% CI; -0.36, -0.01, P value =0.043), and that difference was statistically significant.

Moreover, at the follow-up day (nine months later), the patients who belonged to the group B had on average 0.140 mg/dL (95% CI; +0.02, +0.33, P value =0.041) higher serum magnesium levels than those who belonged to the group A, significantly.

Finally, a general linear model, adjusted for age, showed that patients who belonged to group B had on average 0.101 mg/dL (95% CI; +0.03, +0.18, P value =0.011) higher serum magnesium levels than those who belonged to group A after nine months of consuming of different types of water, regardless of their age. This difference was statistically significant.

4. Discussion

This is the first prospective quasi-experimental study in Greece which examines whether the consumption of magnesium-rich bottled water improves the outcomes of patients suffering from recurring UTIs. The literature review indicates that increased water consumption can be beneficial in the prevention of UTIs [9,10,11,12,14,17,18] . In our study, we observed that there was no statistically significant difference in the number of infections of UTIs, throughout a nine-month period, during which the water which was consumed by individuals belonged to group B was enriched with magnesium.

However, our study demonstrated that the patients which belonged to the group B and were consuming 2.0-2.5 L, of bottled water enriched with magnesium on a daily basis, increased their serum magnesium levels when contrasted to the change recorded in the individuals in the group A, which were consuming 2.0-2.5 L of the local tap drinking water.

A series of recent studies has indicated that magnesium has vasodilatory, anti-inflammatory, anti-ischemic, and antiarrhythmic properties. It is a critically important nutrient and a potentially useful therapeutic agent in cardiovascular medicine. Additionally, a significant association between hypomagnesaemia and new-onset diabetes after kidney transplantation (NODAT), in kidney transplant recipients, for both adult and pediatric patients has been indicated. Moreover, murine studies have shown that the maternal hypomagnesaemia is associated with diabetes mellitus, insulin resistance, dyslipidemia, metabolic syndrome, depression, impaired placental development, impaired fetal growth and increased mortality [28-41]. Bottled water may be an essential and inexpensive source of magnesium and other minerals. In natural mineral water, minerals occur in an ionized form which is very well digestible [42].

In our research, at the study entry, three patients [group A (N=1) and group B (N=2)], had serum magnesium levels below the normal ranges (1.7 mg/dL - 2.2 mg/dL) [43]. At the follow-up day (nine months later), when the study reached completion, five patients who belonged to the group A (four new cases) had serum magnesium levels below the normal ranges, and there were no patients with hypomagnesaemia in the group B.

Finally, our study has some limitations. Chiefly, the sample size of the study (the number of patients) is small. Moreover, more comparisons with other regions (whose

local tap water differs regarding the chemical components) could give more information. Additionally, a different way of research is supplementary, but it was not implemented. We could compare the same bottled water with another (prepared in a laboratory), whose chemical analysis would be the same with the exception of a single component (e.g. calcium).

5. Conclusions

Conclusively, the daily consumption of magnesium-rich bottled water increases the serum magnesium levels in adult patients who experience recurrent UTIs, but has no impact on the reduction of the UTI incidents. However, more studies are necessary to determine the effects of the consumption of magnesium-rich water on individuals, who suffer from recurrent incidents of UTI. Future studies could investigate these effects on a greater sample size suffering for recurrent UTIs. Additional studies should examine a comparison in other regions (whose local tap water differs regarding the chemical components). Another idea is to compare the same bottled water with other (similar), whose chemical analysis would be the same (as the bottled water) with the exception of a single component (e.g. one case is to differ only in magnesium, another case to differ only in calcium etc.).

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Statement of Competing Interests

The authors declare no potential conflicts of interests.

Abbreviations

UTI, urinary tract infection; NODAT, new-onset diabetes after kidney transplantation.

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